Learning Microbiology through Clinical Consultation
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Preface

Overview

This book is intended for medical students and newly qualified doctors, and introduces microbiology and infectious diseases using lifelike case stories linked to microbiology learning points for each topic. The case stories make the subject matter immediate and instantly applicable, and the microbiology discussion pulls out the important points on key microbes, differentials, specimen processing, and antimicrobial therapy for each case.

Each case is a narrative and is a fly on the wall experience for the reader, who can listen to the whole interaction (including any awkward moments), observe the examination and specimen taking techniques, hear what advice should be given, and how the consultation can be drawn to a close. The swabs sent in the story and the results obtained provide a clear link to the more technical information on microbiology, which is then discussed, and by this means each topic is embedded in clinical practice with the relevant microbiological information being brought to the fore.

It is well known that learning information presented as a narrative is highly effective, but it is a fact not yet used by most textbooks. That the information is presented as narrative does not mean the information is trivial. The case stories bring to life both the presentation of the patient, the consultation process and, embedded with it, the microbiology.

Microbiology is an essential part of medicine and is therefore a key part of the curriculum and key knowledge for a working doctor. With modern systems-based and problem-based learning it tends to be taught in an integrated fashion and is incorporated into the teaching of infectious disease, general medicine and surgery. Learning Microbiology through Clinical Consultation also presents the material in an integrated fashion and is therefore an ideal text to use on a systems-based or problem-based course, or for a newly qualified doctor practising independently. The structure of the book is laid out for easy navigation and has clear case story headings to enable 'just in time learning' as well as 'just in case' learning.

Learning Microbiology through Clinical Consultation encompasses not only what medical students and newly qualified doctors need to know for their exams, but also what they need to know to practise medicine.

The importance of consultation

The consultation features strongly in Learning Microbiology through Clinical Consultation, and, as such, is worth a short discussion to try and explain what is going on, and what is meant to be going on, in each interaction.

The consultation is the transaction between doctors and patients. It is central to the whole idea of medicine as well as to the idea of this book. There is a lot going on in every real consultation and, reflecting real life, a lot going on in each of these case stories.

The doctor's introduction to the patient (if you have not met) is essential to every consultation, and, in fact, the doctor's introduction to each colleague is essential to every interaction with the medical team. A description of every introduction has not been included in each case story as this would become repetitive, but in real life it should be happening every single time. Unfortunately,
this element of basic, common courtesy is missed out in real life interactions more often than is admissible.

The point of a consultation would seem obvious: to sort out the patient's medical problem. But the point of each individual consultation is, sometimes, not at all obvious. The patient's agenda and the doctor's agenda are not necessarily at all the same thing.

As the knowledgeable party, the doctor has a duty to assess the patient appropriately, explain things, and advise them as to tests and treatments. And patients want and expect the doctors to do just that. But they will also have their own ideas: about what is happening, what should be done, and what treatments are right. Patients are not usually able to judge if the doctor is clinically any good or not, but they use the doctor's manner and approach as a surrogate for this.

Added to the mix of patient's and doctor's agenda, there is the government's agenda, insisting on certain targets, safety measures, and cost issues, as well as, the public health agenda, a responsibility of the doctor to consider public health measures, preventative treatments, and lifestyle advice, and this is all to be achieved within a certain amount of time (10 minutes for GPs, longer in hospitals) and with a certain (usually large) case load.

To start with, the doctor's agenda is important. This is the basic requirement of each consultation: that the patient should be safely assessed and treated appropriately. This assessment starts with the thorough history familiar to all doctors: the presenting complaint, the history of the presenting complaint, the past medical history, the treatment history, the social history, family history, and allergies. These elements of the consultation should be easily observed in the case stories (although bear in mind that for the GP consultations, the GP has a lot of the background information readily accessible on the computer notes and will therefore not ask it every time) along with certain refinements; the sexual history in the genitourinary medicine (GUM) clinic, the mini-mental test used for dementia assessment and the activities-of-daily-living history in elderly or infirm patients, among others. The history taking can also be refined further, depending on the doctor's differential, leading to noticeably more directive questioning.

The overall look of the patient is very important and is often noted in these case stories, and should be seen as part of the examination. Part of the point of these case stories is to model and describe in detail the physical examination of the patient and also how to take the correct samples and transfer them to the laboratory for identification of microbes.

There are many different consultation models, and all consultation models attempt to address not just the clinical agenda of the doctor but the other agendas mentioned, in particular the patient's. This is where the doctor's additional consultation skills can be observed, and where a patient has felt they have been properly listened to and their worries addressed there is a much better outcome to quite measurable things, such as an improvement in health and mental issues. This is sometimes known as the doctor being the medicine.

Various consultation models have developed over the past 60 years. Because there are lots of models, doctors have to pick and choose techniques that work for them, for the patient, and the time and place. Key consultation models include: Balint, 'The doctor, the patient and his illness', Byrne and Long, 'Doctors talking to patients', Roger Neighbour, 'The inner consultation', and the influential (especially given that candidates are examined on it) Royal College of General Practitioners (RCGP) performance criteria check list.

Each model has its own criteria checklist of which elements are important and which should be included in each consultation. One of the most helpful and intuitive is Roger Neighbour's five stage model: Connecting with the patient, Summarizing the patient's reason for attending (as well as their feelings, concerns, and expectations), Handing over to the patient the agreed plan, Safety netting or advising what to do if something unexpected happens, and Housekeeping to ensure the clinician stays in good shape for the next patient. The influence of this model is apparent by the
way some of his stages have entered common language usage, such as ‘housekeeping’ and ‘safety netting’, and it should be possible to notice some of these stages in the case stories presented.

The RCGP expands some of these stages, for example, marking candidates on picking up cues and responding to them, using psychosocial information and not just medical information and explaining things appropriately with written information as a backup, and specifically checking understanding. These are all useful techniques and some may be observed within some of these case stories.

Medical protection groups have also expanded certain parts of the consultation, specifically ‘connecting’. The connection the doctor has with the patient is a key stage, and it makes a difference to absolutely everything, from the medical assessment to the ultimate outcome. A good connection can benefit everyone. Everything from hospital décor to the doctor’s appearance, voice, tone, and body language will all affect the patient’s first impression. To then have a doctor who is actively listening, who is showing an interest in what the patient has to say, who has good eye contact (and is not just looking at the computer), and who does not immediately interrupt the presenting complaint will all enable an excellent consultation to proceed. If the doctor then acknowledges what has been said by the patient by summarizing it briefly so that patient and doctor are agreed on what the consultation will address, then this all creates a good basis for the consultation to continue and for all further interactions. The consultation, and these consultation models combine, to form a wide-ranging and fascinating subject, only briefly touched on here.

The microbiology relating to each topic also benefits from an overview (see Appendices 1, 2 and 3). Appendix 1: A table of medically important bacteria, describes the classification of bacteria using, for example, positive and negative Gram stains, bacterial shapes, and growth requirements. These characteristics are frequently mentioned in the cases. Appendix 1 also contrasts the difference between bacterial classification for medical purposes and classification based on phylogenetics.

Appendix 2: A table of medically important viruses, explains terms relating to virus classification also frequently mentioned in the cases, for example single-stranded (ss) versus double-stranded (ds) viruses or RNA versus DNA viruses. Appendix 2 also contrasts the difference between viral classification for medical purposes and classification based on scientific conventions related to taxonomy.

Appendix 3: Notification of infectious diseases, includes tables on notifiable diseases (again frequently mentioned in the cases) as well as a description of the purpose and processes of notification.

This introduction is intended to allow a better understanding of the consultation process in particular, as well as to point out the appendices on classification and notification. Knowledge of the consultation models and of these appendices will enable a better understanding of what is going on in each case, and this will allow examples of good practice to be picked out and used; whether of history taking, examination, obtaining microbial specimens, or good use of the laboratory. The cases contained within Learning Microbiology through Clinical Consultation will hopefully allow the microbiology to be absorbed as easily as the clinical scenarios, but will at the very least give a vivid picture of the consultation process.
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<td>+ve</td>
<td>positive</td>
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<td>-ve</td>
<td>negative</td>
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<td>A&amp;E</td>
<td>Accident and Emergency</td>
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<td>ABG</td>
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<td>bacillus Calmette-Guérin</td>
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<td>bd</td>
<td>twice a day</td>
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<td>British National Formulary</td>
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<td>CVA</td>
<td>cerebrovascular accident</td>
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<tr>
<td>CXR</td>
<td>chest X-ray</td>
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<td>DMSA</td>
<td>dimercaptosuccinic acid</td>
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<td>DNA</td>
<td>deoxyribonucleic acid</td>
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<tr>
<td>DOT</td>
<td>directly observed therapy</td>
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<tr>
<td>ds</td>
<td>double strand</td>
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<td>DVT</td>
<td>deep vein thrombosis</td>
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<tr>
<td>EBV</td>
<td>Epstein–Barr virus</td>
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<td>ECG</td>
<td>electrogram</td>
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<td>EDTA</td>
<td>ethylenediaminetetraacetic acid</td>
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<tr>
<td>EIA</td>
<td>enzyme immunoassay</td>
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<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>ENT</td>
<td>ear, nose, and throat</td>
</tr>
<tr>
<td>ERPC</td>
<td>evacuation of retained products of conception</td>
</tr>
<tr>
<td>ESR</td>
<td>erythrocyte sedimentation rate</td>
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<tr>
<td>FBC</td>
<td>full blood count</td>
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<tr>
<td>Fe</td>
<td>iron</td>
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<tr>
<td>FFP</td>
<td>filtering face piece</td>
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<tr>
<td>FI</td>
<td>fusion inhibitors</td>
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<tr>
<td>GA</td>
<td>general anaesthetic</td>
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<tr>
<td>GDH</td>
<td>glutamate dehydrogenase</td>
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<tr>
<td>GI</td>
<td>gastrointestinal</td>
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<td>GP</td>
<td>general practitioner</td>
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<td>GUM</td>
<td>genitourinary medicine</td>
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<tr>
<td>H</td>
<td>haemagglutinin</td>
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<tr>
<td>HAART</td>
<td>highly active anti-retroviral treatment</td>
</tr>
<tr>
<td>HAV</td>
<td>hepatitis A virus</td>
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<tr>
<td>Hb</td>
<td>haemoglobin</td>
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<tr>
<td>HDU</td>
<td>high dependency unit</td>
</tr>
<tr>
<td>HHV-6</td>
<td>human herpesvirus 6</td>
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<tr>
<td>Hib</td>
<td>haemophilus influenzae type b</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>HPV</td>
<td>human papilloma virus</td>
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<tr>
<td>HSV</td>
<td>herpes simplex virus</td>
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<tr>
<td>IBS</td>
<td>irritable bowel syndrome</td>
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<tr>
<td>ICU</td>
<td>intensive care unit</td>
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<tr>
<td>Ig</td>
<td>immunoglobulin</td>
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<tr>
<td>IM</td>
<td>intramuscular</td>
</tr>
<tr>
<td>IU</td>
<td>international units</td>
</tr>
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<td>IUGR</td>
<td>intrauterine growth retardation</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
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<td>LFT</td>
<td>liver function tests</td>
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<td>LPS</td>
<td>lipopolysaccharide</td>
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<td>LRTI</td>
<td>lower respiratory tract infection</td>
</tr>
<tr>
<td>m.c.s.</td>
<td>microscopy, culture and sensitivity</td>
</tr>
<tr>
<td>MALDI-TOF</td>
<td>matrix-assisted-laser-desorption/ionization-time-of-flight</td>
</tr>
<tr>
<td>MERS</td>
<td>Middle East respiratory syndrome</td>
</tr>
<tr>
<td>mL</td>
<td>millilitre</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>μm</td>
<td>micrometre</td>
</tr>
<tr>
<td>MRSA</td>
<td>meticillin-resistant staphylococcus aureus</td>
</tr>
<tr>
<td>MSM</td>
<td>men who have sex with men</td>
</tr>
<tr>
<td>MSU</td>
<td>mid-stream urine</td>
</tr>
<tr>
<td>MTB</td>
<td>mycobacterium tuberculosis</td>
</tr>
<tr>
<td>MU</td>
<td>million units</td>
</tr>
<tr>
<td>N</td>
<td>neuraminase</td>
</tr>
<tr>
<td>NAAT</td>
<td>nucleic acid amplification technology</td>
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<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>nm</td>
<td>nanometre</td>
</tr>
<tr>
<td>NNRTI</td>
<td>non-nucleoside reverse transcriptase inhibitor</td>
</tr>
<tr>
<td>NPA</td>
<td>nasopharyngeal aspirate</td>
</tr>
<tr>
<td>NRTI</td>
<td>nucleoside reverse transcriptase inhibitor</td>
</tr>
<tr>
<td>NSAID</td>
<td>non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>od</td>
<td>once daily</td>
</tr>
<tr>
<td>OE</td>
<td>otitis externa</td>
</tr>
<tr>
<td>OM</td>
<td>otitis media</td>
</tr>
<tr>
<td>OPAT</td>
<td>outpatient parenteral antibiotic treatment</td>
</tr>
<tr>
<td>PABA</td>
<td>para-aminobenzoic acid</td>
</tr>
<tr>
<td>PaO₂</td>
<td>partial pressure of oxygen</td>
</tr>
<tr>
<td>PCP</td>
<td>Pneumocystis pneumonia</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>PI</td>
<td>protease inhibitors</td>
</tr>
<tr>
<td>PICC</td>
<td>peripherally inserted central cannula</td>
</tr>
<tr>
<td>PID</td>
<td>pelvic inflammatory disease</td>
</tr>
<tr>
<td>PMC</td>
<td>pseudomembranous colitis</td>
</tr>
<tr>
<td>po</td>
<td>per oral</td>
</tr>
<tr>
<td>PPE</td>
<td>personal protective equipment</td>
</tr>
<tr>
<td>PVL</td>
<td>Panton–Valentine leukocidin</td>
</tr>
<tr>
<td>qds</td>
<td>four times a day</td>
</tr>
<tr>
<td>R</td>
<td>resistant</td>
</tr>
<tr>
<td>R₀</td>
<td>basic reproductive ratio</td>
</tr>
<tr>
<td>RCC</td>
<td>red cell count</td>
</tr>
<tr>
<td>RCGP</td>
<td>Royal College of General Practitioners</td>
</tr>
<tr>
<td>RIDT</td>
<td>rapid influenza diagnostic tests</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>RSV</td>
<td>respiratory syncytial virus</td>
</tr>
<tr>
<td>RT–PCR</td>
<td>reverse transcriptase polymerase chain reaction</td>
</tr>
<tr>
<td>S</td>
<td>sensitive</td>
</tr>
<tr>
<td>SARS</td>
<td>severe acute respiratory syndrome</td>
</tr>
<tr>
<td>SLE</td>
<td>systemic lupus erythematosus</td>
</tr>
<tr>
<td>SSPE</td>
<td>sub-acute sclerosing panencephalitis</td>
</tr>
<tr>
<td>ss</td>
<td>single strand</td>
</tr>
<tr>
<td>STI</td>
<td>sexually transmitted infection</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>tds</td>
<td>three times a day</td>
</tr>
<tr>
<td>TFT</td>
<td>thyroid function tests</td>
</tr>
<tr>
<td>U&amp;E</td>
<td>urea and electrolytes</td>
</tr>
<tr>
<td>URT</td>
<td>upper respiratory tract</td>
</tr>
<tr>
<td>URTI</td>
<td>upper respiratory tract infection</td>
</tr>
<tr>
<td>U/S</td>
<td>ultrasound</td>
</tr>
<tr>
<td>UTI</td>
<td>urinary tract infection</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>VDRL</td>
<td>Venereal Diseases Reference Laboratory</td>
</tr>
<tr>
<td>VHF</td>
<td>viral haemorrhagic fever</td>
</tr>
<tr>
<td>VLP</td>
<td>virus-like-particle</td>
</tr>
<tr>
<td>VRE</td>
<td>vancomycin-resistant enterococci</td>
</tr>
<tr>
<td>VZIG</td>
<td>varicella zoster immunoglobulin</td>
</tr>
<tr>
<td>VZV</td>
<td>varicella zoster virus</td>
</tr>
<tr>
<td>WCC</td>
<td>white cell count</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Chapter 1

**Gastrointestinal**

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Case 1.1

Viral gastroenteritis

Case example

‘He’s vomiting. Three days. He drinks; he vomits.’

The first phone call of the day is about 2-year-old Ra’id. The history – as brief as it is – has triggered the ‘needs review’ switch in your head. Firstly, because he may not be coping with what sounds like gastroenteritis, and, secondly, in case it is not gastroenteritis but something else. You cut out any further history taking at this stage, offer his mother an appointment for him at 10.30 that morning and move onto the other 18 phone calls you have on your list.

However, although you have called him in, you are also a little reluctant to see him. Viral gastroenteritis is readily spread by aerosol (from the patient sneezing) and by droplet (from the patient vomiting), and there is always a chance you will catch it. But that’s one of the hazards of doctoring; you just have to put up with it.

At about 10.50 you buzz for them to come in. There is a knock at the door and a fumbling sound so you stand up and open the door hospitably. Ra’id’s mum is carrying him with his arms clasped about her neck and her arm around him, as well as holding a bag half hidden under her black hijab and burka. They sit down and Ra’id’s mum pulls at her black drapery so that it is not under her feet but arranged properly over her knees. Ra’id sits on the seat next to her.

You run over the story again; four vomits Saturday night, four during Sunday. One today after some juice but he only woke at 09.30. Ra’id is alert and his colour is ok as he leans against his mother.

‘Any diarrhoea?’

‘No.’

‘Any cough or cold?’

‘No.’

‘Does it hurt anywhere?’

Blank look.

‘Pain?’

‘He say his belly hurts.’

‘Is he still passing urine?’ His mum looks blank again. ‘Was his nappy wet this morning?’

‘Yes. Wet.’

Ra’id looks up when you ask about his nappy. He is alert and listening in.

You rapidly take his temperature and check his ears and his throat, which are fine. At each manoeuvre Ra’id looks horrified (although you tell him what you are doing throughout). He screws up his little face in a soundless look of fear that then slowly relaxes and subsides as each check is less bad than he anticipates. It is cute and you can’t help but smile. Despite his fear he doesn’t wriggle, which helps your examination go quickly.
You listen to his chest, which is fine. You smooth his vest back over his tummy so that your hands will feel less chilly, and then press gently all around his abdomen with the flat of three fingers while he sits on mum’s lap. He is relaxed and not crying and his tummy is soft throughout with no tenderness. Finally you ask him if you can see his fingers. Familiarly enough this untoward apparent intimacy often goes down the least well with an infant. Ra’id moves his hand away even as you hold it and press on his fingertips to check for capillary refill. His fingertip goes white and then immediately pink again. He has nice warm hands and capillary refill is less than 1 second.

This normal examination satisfies you that you are dealing with a viral gastroenteritis. The wet nappies, warm hands, and good capillary refill all indicate that he is not dehydrated.

You sit back having finished your examination and hold your hands a little to one side, not touching anything. This is to remind yourself that they need washing. There is a natural break now while Ra’id’s mum re-dresses him and you get up and walk to the sink and wash your hands.

While you do this you explain your findings to her.

‘He has gastroenteritis.’
‘What?’ Ra’id’s mother says.
‘A viral illness.’
‘?’
‘A stomach bug? A stomach infection?’ you try.
‘Oh. Ok.’
‘It will get better by itself. Better by himself. He is not dehydrated. He is ok.’
‘No medicine?’
‘No he just needs fluids, he needs to drink.’
‘He drink; he vomit.’
‘He needs to drink little amounts. Very often. Not big amounts. Or that will . . . ,’ you mime vomiting.
‘What drink? Juice? Milk?’
‘Not juice or milk. Water is better. Or squash. . . cordial’.
‘What about medicine?’
‘He doesn’t need medicine. Just fluids . . . drink . . . like water. Little amounts.’ You push on. ‘He will get better himself.’ You pause. ‘I could give you oral rehydration salts.’
‘What is that?’
‘It’s like a powder. You mix with water for him to drink. It’s very good for vomiting.’
‘Ok. How much?’
You sit down and print off a prescription of Dioralyte® rehydration salts and write down; 1 sachet in 200 mL.
‘No. How much for him?’
‘Oh. About 700 mL in 24 hours.’
‘No. How much?’
‘How much an hour? Aim for 60 mL per hour.’ You write down these figures as well.
‘If he is worse come back.’
‘Come back?’
‘If he gets worse. Or if you are worried.’
‘Ok.’
She gets up and reaches for Ra’id. She puts her hands under his arms and waits for him to jump a little so that she can lift him more easily onto her hip. You pass her bag to her and the script and open the door for her again.
‘Thank you,’ she says.
‘Thank you. Goodbye’. You wave to Ra’id.

**Microbiology**

Viral gastroenteritis has a number of causes. Rotaviruses account for the majority of cases, norovirus for about a fifth; in addition, adenoviruses, sapoviruses, astroviruses, and other calciviruses can also cause outbreaks.

Rotaviruses are non-enveloped ds RNA viruses, 80 nm in size (see Fig. 1.1.1). Noroviruses are icosahedral ss RNA viruses, and slightly smaller being 30 nm in size, with 32 cuplike indentations in the surface. Formerly known as Norwalk-like virus, it was identified in a small town of this name in Ohio, USA, in 1968. These viruses are also known sometimes as ‘small round structured viruses’ from their electron microscope appearance.

Both sorts of virus infect gut cells (enterocytes) causing villus atrophy. The resulting crypt hyperplasia means there is less absorption of fluids and increased secretion. It is these combined factors that cause the watery diarrhoea. After the infection is cleared the enterocytes are rapidly replaced and the villus architecture is restored leading to resolution of the diarrhoea.

Samples for viral gastroenteritis illnesses are not usually taken. The illness is too common and mostly mild and self-limiting and the identification of a particular virus has no impact on the treatment or prognosis of the illness. However, for the purposes of surveillance, sentinel GP practices send off stool samples. The stool samples are then processed either by immunoassays that detect viral antigen in the faeces, or by PCR, which both detects the virus and identifies different strains.

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**Fig. 1.1.1** A transmission electron micrograph of rotavirus.
Ra’id had his episode of gastroenteritis at the beginning of December (week 48) for which the Public Health England Weekly National Surveillance Report shows a low incidence of rotavirus gastroenteritis, but a slight increase in norovirus, from a summer low of 20 norovirus laboratory reports a week, to the present 100 laboratory reports a week. (But nothing like the peak in 2009 of 700 reports a week). The subtype circulating is identified as GII-4 Sydney-like.

Norovirus is a winter vomiting bug reaching its peak between November and April, although it circulated at a lower level throughout the summer as well.

Incubation for norovirus and rotavirus and the others (astrovirus, calcivirus) tends to be 1–2 days. Many infections are subclinical, which helps the viruses spread nicely. Because there are multiple subtypes of each, adults and especially children can expect to be infected commonly (yearly; possibly more in children). Children tend to be the viral reservoir and spread it to each other and then to their parents or other adults working closely with them (teachers, health care workers.)

Symptoms are self-limiting and can last anything from 12 hours to 7 days. Patients are infectious until their symptoms have settled completely; hence the common advice to stay off work/school at least 24 hours after the last vomit.

Complications are uncommon: dehydration being the most important to look out for. Rarely seen now, it would have been a common sight 100 years ago. Here is a quote from a textbook written at this time to illustrate what we may hopefully never come across ourselves.

The general symptoms may be slight, but in severe examples the infant passes into a state of so-called ‘intoxication’. In this condition the child lies stuperous with sunken, half closed eyes, the arms are flexed and crossed on the chest in the so-called ‘boxer position’, the fontanelle is sunken, the skin inelastic and there is greatly diminished excretion of urine. In some cases the whole disturbance is extremely acute, and death may ensue within 12 hours.

(Conybeare 1946: 236)

Mortality is low in this country nowadays, probably as little as three or four infant deaths a year, but commoner elsewhere, and big efforts have been made to promote the use of oral rehydration therapy so that even the poorest or most illiterate know to use it.

As important is to know what not to use. Treatments such as loperamide (a mild opioid) and kaolin (literally clay powder), both used to slow down the bowel, or antibiotics are not effective or can worsen the outcome of viral gastroenteritis.

Nosocomial outbreaks of norovirus and rotavirus are common. In an average year, for example, 1500 confirmed norovirus outbreaks are reported from hospitals. This leads to ward and bay closures and the subsequent significant impact on the rest of the hospital, health care workers, and patients.

There is exciting news ahead with respect to outbreaks and viral gastroenteritis presentations: the introduction of the live attenuated oral rotavirus vaccine (Rotavac), which covers the five commonest serotypes circulating in the UK, which started in July 2013. This is a two-dose schedule given at 2 months and 3 months of age.

Until now, rotavirus has been responsible for up to 130 000 GP consultations annually with around 13 000 hospitalizations. In other countries that have introduced rotavirus vaccine, a 97% reduction in hospitalizations for rotavirus gastroenteritis has been noted. If a similar effect were achieved in the UK, it would bring down hospitalizations from 13 000 to 400 a year.
Further reading

References
Case 1.2

Food-borne gastroenteritis

Case example

‘Doctor. I have diarrhoea.’ This is Ekme Chikangwe (39) and she has a distinctive African accent. ‘I am very bad, doctor. Every day.’

‘Oh dear, I’m sorry to hear that,’ you say down the telephone. ‘How long for?’

‘For 5 days doctor. Every day.’

‘Any vomiting?’ you ask briskly, and go on to establish that she has no abdominal pain, has had no vomiting and that she is passing stools five to seven times a day, liquid, no blood, and without much improvement in the last few days, but that she is drinking and passing urine all right.

‘And where are you from originally?’ you ask.

‘Nigeria, doctor.’

‘Have you been there recently or any foreign travel?’

‘No. I have not been back for 2 years. Nowhere.’

‘And is anyone at home with you?’

‘Just myself doctor. And my son. But he is grown up and at work.’

‘He’s not got any diarrhoea?’

‘No doctor. He is fine. He didn’t eat any of the take-away.’

‘The take-away? Do you think you ate something funny?’

‘On Tuesday night I had chicken with African rice. On Wednesday I was, mm-mm ok, and then on Thursday early morning I woke up ill.’

‘So it could be food poisoning?’

‘Mm-mm.’

Because Mrs Chikangwe does not have abdominal pain and because she is coping well with fluids you do not bring her in for review but elect to advise over the telephone. The prolonged diarrhoea (over 5 days) and food connection triggers you to request a stool sample.

You advise fluids and suggest oral rehydration salts and explain about how to do the stool test. ‘If you put a sheet of plastic under the toilet seat and pass stool onto that, it’s a good way of getting a pure sample. The sample bottle has a spoon in the lid to help you put it in the bottle. Then put it into the bag and seal it up and hand straight into reception. I’ll label up the stool sample bottle and form now ready for you to collect.’

You write as you speak: food-borne gastroenteritis, take-away rice and chicken 7 days ago, 5 days diarrhoea and tick the boxes for m.c.s. and parasites. ‘That’s ready to pick up from now,’ you say. ‘If it gets worse; like if you are not able to drink, or if you get any tummy pain or any new symptoms, get in touch again. You should gradually start to improve over the next 4–5 days. So if you are not improving, again contact us. I will look out for your stool sample and if there is any problem I will telephone.’

You look out for the stool sample result for the next 1–2 weeks, but you don’t receive anything and you suspect that Mrs Chikangwe did not get round to doing it.
Microbiology

This case illustrates the usual presentation of food-borne gastroenteritis. The incubation is usually between 1 and 3 days: this is because only small numbers of pathogenic bacteria are ingested, and these need to reach the intestine and grow to sufficient numbers to make a patient ill.

In contrast, food poisoning, from pre-formed toxin in food, typically has a much shorter incubation (usually 2–8 hours), vomiting is the predominant symptom and the illness is short lived. This is because there is already enough toxin in the food to make a patient ill immediately.

There are many infective causes of food-borne gastroenteritis, from many typical food sources: these are summarized and compared in Table 1.2.1. The common causes are listed first, but it is important not to overlook the rarer, more serious, types.

Diagnosing the cause of food-borne gastroenteritis or of food poisoning usually starts with sending a faeces (or stool) sample to the laboratory. Aside from the obvious aesthetic issues, there are two practical problems with investigating faeces for pathogenic organisms. Firstly, faeces is full of bacteria, mostly harmless, mixed with bits of food, gut epithelial cells, etc. So looking for pathogens is a needle-in-a-haystack challenge. This is in contrast to, say, blood cultures or cerebral spinal fluid (CSF) examination, where you expect the sample to be sterile, so if you find any bacteria they are probably important. Secondly, there is a wide range of possible causes, and they all have different characteristics. It is a challenge to find a single catch-all method that will find them all. This means that a mixture of different techniques may be needed, adding to the time, trouble, and expense of faeces examination.

The basic set of pathogens usually looked for in laboratories in the UK include Salmonella (Fig. 1.2.1), Campylobacter, and Shigella. Many laboratories look also for Escherichia coli O157

<table>
<thead>
<tr>
<th>Organism</th>
<th>Typical source foods/mode of infection</th>
<th>Mechanism of action</th>
<th>Usual incubation</th>
<th>Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmonella</td>
<td>Eggs, meat of any type, unpasteurized dairy products</td>
<td>Direct infection of the gut</td>
<td>1–3 days</td>
<td>Diarrhoea, fever, vomiting</td>
</tr>
<tr>
<td>Campylobacter enteritis</td>
<td>Meat, especially chicken Unpasteurized dairy</td>
<td>Direct infection of the gut</td>
<td>2–5 days</td>
<td>Diarrhoea, fever, vomiting</td>
</tr>
<tr>
<td>Escherichia coli O157</td>
<td>Lives mainly in cattle— so infection can be acquired from meat, unpasteurized dairy, direct contact with cattle or manure, contaminated drinking water</td>
<td>Direct infection + local toxin production</td>
<td>1–3 days</td>
<td>Diarrhoea—severe, haemorrhagic. Toxin is absorbed and causes haemolysis and renal failure</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Any food can be contaminated during preparation— failure to refrigerate during storage can allow Staph to grow and produce toxin</td>
<td>Pre-formed toxin in food</td>
<td>&lt;1 day (frequently just a few hours)</td>
<td>Vomiting, fever, diarrhoea</td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td>Typically— reheated cooked rice. As with Staph, failure to refrigerate during storage allows organism to grow and make toxin</td>
<td>Pre-formed toxin in food</td>
<td>&lt;1 day</td>
<td>Vomiting, fever, diarrhoea</td>
</tr>
</tbody>
</table>
and Cryptosporidium. In the UK, laboratories are also obliged to look for Clostridium difficile in all patients over 65 years (see Case 1.5, Diarrhoea in hospital), and many laboratories have also introduced molecular tests for norovirus.

There are different laboratory approaches to finding all of these pathogens. Salmonella and Shigella both resemble other Gram-negative rods (‘Coliforms’, or Enterobacteriaceae) when grown on agar (Box 1.2.1). Of course, faeces will always contain coliforms such as E. coli, but Salmonella and Shigella have one important difference—unlike E. coli they do not ferment lactose. Therefore, laboratory media that contain lactose and a pH indicator are used to culture a small amount of faeces. Any lactose fermenters will cause a pH change and produce coloured colonies; uncoloured colonies are therefore possible Salmonella/Shigella and can be picked off to have further biochemical and serological tests.

Campylobacter does not grow in air, and so it was only discovered as a cause of gastroenteritis in the 1970s. It is microaerophilic—it likes a bit of oxygen (unlike anaerobes which cannot tolerate any) but too much oxygen will also inhibit it. To find this organism, agar plates containing antibiotics to suppress other bacteria, and charcoal to absorb molecules that are toxic to Campylobacter are used. The old-fashioned way to get a microaerophilic atmosphere was to seal the plates in a metal jar with a lit candle—the candle would consume the oxygen as it burned and

Box 1.2.1 Why are bacteria different shapes?

It is obvious that bacteria come in different shapes and sizes, but with limited options—round (cocci), long (rods), even longer filaments, and curved or spiral rods. The reasons for this variety are less obvious, and rarely considered in medical microbiology textbooks. Growing as a simple sphere is probably the simplest (in biochemical terms), but if an organism wishes to be motile, and swim through a liquid, it helps to be long—i.e. have a front end and a back end, minimizing drag. This is analogous to the greater efficiency of a bullet than a musket-ball. Thus very few cocci are motile, whereas almost all rods are. There is also some evidence that the curved shape of certain bacteria (such as cholera, which is comma shaped) or the spiral shape of certain other bacteria (such as the syphilis spirochete), aids motility through a viscous surface.
then go out, leaving just enough oxygen to allow the *Campylobacter* to grow. Nowadays, sophisticated catalysts are used to chemically reduce the O$_2$ content of the jars.

*E. coli* O157 is much rarer than the three main pathogens above—but it can cause very serious disease, sometimes in dramatic outbreaks, and sometimes with fatalities, so laboratories are encouraged to test for it despite its rarity. It looks just like any other *E. coli* on agar—but a useful difference is that it usually does not ferment sorbitol (a type of sugar), so sorbitol is added to the agar, along with a pH indicator, to differentiate it from other *E. coli* strains. Suspect isolates can then be tested for O157 antibodies, or for its unique toxin gene using PCR.

Other infectious agents such as *Cryptosporidium*, a parasite, are spread by contaminated drinking water (see Case 1.3, Traveller’s diarrhoea). *Cryptosporidium* does not grow on agar so the diagnostic approach is to stain and then look for it directly under the microscope. Viruses, such as norovirus, are a cause of both food-borne gastroenteritis and ‘ordinary’ gastroenteritis, identified by using automated PCR tests on faeces (see Case 1.1, Viral gastroenteritis).

Causes of food poisoning are more difficult to identify in the laboratory, and are more rarely looked for. Food poisoning with preformed toxin (e.g. *Staphylococcus aureus*, *Bacillus cereus*, or botulism) is particularly difficult to identify, as the amounts of toxin in the faeces may be negligible, and just growing the organisms does not prove they caused the illness. Examining the suspected food for the organism and/or toxin may be more helpful—but usually this is not available, and the diagnosis tends to rest on the clinical picture alone.

**Further reading**

Case 1.3

**Traveller’s diarrhoea**

**Case example**

Nicola Farar is a 24-year-old working as a fundraiser for a charity. She has blonde curly hair, which accentuates her pallor and gives an overall impression of paleness as she walks in.

‘I just flew back 2 days ago. I started to have diarrhoea on the plane and then it’s just got worse,’ she says wanly.

‘Oh dear. Where were you on holiday?’ you ask, thinking ‘traveller’s diarrhoea’ and wondering how exotic it was going to get.

‘North America for 3 weeks. It was great—it was just a holiday, not my charity work. In the middle week we went to Yosemite national park and went hiking, which was amazing! But I wonder if I caught it from the water there; we were drinking water from the lakes. We used chlorine tablets, but not for washing or washing up. I was ok but now I feel really nauseous and I’m passing,’ sotto voce; ‘loads of wind,’ normal voice again; ‘and diarrhoea 12 times a day.’

‘Any vomiting?’ She mutely shakes her head.

‘Any blood or mucus?’

‘No.’

‘Are you drinking enough? You look kind of pale.’

‘I feel dreadful. Dizzy when I stand up. I feel nauseous every time I drink. I tried to go into work yesterday but they sent me home. I guess I’m not drinking much.’

‘What about passing urine? Have you been this morning?’

‘Just a bit. Quite brown looking.’

‘It sounds like you’re not drinking enough. I know you don’t feel like it but it’s your job today just to drink water all day.’ She smiles. ‘Or Diarolyte you know?’ you continue, ‘Rehydration salts?’ She nods.

‘You need to aim for 2 litres of fluids at least today and you need to sip it all day long. Don’t worry about eating unless you feel like it. It’s the drinking that’s important. You need to pass urine of a normal colour at least three to four times a day.’

‘Ok.’

‘Because you’ve picked it up abroad I think we should send a stool sample straight away and that will check for *Giardia*, which can cause lots of wind as well as diarrhoea. And it will check for all the other things that can cause diarrhoea.’ You are thinking rotavirus, norovirus, and bacterial causes such as *E. coli*, *Campylobacter*, *Salmonella*, and *Shigella* (although she has no blood or mucus, she is quite unwell), as well as parasites: particularly *Giardia*, but also *Cryptosporidium* and *Entamoeba histolytica*.

‘If it’s *Giardia* then it’s easily cured with an antibiotic called metronidazole.’
Although you have already come to a conclusion, formulated a plan, and advised the patient, you do then check her blood pressure, temperature, pulse, capillary refill, and abdomen, all of which are unremarkable apart from cold hands.

She is passing stools too frequently though and does look quite peaky, so you advise her to ring back if she’s not coping with fluids or not improving, but also book her for a telephone review in 3 days time to make sure she is on the mend. You advise her not to go back to work until she is symptom free for 48 hours and eating and drinking normally again and also advise her on hand hygiene.

Her stool test is not yet back when you ring her 3 days later; however, to your relief, her diarrhoea is resolving (down to four times a day) and her appetite is returning, so you don’t intervene any further. Later that week you receive the stool result confirming a *Giardia* infection. You write to her to ask that she contact you for treatment.

**Microbiology**

Traveller’s diarrhoea is a catch-all term for diarrhoea caught abroad, usually linked to different hygiene standards in the country being visited. For this reason, general hygiene measures are advised to reduce the chance of catching it; including hand washing, eating freshly cooked hot food rather than cold or reheated food, avoiding salads, drinking hot drinks or bottled drinks and avoiding tap water or ice, and sticking to fruit and vegetables that can be peeled.

Prophylactic antibiotics are not advised but electrolyte solutions are a useful treatment to have in a first-aid kit. Loperamide, which slows down bowel movements, does not help with resolving the infection but can be useful on long bus journeys where there is no ready access to a toilet.

Because it is really a syndrome rather than a diagnosis, the range of causes of ‘traveller’s diarrhoea’ is wide, as mentioned already within the case. Viral causes include rotavirus and norovirus (discussed in Case 1.1, Viral gastroenteritis), bacterial causes include *E. coli* (the commonest), but also *Campylobacter*, *Salmonella*, and *Shigella* (discussed in Case 1.2, Food-borne gastroenteritis). The bacterial causes are more likely to cause severe symptoms such as blood and mucus in the stool and abdominal pain, previously known as *dysentery*, but this term seems to be rarely used these days. Protozoan causes include *Giardia* (the diagnosis here), *Cryptosporidium*, and *Entamoeba histolytica*.

There are over 30 000 protozoal species, of which only a few are pathogenic; many are part of our normal bowel flora. The term ‘protozoan’ is now regarded as a traditional classification term, but is still used in medicine. The term is used to describe single-celled animals (the word means ‘first animals’) and they have some important characteristics. Firstly, they can move, doing this either using cilia, flagellae (like *Giardia*), or pseudopods. Secondly, they can eat, feeding off other microorganisms such as bacteria and some fungi. They digest the food in little organelles called ‘vacuoles,’ consuming 100–1000 bacteria an hour. They range in size from 10 to 52 μm, which means they are bigger than bacteria (usually about 1 μm) and much easier to see and identify under the microscope.

There is a range of important protozoan pathogens. As well as the three discussed here, protozoans cause malaria (discussed in Case 14.2, Malaria), sleeping sickness, leishmaniasis, acanthamoeba keratitis, and *Trichomonas vaginalis*.

When protozoa are actively feeding or proliferating, they are known as *trophozoites*. However, they can also undergo a process called encystation and turn into cysts. Cysts are very durable and the organism can survive for long periods in this state before turning back into trophozoites again (*excystation*).
They are a very disparate group of organisms and analysis of their DNA has found that they are not necessarily related to each other at all and this traditional classification has had to be modified. Those organisms once described as protozoa are now classified under four clades including *excavata*, *amoeba*, *chromalveolata*, and *rhizaria*.

However, going back to the three protozoal species causing diarrhoea in humans: firstly, *Cryptosporidium*. This is an intracellular protozoan which causes self-limiting and mild but prolonged diarrhoea for which there is a very new treatment called nitazoxanide, an anti-parasitic treatment currently used in America but not yet licensed in the UK. The infection is mainly important in immunosuppressed patients such as those with HIV in which it can be very serious.

*Entamoeba histolytica* is interesting in that it can only be looked for microscopically on a ‘hot stool’. This is because there are so many sorts of benign entamoeba living in the bowel that it is impossible to tell one cyst from the next. Diagnosis, then, rests on identifying the more distinguishable trophozoites instead and these can only be seen moving around on a very fresh stool sample; any delay and the trophozoites simply shrivel up and become unidentifiable. This organism is also known for the very severe dysentery it can cause and also liver cysts (diagnosed using serology).

*Giardia lamblia*, our diagnosis here, is described as a flagellated enteric protozoon (Fig. 1.3.1). It was discovered by Lambl in 1859 and for a long time was considered a non-pathogenic parasite. However, interest increased in this organism during the First World War, when it started to be thought of as a cause of ‘trench diarrhoea’ having been found in the stools of numerous soldiers with prolonged diarrhoea.

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**Fig. 1.3.1** A scanning electron micrograph of a *Giardia lamblia* parasite.

At this time, it was thought to be spread mainly by flies landing on food, but is now known to be spread faecal–orally, principally by drinking infected water, as in this case. Interestingly, it can be resistant to chlorine, which may be why the chlorine tablet precautions taken by Nicola were not effective. As few as ten cysts need to be ingested to cause an infection. The incubation is about 1–2 weeks as exocystation takes place and the trophozoites migrate from the stomach to the intestine. This fits reasonably well with the time course in Nicola’s case. Not everyone ingesting *Giardia* cysts will have symptoms; a third of cases will have only a subclinical infection.

Nicola’s stool sample needs to be a liquid stool (laboratories sometimes do not process solid stools) and clearly labelled with her symptoms and a travel history. The protozoa cannot be cultured but due to their large size and distinctive morphology they can be identified on microscopy. Formalin is added to the sample to dissolve fat and kill any organisms before filtering. Some laboratories then centrifuge the sample to concentrate the parasites. A wet preparation is then made that is stained with iodine, which allows any trophozoites and cysts present to be seen using light microscopy.

The treatment for *Giardia* is oral metronidazole. Although Nicola’s symptoms appear to be resolving, it is important to treat to avoid the chance of prolonged diarrhoea, transmission, and rare complications such as liver abscesses.

**Further reading**

Case 1.4

**Duodenal ulcer**

**Case example**

Mrs Katerina Papoudoulou (74) sits in front of you, unassuming, polite, and respectful, still with a slight Cypriot accent, despite her many years in the UK.

‘I have tummy pain doctor. I think it must be my gallstones.’

‘Tell me a bit more. When did it start?’ you say.

‘One week? One week ago? After each time I eat I have tummy pain, bad pain. Here!’ She indicates dramatically under her right breast. ‘Then I have loose stools, dark coloured but now is fine, is fine’.

‘So you’ve got normal stools now?’ She nods. ‘Brown coloured? Not pale? Any black tarry stools? Any blood in the stools?’ A shake of the head for each of these.

At this point you fail to take a further pain history, although the patient has given you some of the information. You don’t know what sort of pain it is, whether it is worse at any time of day or if it gets better with medications.

You are thinking about gallstones. Gallstones, you know, can cause colic, an intermittent pain sometimes associated with eating. The pain is worse when a stone is passing. A gall bladder infection would cause a worsening pain, not a resolving one as here. Biliary obstruction by gallstones would cause jaundice with pale stools and dark urine as well as right upper quadrant pain, but Mrs Papoudoulou says she now has normal colour stools.

You ask if you may examine her and she agrees. She has difficulty getting herself on to the couch because of her short stature and plumpness, but she manages by first hitching her bottom up on one side, and then levering the rest of herself up with great concentration and determination.

While she is getting her breath back you take her basic observations. Her temperature is 36.7°C, her heart rate is 68 and her respiratory rate is 20 (after the climb). She is lying a little lopsidedly on the couch with her hands clasped across her tummy, lifting her head up to look at you. You ask her to lie nice and straight and rest her head back.

‘Can you put your arms like this?’ you demonstrate putting them straight by your sides. She quickly moves her arms into the right position.

‘Can I lift this up?’ you ask and when she nods you lift up her blouse and vest and help her shift down her skirt a little ‘So I can see your whole tummy.’

Her abdomen looks normal, her movements quite free; not limited by pain. ‘Where does it hurt again?’ you ask. She points to her right side and then pops her arms back into place.

As you palpate her abdomen you watch her face. ‘Is this all right? And this?’ To examine her right upper quadrant you press, gently at first, and then more firmly. You get her to breathe in and then as she breathes out you press firmly on the right side and move up an inch at each exhalation trying to feel the liver edge. Because she is overweight you use both hands to press, and when you reach the right costal margin you really press firmly under her rib cage. But her right upper quadrant
area and epigastric area are both non-tender. There is no hepatosplenomegaly and no masses that you can feel.

‘And are you eating again normally?’

‘A bit less doctor but better, better’.

“Well it all feels very normal to me,’ you say positively, helping her to sit up and then slip gingerly off the couch. You then draw the curtain around her to allow her to get dressed.

When she is sitting again you say, ‘Quite often with gallstones they don’t cause any problems and are best left alone. But if they are starting to cause pain then I can refer you to a surgeon to discuss the idea of an operation if you wish’.

She nods seriously.

‘But first of all let’s get you an ultrasound scan of your tummy to see if you really do have any stones. Because I can’t tell just by feeling your tummy, but an ultrasound will be able to look at any stones directly.’

She agrees to the ultrasound, pleased.

You write out the form and explain how and where to get the scan, that she should come and see you about a week after she has had the scan, to give the report time to come through, and that if the pain gets worse or changes or should she get any new symptoms she should come back and see you. She agrees to all of this and you say goodbye and move on to the next patient.

Luckily for you, Mrs Papoudoulou manages to get an ultrasound quite quickly, within 3 weeks (you hadn’t asked for an urgent one). As you had planned, she comes in exactly a week later.

As she is coming up the stairs you flick into your own notes and read:

Presentation: Abd pain. History: 1 week. After meals. Episodes of dark stools, not smelly, then fine, no blood. Examination; soft abd, no masses, no hepatomegaly, no ruq pain. Comment; discussed, review if worse. For u/s to check gallstones.

When you read your own notes coupled with the ultrasound report, you kick yourself for your omissions. The ultrasound report reads: some thickening to the duodenal wall but is otherwise normal. No gallstones.

Mrs Papoudoulou is so clearly describing a duodenal ulcer pain with an episode of melaena that you feel quite hot with anxiety.

She greets you all smiles and asks after the ultrasound result. ‘Yes, I have it here. But how are you?’ you say.

‘Oh not too bad, not too bad,’ she says. ‘I’m feeling quite tired for the last few weeks. I had two more of those DARK stools,’ she adds conspiratorially. ‘But they are ok again.’

You ask anxiously after her weight and appetite but these are both fine.

‘Well your ultrasound is fine. No gallstones,’ you say.

‘Good, good,’ she says nodding and smiling.

‘But it does show something in your intestine. I think you might have a sore patch or an ulcer in your intestine that’s making the pain and making your stools go dark’.

‘Oh. Oh all right,’ she nods.

‘So I think we need to get you another test. The telescope test where they look right into your stomach using a long tube. It’s called an endoscopy. Are you free in the next 2 weeks?’
'Yes,’ she says.
‘That’s great. The appointment should be quite quick, within two weeks. And while we are waiting to hear about the appointment, I’ll get you to have a blood test to check for anaemia.’

Mrs Papoudoulou is as prompt as before. Her haemoglobin comes back within a few days as 9.1 with an MCV of 68.6 (iron-deficient anaemia). You are just as prompt and a fax goes off to the 2-week rule gastroenterology clinic that day. Within a week she has had an endoscopy of her upper gastrointestinal. When the report comes through, you are on the lookout for it and read:

Pyloric oedema, ulcer duodenum 10 mm deep CLO +ve. To start omeprazole 20 mg bd and H. pylori eradication therapy. A&E if further melena/dizzy/unwell. Repeat endoscopy and FBC 6 weeks and clinic review outpatients 8 weeks.

When she is reviewed by the outpatient clinic, her repeat endoscopy is clear and her symptoms have resolved. She is discharged from the clinic. You repeat the FBC as requested and have the satisfaction of seeing it gradually improve on iron (prescribed by yourself) until it reaches 11.7 6 months later.

Microbiology

Patients with illness suggesting gastric or duodenal ulcers have been described in antiquity, and in the 1500s ulcers were first observed at autopsy. Through the nineteenth and most of the twentieth century it was assumed that the main cause was damage to the intestinal mucosa, perhaps due to foods, alcohol, or other irritants. Therefore, the main treatments consisted of dietary modification, antacids, or various types of surgery to remove ulcerated tissue.

Then in the early 1980s, two Australian physicians, Warren and Marshall, isolated spiral bacteria in the gastric mucosa, and claimed that these bacteria could cause ulcer disease. There was initially much scepticism and resistance to this idea, and Marshall famously carried out an experiment on himself, ingesting a culture of Helicobacter pylori (mixed in chicken soup) and developing bloating, halitosis, and vomiting a few days later. Endoscopy confirmed both the gastritis and the presence of the bacteria, and antibiotic treatment cured the gastritis and got rid of the bacteria.

Increasing acceptance of this hypothesis followed, as well as a worldwide series of clinical trials. These provided further evidence of both the role of H. pylori in gastric and duodenal ulcers, and the benefit of eradicating them with antibiotics. Warren and Marshall were awarded the Nobel Prize for Medicine in 2005.

H. pylori is a small (0.5 × 3 μm) helix-shaped (hence the name) flagellate Gram-negative organism. It is strongly urease-positive, and is microaerophilic (grows best in the presence of a lower concentration of oxygen than is found in air). It is found exclusively in humans, its normal habitat being the mucus lining of the stomach. Its spiral shape and flagellae make it highly motile and allow it to burrow into the mucus, where it is protected from the toxic gastric acid. H. pylori’s high production of urease enzyme also helps protect it from acidity, by converting urea to (alkaline) ammonia, and increasing the pH in its immediate local environment.

Despite the association of H. pylori with peptic ulcer disease, the fact that the infection is almost universal in developing countries means the association of H. pylori with disease is not straightforward (Box 1.4.1).

Transmission is not well understood but recent research in the USA has established that H. pylori is spread within families following exposure to an infected person who also has gastroenteritis, particularly if that person is vomiting.
Many colonized patients remain asymptomatic, but some patients can develop a range of upper GI illnesses. Syndromes with a strong statistical link with *H. pylori* include chronic gastritis, gastric ulceration (except where associated with NSAIDs), duodenal ulceration, gastric carcinoma, and gastric lymphoma. Carriage of *H. pylori* seems to be actually protective against some diseases—namely oesophageal reflux and carcinoma. The reasons why patients can get such different responses to infection with the same organism are not fully understood. This may be partly due to differences in strain virulence—cagA+ strains are more associated with duodenal ulceration and gastric carcinoma, for example—but there are probably other complex factors also.

*H. pylori* infection is diagnosed by biopsy during endoscopy as in this case. The biopsies can either be cultured or examined for the presence of spiral organisms by histology, or, as is more usual, by the rapid urease test. In this test, biopsies are incubated in a vial containing urea and phenol red, which is a pH indicator. If there are urease-positive organisms present, the urea will be split (sometimes within minutes, maybe up to a few hours), and the medium will change from yellow to red, indicating that *H. pylori* is present. This test is sometimes called the CLO test, from *Campylobacter*-like-organism, an old name for *Helicobacter* and it is the test that Mrs Papoudoulou has had reported.

The presence of urease can also be measured without an endoscopy, using the urea breath test. But the standard recommended test in primary care is to check the faeces for *H. pylori* antigens; this is both the most reliable test and the cheapest.

The treatment of epigastric pain or duodenal ulcers with the presence of *H. pylori* is with a combination of proton pump inhibitors, for example omeprazole, and two antibiotics (usually two of amoxicillin, clarithromycin, and metronidazole).

It is worth noting that this case highlights a major error on the part of the doctor. It is an example of ‘anchoring’; the doctor has latched on to the original idea of the patient and fails to
widen the differential diagnosis and is one of a group of common errors that all doctors are prone to (see Further reading).

**Further reading**


Case 1.5

Diarrhoea in hospital

Case example

As you walk onto the ward you are hit by the smell—it reminds you of a farmyard, or of visiting the zoo as a child. You have come to see a patient with a new diagnosis of *Clostridium difficile* infection, but the smell suggests there may be more than one case. Sure enough, when you greet the ward sister, she looks worried and says, ‘I thought we’d be seeing you lot today! I was just going to phone the infection control nurses, but a microbiologist will do.’ She explains there have been three new cases of diarrhoea overnight, in addition to the one case you already know about. The three new cases are all in the same six-bed bay; the first patient had also been in the same bay but has been moved to a single room.

Mrs Mundy, the 82-year-old female patient whom you have come to see, is too drowsy to answer your questions. She has known dementia and was admitted from a nursing home about 3 weeks ago with an illness diagnosed as ‘?UTI/LRTI?’ In other words, either pneumonia, or urinary sepsis, or possibly both. She was on antibiotics from admission until 4 days ago, initially oral co-amoxiclav plus clarithromycin for 5 days. At that stage her urine culture grew *Pseudomonas* with raised white cells, so she was switched to oral ciprofloxacin.

The ward sister tells you that the diarrhoea began 3 days ago, gradually becoming more severe. She has been passing stool almost every hour overnight, but the diarrhoea has seemed to ease in the last few hours. Nonetheless, she is now hypotensive and extremely weak; she has been started on intravenous fluids, and her medical team are discussing transfer to the high-dependency unit. She was started on oral metronidazole empirically yesterday, when the stool sample was sent, but has only managed to take one dose and is now too ill to swallow.

You track down Mrs Mundy’s medical team, and suggest that, since she is unable to take oral medications, she should be given intravenous metronidazole. They should also consider placing a nasogastric tube, to allow her to have oral vancomycin. She is at risk of paralytic ileus and toxic megacolon as a result of the infection, and may need a surgical opinion because of the risk of gut perforation.

You then discuss with the ward sister the three other cases. *C. difficile* is obviously the most likely cause, but it is important to consider other possibilities; norovirus in particular often causes hospital outbreaks. You request stool samples from all the patients with diarrhoea to be tested for *C. difficile* and norovirus, as well as the ‘usual suspects’ (*Salmonella, Shigella, Campylobacter*, etc.). Other important non-infectious causes of loose stools are also worth considering, including laxatives, and patients on nasogastric feed.

You advise that the new cases should be nursed with full barrier precautions—i.e. staff should wear gloves and plastic aprons, hands should be washed after every patient contact, patients should be either moved to a single room, or kept in the same bay, which should be closed to further admissions. The patients need to be carefully reviewed and if necessary empirical treatment for *C. difficile* started. Their medications should be checked, and unnecessary antibiotics stopped (this may not be possible, of course, if the patients still have active serious infections).
The next day you find that samples have been received from only two of the three new cases. You also find repeat samples from Mrs Mundy (which have not been processed). Both processed samples are reported, ‘GDH positive, CDT toxin positive. Consistent with C. difficile disease’. The norovirus tests are all negative.

Mrs Mundy is still critically ill, and her team is in discussion with the family regarding what level of escalation is appropriate. The other patients have continuing diarrhoea, but there are no further cases.

**Microbiology**

Even before antibiotics were widely used in humans, it was realized during early experiments with penicillin in the 1940s that guinea pigs sometimes developed ‘typhilitis’—although the cause was unknown. In the 1950s and 1960s, it was realized that patients on antibiotics often developed diarrhoea that was sometimes mild, but could develop into a severe form known as pseudomembranous colitis (PMC). It was initially thought that *Staphylococcus aureus* was the cause, and so patients were treated with oral vancomycin, and this sometimes worked. In the late 1970s, researchers recognized that the stool from patients with PMC caused colitis in hamsters, as well as cytotoxicity in cell cultures—and the same effects could be produced with *C. difficile* grown from faeces—but not with *S. aureus*.

*C. difficile*, 8 by 0.5 μm in size (Fig. 1.5.1) is actually very widespread in the environment—mainly in soil—but it has several attributes that help it cause antibiotic-associated diarrhoea. It forms hardy spores that can survive for months or years (including in dust and dirt in hospitals), and is easily spread between patients. It is resistant to many antibiotics, including the penicillins and cephalosporins, and ciprofloxacin—so it can survive and thrive in the gut when most other bacteria have been wiped out during antibiotic treatment. Many strains produce cytotoxins: in particular the two main types, Toxin A and Toxin B. These toxins damage the gut epithelial cells, leading to inflammation and diarrhoea. Some strains are hyper producers of toxin, associated with more severe disease and a high mortality in elderly patients.

*C. difficile* diarrhoea can be associated with most antibiotics. Clindamycin was regarded initially as the main culprit, but in the last decade many cases have been linked to either cephalosporins or ciprofloxacin.

**Fig. 1.5.1** A scanning electron micrograph of the expanding edge of a colony of *Clostridium difficile* on an agar plate. Both cells and spores are visible.

It is interesting to note that the organism produces a cresol-like compound. This does not help it cause disease, but it does give the faeces (and colonies on agar) a distinctive odour resembling animal manure.

The organism can be grown from faeces, but this is slow (taking several days) and needs specialized media in anaerobic conditions. Finding *C. difficile* does not prove it is the cause of the diarrhoea, because it might not be a toxin producer, or even if it is, detection in the stool might reflect carriage of the organism rather than disease (2–5% of people carry *C. difficile*). A more reliable approach is to detect toxin in the stool—this is usually done by an enzyme immunoassay.

A limited range of antibiotics can be used for treatment. Metronidazole is the usual choice—as an anaerobe, *C. difficile* is sensitive, and significant resistance has not been detected (yet). Vancomycin can be given orally for more severe or persistent disease—it has the advantage of not being absorbed systemically when given this way, so all its action is focused in the gut. A new antibiotic, fidaxomicin, has recently been licensed for *C. difficile* treatment that is as effective as vancomycin, but appears to be better at preventing relapsing infections. It is much more expensive than the older agents.

Since the disease results from a reduction in normal gut bacteria, there have been many attempts at replacing the flora in some way. Trials with live yoghurt, or *Saccharomyces* (brewer’s yeast) have been inconclusive, but a more drastic method—donor faeces to replace damaged gut flora—has been very successful in a small number of trials. There are operational and aesthetic concerns in carrying out this treatment, and it tends to be tried only when all other measures have failed.

With regard to infection control, enforcing barrier nursing precautions can be challenging, especially in a busy overcrowded ward with not enough single rooms and pressure to keep admitting patients. Varying mixtures of persuasion, coercion, and education may be necessary.

A further, even more interesting, challenge with *C. difficile* is to try to prevent outbreaks in the first place. As well as being an increasing issue in British hospitals, *C. difficile* has been identified as a ‘never’ event in American hospitals. That is, it is iatrogenic and it should never occur. In fact American insurance companies began to refuse to pay for inpatient *C. difficile* care. The costs were thrust on to the hospitals themselves and so the hospitals rapidly got to grips with reducing *C. difficile* rates. They did this by ensuring that antibiotics were only used where absolutely necessary and for as short a time as necessary. This has given rise to a whole new area of expertise, ‘antimicrobial stewardship’, the art (or science) of persuading doctors to use antibiotics with restraint and caution.

**Further reading**

Kuehn BM. CDC: Hospital antibiotic use promotes resistance, checklist can improve practices. *JAMA* 2014; 311:1485

Case example

Ricardo Launceston is 29 and has irritable bowel syndrome (IBS). At least that’s what you think. You have seen him on a number of occasions with longstanding intermittent tummy pains and so have your colleagues. The NICE guidelines for IBS have been carefully followed by you. He has a number of classic symptoms, including bloating, alternating diarrhoea, and constipation, and his bloods (including inflammatory markers, a coeliac antibody screen, and haemoglobin) are all normal. You have tried advising more fibre, less fibre, antispasmodics, and peppermint oil (this last helped a bit). He is very pleasant, although of an anxious disposition, and tries the things you suggest. You greet him cheerfully and ask how you can help.

He explains he has come in for an antibiotic called Yodoxin. ‘I’ve been diagnosed with Blastocystis hominis.’

You sit there waiting for information to come in to your brain, to click on to the words blastocystis and Yodoxin, but nothing happens. Your mind is a sort of more or less empty speech bubble with, ‘Amoeba’, floating across.

You really have no idea what he is talking about. You look up Yodoxin and find it doesn’t even exist in the BNF.

Ricardo explains. ‘You see, after I’d been to see you last time I was talking to my friend who also has similar symptoms and she recommended her kinesiologist. And she was really nice and we talked through all my symptoms, and she said that quite often IBS is due to an imbalance of the right bacteria in the intestine. And she recommended a stool test with ’GastroSense Diagnostics’ to check my balance. Like they count the number of each bacteria in the sample to see what’s going on’.

Absolutely fascinated, you beg for a copy of the results and promise to look into it for him. He leaves the report for you at the surgery later that day. You read it with great attention.

Some of it is on familiar territory; for example:

- Campylobacter negative
- E. coli shiga-like toxin negative
- Giardia lamblia negative
- Entamoeba histolytica negative
- Cryptosporidium negative
- Mycology negative

Some of the report at least names familiar bacteria:

- Lactobacillus species 1+
- E. coli 4+
- Bifidobacterium 1+
The rest is entirely unfamiliar and it reminds you just how many bacteria there are in the human body and how few are actually checked for, usually just a few of the common pathogens.

According to the report Ricardo also has some ‘additional bacteria’:

| Streptococcus agalactiae gp B 3+ (potential pathogen) |
| Citrobacter braakii 4+ (potential pathogen). ciprofloxacin; S, tetracycline; S. |

The report is also sprinkled with advice such as,

Lactobacilli and bifidobacteria are important for GI function as they are involved with vitamin synthesis, natural antibiotic production, immune defence, digestion, detoxification of pro-carcinogens, and a host of other activities.

Apparently Ricardo’s levels of friendly bacteria, including the above-mentioned Lactobacillus and Bifidobacterium, are a bit low. You wonder what the treatment for this might be.

At the end there is a photo of the offending microbe Blastocystis hominis. Nearby is the advice, ‘Blastocystis hominis is considered by most authorities to be a pathogen.’ You look it up and find out it is a single celled protozoan parasite similar to algae.

When you ring up the microbiology consultant to ask his advice about Yodoxin antibiotics for B. hominis he is absolutely scoffing. ‘If I had a pound for every completely pointless microorganism those labs identify I’d be a millionaire,’ he says.

He advises you B. hominis is a harmless bowel flora and advises not to treat, but that if the patient has his heart set on treatment, to use the most benign antibiotic available for as short a course as possible, and he suggests oral metronidazole.

**Microbiology**

Alternative or Complementary Medicine is a fact of modern life, however much rational doctors and scientists may decry it, and as this case shows it even pervades the world of microbiology. As also shown by this case, it is very difficult to know where to draw the line between ‘proper’ alternative medicine and mere quackery (of course, some would maintain there is no difference, but that is a separate debate).

It is true that there are some more unorthodox providers of microbiology laboratory services, and sometimes microbiologists, and GPs, are faced with the challenge of interpreting their results, often presented by an enthusiastic or desperate patient who does not want to be let down by being told that the tests they have paid for are probably meaningless—or at least, won’t help treat their illnesses.

The scientific reality underlying these tests is that there really are ‘friendly’ bacteria, and we are covered inside and out with them—it is sobering to reflect that 90% of the cells in or on us are actually bacteria, not human cells. The bulk of these bacteria live in the gut—and the further down you go, the more there are; faeces has about $10^{11}$ bacteria per gram.

The make-up of these bacteria varies with age, with diet, possibly with the genetics of the human host, and definitely with the use of antibiotics.

Not only are there a huge number of bacteria, there are also hundreds of species. Broadly, the lower gut flora is dominated by anaerobes such as Bacteroides, Clostridia, and Bifidobacteria, and...
smaller numbers of other aerobic bacteria such as *E. coli* and other ‘Coliforms’ (see Case 13.2, Complex intra-abdominal infection) as well as *Enterococci* and some *Lactobacilli*. These bacteria aren’t just passengers—they interact with their host in many ways, most of them beneficial. They may help break down some food molecules into more digestible compounds, they play a role in the development of the immune system, by challenging it with a wide range of foreign antigens, and some bacteria synthesize vitamin K—although with a normal diet the amount made by bacteria may not be essential. Most importantly, gut bacteria provide colonization resistance—they protect the gut from being colonized by other more harmful microorganisms. The most dramatic example of this effect is when patients acquire *Clostridium difficile* infection and diarrhoea after their own bacteria have been reduced by antibiotics (see Case 1.5, Diarrhoea in hospital).

There may be some situations where the normal gut bacteria are not so friendly. Bacteroides can produce carcinogens, and there is some evidence to suggest that inflammatory bowel disease may be associated with alterations in bowel flora. However, the clinical impact of these alterations for patients with Crohn’s or ulcerative colitis is unclear at present. There is some evidence of benefit from probiotic therapy (replacing some of the supposedly beneficial bacteria such as bifidobacteria) in patients with ulcerative colitis, but no real evidence for Crohn’s. The situation with irritable bowel disease is even less clear—some studies do suggest that probiotics may also be beneficial, and given that they are harmless, there is probably no harm in trying them. One practical issue is that probiotics are regarded as foods, and are not regulated in the same way as medicines, so the dosing is highly uncertain, especially if the patient takes live yoghurt rather than capsules of bacteria.

The other issue raised by this case is that of ‘unorthodox’ microbiological investigations and how to make sense of them. Most developed countries have a rigorous accreditation system for ensuring diagnostic laboratories meet minimum standards, and it would be surprising if a nationally accredited laboratory issued a report like this. Merely counting the bacteria in a stool sample may provide an impressive list for a patient, but it is clinically unhelpful and possibly misleading—finding more or fewer different bacteria may be interesting, but does not really explain the patient’s diagnosis, or provide a reliable guide to treatment. Furthermore, since many of the gut bacteria do not grow easily or at all in the laboratory, culture-based techniques are not really reliable—to get an accurate estimate of what is there in what proportion, you would need much more sophisticated molecular techniques, using a combination of DNA extraction, PCR (probably targeted at the Bacterial 16S ribosomal gene), and sequencing. It is highly unlikely that the laboratory that processed Ricardo’s sample did this.

Lastly, there is also the issue of the *Blastocystis* parasite. This is a controversial area—scientific opinion is split on its importance: there is no doubt that some people can carry it without symptoms, yet it is also found in some people with diarrhoea and in some with irritable bowel disease. It would be important to explain this to the patient, and also to explain that treatment is not generally advised, and if it is treated there is no guarantee that the symptoms would improve. The antibiotic mentioned in this case, *Yodoxin®*, is the trade name of an anti-parasitic agent unavailable in the UK, but other more widely available treatments can be tried, including metronidazole.

**Further reading**

Hepatitis A

Case example

The telephone rings and you pick up the phone. ‘Hello, this is the on-call health protection consultant speaking. How can I help?’ you say.

‘I’ve got Dr Lewin from the lab on the phone,’ says Joyce, the secretary who works for the Health Protection Team. ‘He says he needs to tell you about a boy with hepatitis A. I’ll put him through.’ You wait for the call to come through.

‘Hello, Elliott here at the lab, I’ve got something for you that might cause a bit of work. It’s hepatitis A in a 6 year old, Sanjeev Pathak. He was seen at the hospital with jaundice after returning from Pakistan. He went there with his parents and three siblings for 4 weeks during the school holidays. It’s the first time the children have been back to Pakistan since they were born. They all came back 2 weeks ago, the boy became unwell 10 days ago, initially with some diarrhoea and then jaundice 4 days later. He was seen by his GP who sent him up to the paediatrician. The paediatrician took blood for LFTs and screened him for hepatitis, and the hepatitis A IgM result was positive.’ He pauses. ‘They told me they thought it might be hepatitis A when they first saw him. I asked them if they had notified it at the time and they said that they were waiting for the results first. I’ll let you sort that out with them. I was initially concerned about infection control in the hospital but in fact they never admitted him. I’ve spoken to the GP, and he tells me that some of the siblings might be unwell. Clearly this needs public health to get involved now, especially given that the other kids went back to school a fortnight ago; chances are that they were infectious then. What’s more, one of them is at nursery.’

This might take a bit of sorting out. ‘Do you know what the parents do? They’re not food handlers are they?’ you ask. You can hear Dr Lewin smiling when he says, ‘No, luckily. I asked the GP about that. They’re both accountants. They were born in Pakistan and came over here to go to university. The likelihood is that they would have been infected with hepatitis A as children growing up in Pakistan anyway and would have been immune since then, but the children having been born here, with such a low incidence of hepatitis A in this country, are susceptible. They should have been immunized before they went. We can test the parents for immunity if you want and test the other children to see if they really have hepatitis A. I might be wrong and it might be that only one has hepatitis A and the others have something else, then you wouldn’t have to immunize any.’

You know the virus is spread faecal–orally with an incubation period of about 4 weeks, so from the dates it is very likely that infection was acquired on holiday. The 6 year old would have been infectious 1 week before the onset of jaundice and 1 week after, but usually any spread outside of the household is rare except with infants or food handlers. ‘Do you know the ages of the other children, Elliott?’ you ask.

‘18 months and the others are twin girls of 13.’ You note down the contact details of the case and thank Elliot absently at the same time wishing the paediatricians had notified you earlier as this would have given you more leeway. The first priority is the child at the nursery because if he has it, then all the contacts will need vaccination. The twins and the 6 year old are less of a problem; they need to be off school until they are no longer infectious but other interventions are probably not needed.
**Microbiology**

Although hepatitis A virus (HAV) has specifically been diagnosed in Sanjeev, the presentation of jaundice can be caused by a number of viruses. Hepatitis A, B, C, D, and E are all in the differential but it is important to note that these viruses are not in the slightest bit related to each other, despite their names. Hepatitis A and E are both spread faecal–orally, and both are RNA viruses. However, hepatitis A is of the Picornavirus family, whereas hepatitis E is of the Hepevirus family. Hepatitis B and C are both blood-borne viruses, but hepatitis B is a DNA virus and hepatitis C an RNA virus. Hepatitis D or delta virus, is a defective RNA virus whose replication requires co-infection with hepatitis B (together they increase the likelihood of fulminant hepatitis).

Other viruses that can sometimes cause jaundice particularly include EBV and CMV, but rarely HSV, measles, rubella, and coxsackie viruses. Lastly there are some arboviruses (this simply means spread by arthropods; no other relation between the viruses is necessarily implied) that cause jaundice, such as dengue virus and yellow fever virus.

To go back to hepatitis A, the subject in this case, it was first identified in 1973 by electron microscopy of stool. It is a 27-nm icosahedral non-enveloped +ve linear ss RNA virus (Fig. 1.7.1). Because of its faecal–oral spread it tends to be found in countries without fully developed hygiene systems, and here it is a childhood disease with $>90\%$ seroconversion rate, the great majority subclinical. Sanjeev’s parents, both brought up in Pakistan, are very likely to be immune. In more developed countries, outbreaks can occur from returned travellers, as here, or in groups where hygiene practices are likely to be reduced such as nurseries or homeless shelters and is also associated with men who have sex with men (MSM). Occasional outbreaks occur associated with food handling, hence the concerns of the public health consultant in this case.

Diagnosis of acute infection is by anti-HAV IgM using immunosorbent assays (see Box 1.7.1). These become positive early and remain present for 3–6 months, after which anti-HAV IgG is identifiable lifelong.

Early diagnosis using immunoassays and early involvement of the public health consultant are both essential in the event of hepatitis A being diagnosed. This is because post-exposure prophylaxis really needs to be given within 8 days for the vaccine to be effective, or 14 days if using immunoglobulin. There is still time in this case (2 days), but the consultant will have to move swiftly to test the other three children and then identify un-immunized contacts.

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**Fig. 1.7.1** An electron micrograph of hepatitis A virus.

Household contacts of Sanjeev (e.g. his twin sisters) if uninfected will need an accelerated course of the inactivated hepatitis A vaccine. If they do have the infection then they should be kept off school, but school contacts do not need hepatitis A prophylaxis. If Sanjeev’s younger brother has the infection, then his nursery contacts will need to be immunized, or if less than 12 months old they will need a dose of hepatitis A immunoglobulin.

The treatment of Sanjeev is not the public health consultant’s concern but the paediatric team’s, who should be advising rest and avoidance of paracetamol (and in adults, alcohol) and increased hand hygiene. There is no active treatment.

Further reading


Case example

The next patient is Carme Berta Port (29). You suspect from the first part of her name that she is not British. You check her current notes and see a recall letter for blood results. You also see a public health notification letter. You bring up her results and immediately notice her hepatitis B results. As usual for hepatitis B results, they are complicated and need interpreting. The result reads:

\[ \text{HBsAg +ve, anti-HBc +ve, anti-Hc IgM –ve, anti-HBs –ve.} \]

This is not good news. You ask her to come in, introduce yourself and ask how you can help. As you expect, she explains she has had a letter from the surgery asking her to come in and discuss her blood results. You are curious about her accent combined with her name, but she is expectantly waiting for your reply.

At this point you know you are about to convey some quite bad news. First you check what she knows already.

‘Did anyone tell you your results on the phone?’
‘No, no. Just a letter, to come in.’
‘Ok. It’s the hepatitis result that we are worried about, the liver result. Did you know you were having a liver check?’ This is the warning shot.
She nods. ‘Yes, because of tummy pain’, she points. ‘They check’.
‘Ok, I see. Well it’s the hepatitis B result. It’s positive’. You pause, watching her face.
She doesn’t react much. ‘Hepatitis B?’
‘Yes. It’s a virus, a liver virus called hepatitis B.’
‘And I have it?’
‘Yes.’
She purses her lips and doesn’t quite shrug.
You say, ‘It’s quite important. Most people get better from it but some people don’t. It can cause liver scarring and liver problems in the future.’
She nods slowly.
‘You can catch it from blood, or sometimes from sex. Did you ever have a tattoo? Or a piercing? Or IV drugs?’
‘Piercing yes. No tattoo, no IV drugs’.
‘And do you have a partner?’
‘Yes, my husband, 8 years.’
‘And when was your last partner?’
‘No other partners.’
‘Any children?’
‘Yes, one daughter, 8 years old’. Then unexpectedly, ‘I think my mother has this hepatitis B. And my sister. And my nephew and my niece.’
‘Oh.’ You say pausing. ‘Where are you from originally?’ She tells you.
‘Does your mother have any treatment?’
‘No’.
‘Maybe you caught it from back home. We need to check your daughter and your partner. And I will refer you. There are some good treatments available now so when you see the specialist they will advise you.’

You arrange to repeat the blood test to check for hepatitis B viral load and an ultrasound before referring her. You also ask to see her partner for testing and give her a blood form for her daughter. You don’t have a good feeling about what their results will be.

The results come back as follows:

**Mr Port:** HBsAg −ve, anti-HBc −ve, anti-HBs +ve
**Francesca Port:** HBsAg −ve, anti-HBc −ve, anti-HBs −ve

You are surprised and pleased at these results and arrange to immunize Francesca. It turns out Carme’s partner is from the UK and works in the health service. Her viral load comes back as >2000 IU/mL confirming your plan to refer her.

**Microbiology**

Hepatitis B is a 20–40-nm icosahedral DNA virus of the Hepadnaviridae family (Fig. 1.8.1), initially identified in 1965.

Although it can present acutely with malaise, raised temperature, and jaundice (or very rarely (0.1%) with fulminant hepatitis; liver failure, and death within 10 days), the great majority of doctor encounters with hepatitis B (and hepatitis C) come as a result of screening, following subclinical infection.

![Figure 1.8.1 An electron micrograph of hepatitis B virus (the central circular particles). See also the elongated Dane particles, which are excess virus capsular material and non-infectious. Reproduced from Centers for Disease Control and Prevention, Public Health Image Library (PHIL), Image ID#5631, available from http://phil.cdc.gov/phil/details.asp?pid=5631](image-url)
Because the virus is transmitted via blood, sexual intercourse, or vertical transmission from mother to child, then screening is directed at certain groups, for example in patients using IV drugs, sex workers, MSM, and people who have HIV. Antenatal screening for hepatitis B was introduced in 1997. In Carme’s case it is being checked for as part of a differential for a non-specific symptom: abdominal pain.

The test results for hepatitis B need interpreting, and it is often advisable to discuss them in detail with the on-call virology team (Table 1.8.1).

The most important marker is the HBsAg, which stands for Hepatitis B surface antigen. This is a protein found on the surface of the virus and detected at high levels within 6 weeks of an acute infection. Its presence indicates that the patient is infectious. The patient usually then produces antibodies to the surface antigen: anti-HBs, which clear the infection.

Anti-HBc stands for antibodies to hepatitis B core protein. Following infection these core antibodies are present for life.

Interestingly, following hepatitis B immunization, anti-HBc is −ve. This is because the vaccine is made using recombinant DNA technology in yeast cells, producing a subunit vaccine, and this consists only of HBsAg and not the whole virus.

The final test mentioned in the Table 1.8.1 is anti-HBc IgM: the immunoglobulin M denoting an acute infection.

The concern with hepatitis B is the 10% of acute and subclinical cases that progress to chronic infection, as it has done with Carme. If this is the case then HBsAg persists for over 6 months and no anti-HBs is detected. Chronic hepatitis B can lead to cirrhosis in 15–40% and hepatocellular cancer in 2%.

Therefore, following a positive result for HBsAg, the patient will need further tests to confirm the infection, and to check liver function. The doctor in this case requests hepatitis B DNA as well as repeat serology and an ultrasound; it would also be advisable to check for hepatitis C, hepatitis A, hepatitis D, HIV, and further less specific tests such as LFT, FBC, and PT if these have not already been done, with a view to referral to the hepatologist.

If Carme has reduced liver function, then peginterferon alfa 2a is the first-line treatment; close monitoring of hepatitis B virus load is necessary to check drug effectiveness (the response rate is approximately 40%). The second-line treatment includes antivirals such as entecavir and tenofovir disoproxil (see NICE guidance). If Carme’s viral load was <2000 IU/mL and her liver healthy, she would be monitored 6–12 monthly by liver function tests and ultrasound assessment.

Hepatitis B has a very low prevalence in the UK (0.14%) based on antenatal screening, or about 600–800 cases per year. High-risk countries have a prevalence of >8%, medium 2–8%, and low <2%. In areas of high prevalence such as sub-Saharan Africa and Asia, infection is predominantly acquired in childhood, either vertically during childbirth or horizontally from other children. In low-prevalence countries infection is usually acquired in adulthood through needle sharing.
or sexual transmission, typical in the UK. In areas of intermediate prevalence the pattern of infection is mixed, but also includes nosocomial infection, for example through infected blood products.

It seems likely from Carme’s low-risk lifestyle that she acquired hepatitis B vertically from her mother. That Carme is in fact a recent immigrant from a European country makes the history painful hearing, a health system failure. It is known that approximately 95% of neonates will catch hepatitis B if their mother is infected: 10% during pregnancy and the rest through contact with blood and fluids during the birth. However, post-exposure prophylactic immunization is highly effective, and the great majority of neonatal infections can be prevented by early immunization and hepatitis B immunoglobulin, as long as the infection is known about.

The chances were high that Carme’s daughter and husband had acquired the infection, and so it is good news indeed to find that on analysis of their results, the husband has in fact been previously immunized, and her daughter is hepatitis B susceptible and therefore eligible for immunization.

**Further reading**

Interpretation of Hepatitis B Serologic Test Results. [www.cdc.gov/hepatitis](http://www.cdc.gov/hepatitis)

Hepatitis B (chronic) CG165 NICE Guidance June 2013.
Case 1.9

Hepatitis C

Case example

Richard Jameson has come in because he thinks he has bowel cancer. He is 29. He is a wiry, nervous looking person, or perhaps not so much nervou but tense, out of his comfort zone.

Although you think it pretty unlikely Richard has cancer, you take a careful history of his abdominal pain, bowel habit, and weight and appetite; all fine. You also opportunistically pick up some information to be part of a general health check, including his alcohol intake (10 beers a night) and smoking (25 a day). Encouraged by this affirmative answer you ask if he takes any other drugs.

‘Marijuana two times a week.’

‘Any IV drugs?’

‘No.’

‘Tattoos? Piercings?’ He does have a large black tattoo on one arm and so you suggest testing for hepatitis C and he nods, not that interested.

You take his height (181 cm), and weight (74 kg), (BMI 22.59), and examine his abdomen. He has a 2-cm liver edge and is tender in the epigastric area.

This could all be related to his alcohol intake or it could be gastro-oesophageal reflux disease. You ask more about himself and you find that he lives with his daughter, an 11 year old. He doesn’t work; his daughter quite often stays at the grandparents, especially when Richard is binge drinking with his friends. The mother is not around. Sometimes he does casual labour at the garage.

You decide to arrange for a series of blood tests including, hepatitis B, C, HIV, syphilis, iron, FBC, U&E, glucose and cholesterol, and stool Helicobacter pylori, and suggest a review to go through the tests.

Because of his poor eye contact and health worries you then ask him about his mood, which is ok and have a further long discussion about his alcohol intake as related to this epigastric pain. He seems keen to cut down and you talk about the positive impact this will have on his daughter as well as himself. He suggests he may be able to cut down by avoiding the houses of friends he knows drink a lot of alcohol. You are enthusiastic and agree this is a good plan. You suggest involving the drug and alcohol worker, who you know is very good, but Richard has met him before and says he prefers to go independently for the present. Or rather he says, ‘Naaaah. I’ll do it myself’.

Your next interaction with Richard Jameson is less than a week later when his blood results return.

HepA IgM not detected
HBsAG not detected
HCV Ab detected
HCV Ag not detected
Richard has a positive hepatitis C antibody result but further tests are needed. You note his other results are normal.

You ask the receptionist to request him to come in to discuss his blood results. He doesn’t come. You ask again.

When Richard has failed to show for three appointments you telephone him. It takes several tries on different days to get through to him. Eventually, one day, he answers. You get the impression he is driving along in his car, but he says he is the passenger.

‘Richard, it’s the Doctor from the surgery. Do you remember we met? I need to see you to talk about your blood results.’

It was never your intention to tell him over the phone about such a serious and life-changing diagnosis, but Richard drives you to it. He says he is unable to come in, he is living out of the city with his girlfriend and can’t get lifts, is busy, etc.

When you tell him there is a long silence.

You explain that it’s not for sure, the test has to be repeated so that it can be checked for actual HCV (hepatitis C RNA assay) to see if he has cleared the infection or not.

‘But how could I have caught it?’ he asks.

‘Usually through blood contact like using IV drugs or tattoos or piercing. It can happen through sex but very rarely.’

‘Those bastards in prison’, he says, ‘They should have said.’

‘What do you mean?’ you ask.

‘IV drugs.’

‘Do you still use IV drugs?’ you ask.

‘Yes, but only with my girlfriend and we have our own needles.’ Revealing that he is in two other high-risk categories not previously mentioned, despite direct questioning.

Then he remembers his daughter and after that his concern is only for her. Could his daughter have caught it? Should she have a blood test? Should he tell her that he is hepatitis C positive? You agree that he’ll wait for the second check before telling her and ask him to come and see you, and in the meantime to think of any needle sharing contacts.

You see him 3 days later. Your notes read:

Richard’s hepatitis C viral load comes back negative and his ultrasound is normal.

You again inform him of the (this time good) news over the telephone. In the future when he has his yearly hepatitis C check he will need the hepatitis C RNA assay each time to see if he has any new infection, as his hepatitis C serology will always be positive. You say you look forward
to discussing any questions he has when you see him with his daughter for her blood tests. Later, you discuss a social services referral for Richard’s daughter with the rest of your team. Richard and his daughter do not attend the health check. You don’t see him again.

Microbiology

Hepatitis C belongs to a completely different family from hepatitis B and is in fact a +ve ss RNA virus of the Flavivirus family, 30 nm in diameter. It was initially part of a group of viruses known as non-A non-B hepatitis before it was named in 1989. Hepatitis C has emerged as an important infection because of the high rate of infections that progress to chronic infection, not 10% like hepatitis B, but 85%. Having a diagnosis of chronic hepatitis C infection gives a 5–25% chance of progressing to fibrosis and cancer after 10–20 years.

Because the great majority of infections are in fact subclinical (75%) the drive has been to increase screening. Earlier diagnosis allows for transmission avoidance and earlier treatment once effective treatment became available around 2001. The infection is spread via blood; at-risk groups include IV drug users, and people with tattoos and piercings rather than sexual or vertical transmission as in hepatitis B. The prevalence worldwide is 0.5–2%, lower than hepatitis B.

Blood tests involve serology as Richard has had, which will detect HCV antibody within 6 weeks of infection. Following a positive antibody test RT–PCR is done, as here, to look for viral RNA, the presence of which would indicate an ongoing infection. If Richard’s viral load was positive he would then have been referred to a hepatologist with a view to assessment of liver function either by liver biopsy or more recently by elastography/fibroscan: a special ultrasound that measures the elasticity of the liver, giving a surrogate measure of cirrhosis and scarring.

The treatments are similar to hepatitis B; peginterferon alfa but combined with an antiviral ribavirin. Different hepatitis C genotypes have different response rates and so a patient’s viral load needs careful monitoring. This is a rapidly evolving field with new, very effective but expensive antivirals coming through.

Richard has had hepatitis C and cleared it, but his lifestyle is still high risk for picking up other hepatitis C genotypes and other blood-borne diseases such as HIV and hepatitis B.

Further reading


Hepatitis B and C; ways to promote and offer testing to people at increased risk of infection (PH43). NICE Guidance Dec 2012.
Case example

‘It’s an itchy bottom,’ Lucy’s mum says. Lucy Godfrey (4), a bit shy, hides her head in mum’s arm. Her younger brother sits unconcernedly kicking his heels in his little chair.

‘Oh dear’ you say. ‘Can you tell me a bit more?’

‘Well it’s been going on for a bit’ says her mother Lisa Godfrey. ‘She’s had it for about 2 months, before that she was fine. She’s been itchy during the day but for the last few nights she’s been waking up screaming and I’ve even had to get her up and wash her bottom before she settles. It’s been quite awful actually.’

‘Is there anything to see?’ you ask. Her mum shakes her head. ‘Just a bit pink around the, you know, back bottom.’

‘Any pets at home?’ you ask. ‘Or does Lucy suck her thumb or bite her nails at all?’

‘No pets. But she does suck her fingers at night. She has done since she was small.’ Lucy holds up the first two fingers of her left hand and demonstrates unnecessarily.

‘Because I’m thinking of worms,’ you say.

‘Oh,’ says the mum.

‘Well, there are other things that cause an itchy bottom. In fact, it’s so common it’s got a special name: pruritis ani. Hygiene is the first to mention because sometimes children this age have difficulty wiping their bottoms properly and any poo left behind is a great irritant to the skin and can cause itching.’ You glance at the mum who nods slowly and says ‘Lucy’s not too bad for that.’

You continue, ‘OK. Another common cause is a thrush infection, which can be easily treated with Canesten. There are other conditions related to eczema like something called lichen sclerosis but that’s more common in adults, not really children. But the reason I’m thinking of worms rather than hygiene or eczema is because worms come out of the back passage at night to lay their eggs and that’s when the bottom is itchiest. It fits best with your description of what has been happening with Lucy.’

Lisa Godfrey is nodding. ‘Ok. I had worms once as a child. It was disgusting but I grew up on a farm.’

‘Because Lucy sucks her fingers it means if she does have a threadworm infection and scratches her bottom she can get the eggs under her nails and then re-ingest them. That’s how people get an infestation of worms. Apparently a lot of us have a threadworm infection quite often but if we don’t re-ingest the eggs it’s just one worm and it eventually dies. It’s very easily treated,’ you add.

‘But you have to treat the whole family, all at the same time. It’s a one-off treatment; a liquid that you swallow.’

‘Can we test for it?’ Lucy’s mum asks.

‘We can send off a stool sample, and the classic test is to go in at night with a torch and check the child’s bottom to see if there are any worms there.’ Mrs Godfrey grimaces. ‘Or other people put
Sellotape over the bottom to capture the worm or eggs that way . . . Or we could just swab and then treat. Can I have a look at Lucy’s bottom?’

Lucy is not keen but her mum convinces her to stand on her lap and lowers her pants. Her younger brother wanders around the room ignoring the commotion. You put on some gloves and pause. This examination position is not ideal. ‘Let’s get you over here on my special bed,’ you suggest to Lucy. Her mum carries Lucy over objecting strenuously. ‘If you just lie on your side and tuck your legs up,’ you request. Lucy curls up her legs firmly together. You keep mum at Lucy’s head end cuddling her, and say ‘Now I’m just going to look at your bottom. I’ll be very quick.’

Lucy’s anus is a normal colour, it is clean, there is no surrounding redness or lesions, and no obvious threadworm. Threadworm eggs are too small to see except under a microscope. You take a plain swab (no gel in the base) and moisten it with saline from a saline pod. ‘I’m just going to take the swab,’ you say to Mrs Godfrey and then to Lucy, ‘I’m just going to take a swab with this special cotton wool on a stick. You might feel a tickly feeling on your bottom,’ and quickly but gently wipe the swab around and over the anus to pick up any possible eggs present before Lucy has time to wriggle too much.

‘All done,’ you say. ‘That looks fine, no thrush, nice and clean . . . What shall we do then?’ you ask the mum who is pulling up Lucy’s things. Lucy jumps down and joins her brother.

‘Can you give enough treatment for the four of us?’ asks Mrs Godfrey.

You nod and also print off a leaflet and circle the paragraphs about nail cleaning, washing in the morning, and also on hand washing before food preparation and cleaning the bedding. ‘Here’s the prescription. It’s for a liquid called mebendazole. Get everyone to take it tonight and then again in a week’s time.’

Lisa Godfrey is reading the leaflet as you speak and looks up and nods, folding it to look at properly later. ‘Ok, thank you. If we have any other problems we’ll get back in touch.’

One week later you receive confirmation from the laboratory that threadworm ova were present on the swab.

**Microbiology**

There are three sorts of parasitic worms that affect humans: firstly Trematodes (or flukes); these are leaf-shaped organisms with an oral and a ventral sucker. Schistosomes are an example (discussed in Case 5.3, Schistosomiasis).

Secondly, Cestodes (or tapeworms); these are flat organisms that have a head with suckers or hooks (or both), a short neck, and a segmented tail. Tapeworms are often caught from undercooked meat or fish.

Lastly, Nematodes (or roundworms); these are elongated, cylindrical, non-segmented organisms, with a smooth cuticle and a body cavity containing a digestive tract and a reproductive tract. Threadworms are an example (the diagnosis from our pruritis ani case) along with many other species.

There are over 60 pathogenic nematodes that infect humans and these are a major and important cause of ill health in developing countries. Some species of nematodes live within the intestine, including threadworm (Enterobius vermicularis), but also hookworm (Ancylostoma duodenale), whipworm (Trichuris trichiura), and the cause of strongyloidiasis (Strongyloides stercoralis). Other species live within the body tissue, including the guinea worm (Dracunculus medinensis) and the cause of river blindness (Onchocerca volvulus).
However, nematodes are less common in developed countries and of these examples *Enterobius vermicularis*—our threadworm—is the most common.

Threadworms look like pieces of white cotton thread, about 10 mm long and 0.5 mm wide. They particularly affect children. It is a human species only and is not caught from farm animals or pets (although other worms can be, such as dog and cat hookworms).

The adult female threadworm lays massive numbers of eggs (10,000). She comes out at night and embeds the eggs in mucus to lay them around the anus. It is thought that the mucus is an irritant and is what causes the anal itchiness. The eggs are microscopic and therefore cannot be seen by the naked eye, if they are not re-ingested then the person is not re-infected and the worm, which has a short lifespan, simply dies after about 6 weeks.

Some sources say an infestation can be treated by purely hygienic methods (important, for example, in pregnancy when mebendazole cannot be prescribed). These methods include wearing underpants at night to avoid scratching, washing the perineum in the morning to remove eggs, and cleaning under the nails each morning. Also, washing the hands before preparing food or eating, cleaning bedding, clothes and towels, and damp dusting the house to remove any eggs. The eggs can survive for up to 2 weeks in the environment.

This hygiene advice has been passed to Lucy Godfrey’s mother, reinforced by a leaflet. The doctor has examined Lucy carefully (sexual abuse must always be considered in these cases), mainly to exclude other causes of pruritus ani, not because the doctor expected to find evidence of a threadworm infection. A carefully taken anal swab, moistened in saline first, is the best way to gather ova, as is done in this case. It should be transported dry to the laboratory (i.e. not put into transport medium) and then moistened again and rolled onto a microscope slide.

Faecal samples are mentioned in the case and these are used to check for other helminth infections (for threadworms the sensitivity is low: less than 5%). At least three samples are needed over 7–10 days, as excretion of helminths or ova can be intermittent. At the laboratory the stool is then mixed with formalin to kill any harmful organisms. Ethyl acetate is mixed in to dissolve any fat and debris and the sample is then centrifuged to concentrate the parasites at the bottom of the tube. The sample is then examined on a slide using light microscopy, checking for any small helminths and for ova. The species can often be identified by the characteristic shape of the ova of each species (Fig. 1.10.1).

Fig. 1.10.1 A photomicrograph of threadworm eggs (50 μm long) in a smear.

This method of diagnosing using microscopy has been in place for decades and the hygiene advice has also been well known for many years. Not so the treatment, which around the time of the Second World War was to, ‘Wash out the rectum with 1/40 infusion of quassia every other day for a fortnight.’ Nowadays the mebendazole treatment (used since 1971) kills the nematodes by preventing them from absorbing the sugar that they need for survival. Mebendazole does not kill the ova, which is why the hygiene measures and the second treatment 2 weeks later are necessary.

Further reading

Chapter 2

Cardiovascular

Case 2.1 Infective endocarditis 43
Case example

You are the cardiology registrar on duty one sunny August morning. You are called by an A&E doctor who has just assessed a 72-year-old man, Mr Walter Merrick. He thinks he may have endocarditis. The A&E doctor is clearly anxious and the patient sounds unwell, so you hurry to get down to the department as soon as the cardiology unit can spare you.

When you arrive they give you his A&E notes—his full notes are not available—and the GP referral letter. You read the letter first. Mr Merrick has apparently been ill for several weeks, with symptoms of tiredness and loss of appetite. However, his wife telephoned the GP this morning saying he had been a lot worse in the last 2 days, with weakness and breathlessness, and now was barely able to get out of bed. In view of the new breathlessness and reduced mobility, the GP had therefore arranged for him to be taken directly to A&E by ambulance. Mr Merrick is normally otherwise well, on ramipril for hypertension but no other cardiac history, and is a non-smoker.

The A&E nurses have documented his observations; his temperature is 38.7°C, blood pressure 108/65, pulse 90/min, respiratory rate 24/min, and $O_2$ saturation is not too bad at 95%. They have done an ECG (normal) and also taken bloods. His Hb is 110 g/L, WBC $14 \times 10^9$/L, and CRP 243 mg/L. You are still awaiting the clotting, LFT, and U&E results. A urine dip shows blood ++ and has been sent for culture. He has an IV cannula and fluids written up but blood cultures have not been taken yet. Most relevant to you, as a cardiology registrar, is the fact that the A&E doctor has noted an apparently new murmur and also petechiae.

Mr Merrick is thin and pale; he seems asleep and does not move much when you walk in. You say hello to the anxious woman sitting by the bed and introduce yourself, and check that she is indeed his wife. You then speak to the patient. ‘Hello Mr Merrick—can you hear me?’ He opens his eyes and makes brief eye contact, and mumbles something but then turns away and closes his eyes again. His appearance and reduced mental alertness, coupled with his decompensating vital signs and abnormal bloods, make you feel that there is a strong likelihood of not just septicaemia but of endocarditis, as the A&E doctor has surmised.

Because Mr Merrick is not up to giving a history, you speak to his wife and she confirms the details in the GPs letter. She mentions his symptoms began, ‘After the dentist’, and when you ask further, she says that he had had a bad tooth removed about 2 months previously, and his problems started a few weeks later. She thinks he might have lost some weight, and says she had noticed he appeared to have a fever sometimes overnight. You examine Mr Merrick and confirm the examination findings of the A&E doctor; a dozen non-blanching purple blotches on his arms, upper chest, and legs, from a few millimetres to a centimetre across and a loud systolic heart murmur loudest over the left heart border, and a softer diastolic murmur. You look at his nails for clubbing and splinter haemorrhages, his palms for Janeway lesions and Osler’s nodes, and finally you examine his abdomen for splenomegaly. You don’t find any other specific signs of endocarditis though and his chest is also clear.
‘What do you think is wrong, doctor?’ says Mrs Merrick. ‘They said something about his heart?’

‘Well, Mr Merrick does look very unwell and we need to look after him carefully and start treatment . . . try treatment . . . these infections can be very serious. We don’t know for sure if it is a heart infection, but he definitely has a serious infection of some sort. I will be coming and talking with you again as we find out more, so you know what is going on as things happen. Right now I’m going to take another blood sample, and then we can give Mr Merrick his first dose of antibiotics and fix up for him to have a scan of his heart.’

You collect the equipment for taking blood cultures quickly and come back into the room pushing it all on a steel topped trolley that you have just cleaned with alcohol. You want to obtain as clean a sample as possible for the blood cultures. You wipe Mr Merrick’s arm with an alcohol wipe and then some iodine solution. Mrs Merrick holds his hand to help keep him still after you have put on the tourniquet.

You unwrap the syringe and needles and take the lids off the culture bottles and put them all on the clean covered surface of the trolley before washing your hands and putting on gloves. You sit down and arrange yourself so you are comfortable and feel for a vein on Mr Merrick’s arm before inserting the needle. You are pleased to see a flashback in the needle and hold it absolutely still as you pull back on the syringe to take the 15 mL of blood. It comes very slowly and you feel a film of sweat build up on your face as you keep your position. Finally you unsnap the tourniquet and withdraw the needle, asking Mrs Merrick to press on the area with cotton wool for 5 minutes. You change the needle on the syringe, clean the septums of the bottles, and inject 7 mL through the septum of the first culture bottle, change needles again and then 7 mL into the second bottle. You dispose of the needles in the sharps box before labelling the bottles. The bottles are taken straight to the laboratory.

You now call the Microbiology doctor on duty to discuss the antibiotics. After discussing the case, the time course and the dental visit Mr Merrick had, she advises you to give flucloxacillin and gentamicin for ‘acute’ endocarditis, which will cover Staphylococcus aureus as well as the more common streps. You write up the IV antibiotics immediately, as well as fluids and a form for an urgent transthoracic echo and then arrange admission to the cardiology ward. Mr Merrick’s echo, which comes back later that day, shows a 1.5-cm mobile mass on the posterior leaflet of the mitral valve, strongly suggestive of endocarditis. You return to Mrs Merrick and have a difficult conversation about her husband’s condition, although she had already understood from your serious demeanour earlier how ill her husband was.

The next morning both sets of blood cultures are positive, with Gram-positive cocci in chains, resembling streptococci and the following day, the blood culture isolates have been identified as a Streptococcus sanguinis, one of the viridans streptococci, an alpha haemolytic strep sensitive to penicillin, vancomycin and gentamicin. The microbiologist advises modifying the treatment to penicillin and gentamicin, and says that Mr Merrick will need antibiotics for at least 4 weeks, although the gentamicin can be stopped after 2 weeks.

Mr Merrick improves over the next few days, but his course in hospital is not straightforward. He develops a cannula infection during his second week, and then develops a hospital-acquired pneumonia and is transferred to ICU. He finally struggles though his course of 4 weeks of antibiotics for endocarditis, and your colleagues are happy the infection is cleared. He remains very weak and debilitated and he and his wife are warned to plan for a prolonged convalescence.
Infective endocarditis can be due to a wide range of organisms. Most cases are due to viridans streptococci, (usually 1 μm in diameter) (Fig. 2.1.1) as seen with Mr Merrick (see Case 9.2, Tonsillitis, for a discussion of streptococcal classification). These bacteria normally inhabit the mouth and can gain entry to the bloodstream during dental procedures. Other causes of endocarditis include a variety of staphylococci, including S. aureus (which normally inhabits the skin or nostrils) and a significant minority are due to enterococci (which normally inhabit the gut) or are due to yeasts.

Endocarditis was first described by a number of different physicians and pathologists in the nineteenth century. When post-mortem examinations of the valve vegetations were done, they were found to be composed of platelets, fibrin, and bacteria—in other words, they were an infected clot stuck to the heart valve. The early physicians realized the sobering fact that patients never recovered. Until the discovery of antibiotics there was no effective cure. They also noted that the presentation could be extremely varied, often with vague non-specific features, as here. When taken with the relative rarity of the disease, this meant (and still means) that diagnosis was often confused and delayed.

Most of the bacteria that cause endocarditis arise either from the mouth, intravenous lines, or injecting drug use. However, a bacteraemia alone is not enough—most bacteria won’t stick to normal endocardium even if they do get into the bloodstream. It is thought that, in damaged or abnormal valves, turbulent blood flow leads to trauma to the valve endothelium and this leads to adherence of platelets and fibrin. Bacteria can then adhere to these sterile clots, and once there they attract more platelets and fibrin. As the bacteria thrive on the clot they spill into the bloodstream, causing bacteraemia, and growth of the vegetation. The bacteria within the vegetation are protected from the immune system, and this is the key reason why the infection is uniformly fatal without antibiotics.

It is essential to have a properly taken blood culture, as is done here, to get an accurate diagnosis. The blood cultures bottles that the cardiology registrar has obtained contain a liquid with plenty
of nutrients to allow bacteria to grow. The earliest blood culture media were basically a clear ‘meat consommé’—nowadays, the composition is more complex. They may contain agents such as resin or charcoal to bind or neutralize any toxic chemicals in the blood and additives such as PABA and thymidine to neutralize any residual antibiotics and aid the growth of any bacteria in the sample. Modern blood culture bottles also contain an indicator of bacterial growth—usually a pH indicator, and this responds to a rise in acidity with a change in colour. Such a rise in acidity is usually due to CO₂ production by growing bacteria. There are specialized bottles that are designed for small-volume paediatric samples, or for the growth of anaerobic organisms or mycobacteria. For adult patients, it is usual to inoculate two bottles—one for aerobic organisms, and one for anaerobes.

Once received in the laboratory, the bottles are incubated at about 37°C for up to 5 days, although most positives occur in the first 48 hours. Previously, the bottles would be left in a hot room and examined several times a day to see if they had gone cloudy, indicating bacterial growth; this was obviously a very laborious process. Nowadays, blood cultures are incubated in automated continuous monitoring systems. These are machines that contain a warming block with numerous cells to hold each bottle and a light sensor at the base of each cell to monitor the colour of the pH indicator. If a significant change in colour is detected at any stage, the machine flags the bottle as positive. This system allows the bottles to be continuously agitated which helps the bacteria to grow and reduces the ‘time to positivity,’ thus aiding earlier diagnosis and refinement of IV antimicrobial therapy.

If the sample is flagged as positive, a few drops are put onto a microscope slide and a Gram stain performed. This allows the clinician to be immediately informed of the broad group of bacteria likely to be infecting the patient, which may be useful in guiding therapy. The sample is then cultured further, on agar, to allow the exact species to be identified, and the testing of antibiotic sensitivities.

Which types of agar it will be cultured on will depend in part on the provisional Gram stain result, and in part on the preferences of the individual laboratory. Most blood cultures will be inoculated onto blood agar aerobically, and either blood agar anaerobically or a specialist anaerobic agar. If fastidious bacteria are suspected, then chocolate agar may be used. Once the agar plates have been incubated, the sensitivity results are read and reported and the organisms further examined by various methods, including biochemical and serological. Usually overnight culture is necessary to get enough growth, meaning another day before the results are available, as happens with Mr Merrick, but sometimes same-day cultures (if begun early in the morning) show enough growth.

Interpreting the initial Gram stain, and the later culture results, is based mainly on the microbiologist’s experience of what is common and the typical sources of different organisms. Another important point to establish is whether the culture is actually significant, or reflects a contaminated sample. Up to 50% of positive blood cultures may be contaminants, so it is important to identify contaminants, rather than waste time, and endanger patients, by needlessly changing antibiotics or ordering further investigations.

Further reading

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Case 3.1

Community-acquired pneumonia

Case example

It is 9 p.m. exactly half way through your 24-hour shift as duty doctor for an isolated rural hospital. You have been called to the emergency department to assess a patient with a possible stroke and a patient from a nursing home with urinary retention. When you get there however, the stroke patient has not yet arrived. The patient with urinary retention is already in a bed, but there is another patient, a breathless patient, just being wheeled in.

No one had mentioned this breathless lady and you glance at her almost as an aside, but then think, ‘She looks sick, like really ill’. She is sitting up holding the edges of her wheelchair with both hands. She looks sallow, thin, and elderly. She is breathing fast. The nurse transfers her into a bed and does her basic observations. She directs you to sort this patient out first while she sorts out the paperwork for the urinary retention lady.

The name of the breathless patient is Mrs Jean Granger; she is 84. You check her basic observations first. Her oxygen saturations are 89% on 4 L of oxygen, her pulse 92, blood pressure 122/68, and you personally count her respiratory rate, which is 24 per minute. She is using accessory muscles to breathe.

You take her history, which she gives in short sentences. She is normally well apart from high blood pressure. She lives on her own and does her own shopping and regularly visits her husband in the nursing home. She’s never smoked. She has had pneumonia before and tends to leave it too late to seek help. This time she’s had a cough for 2 days. All of yesterday she stayed in bed and today she wasn’t drinking much. She’s passed urine once.

Her responses to your questions make sense and she drinks water when you pass it to her, although she seems tired and keeps dropping off. You listen to her chest. She has a clear right side and crackles on the left in the middle zone. The picture you hear is loud and clear like a crisp photograph and you even draw a little diagram of it in your notes.

You know she is very sick, her observations confirm she is very sick, and she has a crystal clear left-sided pneumonia. You write a plan in the notes: admit, IV access, IV antibiotics (co-amoxiclav plus erythromycin), IV fluids, oxygen 4–6 L, regular observations, fluid balance, ECG, blood cultures, sputum, and MSU. You also plan a CXR and further bloods (FBC, U&E, etc.) in the morning. There is no on-site pathology although you do have access to radiology, but the radiographer has to be called up and you know what the CXR will show anyway.

Afterwards you regret your omissions here.

So far you have done nothing to actually help this lady. So now you hustle to collect blood cultures and bloods and gain IV access so that the first antibiotics can be given as soon as possible. You write up a drug chart and fluid chart.

Even though you badger the nurse it takes another half an hour before she gets round to giving the antibiotics. The history and examination took 15 minutes and the IV access and bloods another 15 minutes.
You have temporarily finished with Mrs Granger and move on to the next patient who is being wheeled in fitting, and later on you assess the nursing home patient.

Time has passed fast, it is now 11.30 p.m. The emergency department is now empty, Mrs Granger has been transferred to the ward and the other two patients transferred to the city hospital. Through the emergency department ambulance entrance the night air comes in. You have a moment to zone out.

It comes to you that Mrs Granger is still your responsibility and is pretty ill and is definitely worth a review now, 3 hours after your initial assessment. You walk up the quiet and dim corridor to the ward and find her in a room right opposite the nurse’s desk.

The room is lit only with a lamp and all is peaceful on the ward except Mrs Granger, who is no better. Her respiratory rate is still fast and her oxygen saturations still 89% but now she is on 6 L of oxygen. Although she has passed some urine her chest has more crackles now and on both bases. You slow down the fluids and go home to bed. In the night you dream about her and in you dream you think, ‘. . . Well she’s on the antibiotics . . . now we have to give her time to get better . . . ’

At 4 a.m. your mobile rings. Mrs Granger is worse.

When you go to the hospital you find her respiratory rate is 32 and her accessory muscles are really working. Her urine output has slowed right down and is less than 20 mL per hour.

You telephone the base hospital for advice and they suggest you use CPAP (continuous positive airways pressure). Luckily, one of the nurses knows how to use it and the mask is strapped on her face and the machine starts to take over the work of breathing. Although visibly fearful at first, it is clear that Mrs Granger is being helped as her oxygen saturations improve.

You arrange her transfer to the base hospital and call up the paramedics. They only got back from their last transfer at 2.30 a.m. They limp in bleary eyed.

The patient is transferred on CPAP. Later you ring the ICU registrar who informs you that Mrs Granger was monitored on CPAP until 2 p.m. and then because her oxygen saturations were dropping again she was transferred to ICU and intubated. The ICU registrar is sympathetic with your concerns that you delayed her transfer. ‘One day I guess I will be in a rural hospital having to make that call. The thing is, there is a process, and this patient has had it. I mean oxygen and fluids then CPAP then ICU. We intubated her because the pre-fitness level that you documented was high.’

A few days later, Mrs Granger’s blood culture result comes back into your tray, confirming *Streptococcus pneumoniae*.

Mrs Granger survives. Three weeks later you find her back at your own hospital in her room, sitting dressed and in an easy chair on the point of discharge. ‘I want to thank you for looking after me,’ she says, smiling.

**Microbiology**

In many cases of community-acquired pneumonia the cause is in fact never confirmed. When a range of advanced and costly diagnostic tests are used, about one-third of cases are found to be due to *S. pneumoniae*, the focus of the case here. A further one-third are due to a mixture of other organisms, and the remaining third are still of unknown cause. The non-pneumococcal causes include bacteria such as *Mycoplasma pneumoniae*, *Haemophilus influenzae*, *Legionella pneumophila*, Enterobacteriaceae (commonly termed Coliforms—see Case 13.2, Complex
intra-abdominal infection), *Chlamydia pneumoniae*, and *Chlamydia psittaci* (famous as the cause of psittacosis—pneumonia acquired from parrots and other psittacine birds). Viral causes include influenza and adenovirus (see Case 3.8, Viral pneumonia).

The doctor in this case is concerned when thinking about the case afterwards that usual procedures weren’t followed, for example urea, arterial blood gases (ABG), and CXR. If the CURB-65 score (score 1 point each of Confusion, Urea >7 mmol/L, Respiratory rate >30/min, systolic blood pressure <90 mmHg, or diastolic blood pressure <60 mmHg, age >65) had been followed, Mrs Granger would have scored 2, implying she may need hospital management. However, it is clear already to the doctor that the patient is very sick and hospital management is not in question. It is possible though that ABG or a CXR may have provided evidence facilitating an earlier discussion with the consultant at the base hospital and allowing earlier transfer.

The doctor in this case has been thorough regarding blood cultures, sputum, and urine, and is clearly trying to get a door to needle time for the IV antibiotics for less than an hour as per the sepsis guidelines (see Case 13.1, Sepsis (UTI)).

A sputum sample is less useful than it sounds though, being frequently contaminated with mouth flora and providing a useful result less than 50% of the time (see Case 3.3, COPD exacerbation for further discussion).

An alternative to the sputum sample is to detect pneumococcal proteins in the patient’s urine. This is a laboratory-based test. The principle of the urinary antigen test is that in a pneumococcal infection some of the bacteria die, and fragments of the organism enter the bloodstream and are filtered into the urine. These are detected by a membrane-bound-enzyme immunoassay, which uses similar technology to over-the-counter pregnancy tests: a drop of urine and a drop of reagent containing antibodies to the pneumococcus are added to a special card that contains a membrane. Any pneumococcal antigens in the urine will bind to the antibodies in the reagent and diffuse through the membrane. The membrane contains an area of further antibodies that capture the antigen–antibody complexes, forming a visible line. This test is quick, and not affected by recent antibiotic use, and is therefore better than culture for making a diagnosis. The disadvantage is that no bacteria are cultured, so no sensitivity testing can be performed. Note that it is also not validated in children, as they may give a positive result even if they are merely colonized by the *Pneumococcus*.

Mrs Granger’s blood culture is positive for *S. pneumoniae*; patients with *S. pneumoniae* will have positive blood cultures about 25% of the time. Blood cultures can be cultured using blood agar for *S. pneumoniae*. This organism forms short chains or pairs of leaf-shaped Gram-positive cocci, 1 µm in size (Fig. 3.1.1). The old name for this organism was diplococcus, because of the frequent finding of pairs of bacteria. It is typically either alpha-haemolytic (green/brown discoulouration of blood agar) or non-haemolytic (no colour change).

The colonies that form have an unusual appearance. They grow into a dome shape, as with other bacteria, but then collapse in the middle resulting in a flattened colony. This is described in textbooks as a draughtsman colony, from the resemblance to the board game pieces. The colonies collapse in the middle because the bacteria contain an autolytic protein that activates when the organism reaches a stationary growth phase. This causes the cell walls to rupture, leading to bacterial death, hence the dimple. The purpose of this bacterial autolysis is unclear—it may play a part in virulence by reducing the immune response.

The autolytic enzyme is also responsible for the fact that the organism may grow well to start with in blood cultures, triggering a positive culture in an automated system, but when examined a few hours later, the bacteria have disappeared, leading to a negative Gram stain and no growth on agar.

Another unique feature of Pneumococcus is the fact that it is sensitive to the chemical optochin, unlike all the other alpha-haemolytic streptococci. This feature is used to identify *S. pneumoniae*,
by placing a paper disc of optochin on the agar plate. If there is a zone of inhibition after incubation, this suggests the suspected organism is definitely Pneumococcus.

The Pneumococcus is usually sensitive to penicillin in the UK and is treated with the penicillin group antibiotics (e.g. intravenous penicillin, or co-amoxiclav, depending on severity) and erythromycin or clarithromycin as used here.

Worldwide, rates of penicillin resistance vary widely, from <5% to 90%, so when treating serious pneumococcal infection it is always worth considering any recent travel history of the patient.

**Further reading**

Case example

It is a busy day for you as the on-call doctor for haematology. You have just been bleeped once again, this time from one of the nurses in the oncology assessment area who has a patient she would like you to see. ‘It’s Mrs Hanley. She seems pretty breathless so I’ll pop her on some oxygen and do a septic screen while we’re waiting for you to come down.’

The haematology consultant happens to be in the doctor’s office with you when you receive the call. ‘Oh, Mrs Hanley, she’s a talker. Be careful you don’t get trapped taking a long, long history!’ Your heart sinks. A ‘talker’ is the last thing you need right now. You have a list of jobs to do as a result of the ward round and you feel under pressure to complete them before your handover in 4 hours’ time. You need to make this consultation thorough but swift.

On arriving at the assessment area you are more worried than relieved to find that Mrs Hanley is far too breathless to qualify as a ‘talker’. She has been saturating at 87% on air prior to donning an oxygen mask, and an arterial blood gas on air shows a pO$_2$ of 6.6. Her temperature is 38°C. She is a pink-faced and cheerful 71-year-old retired chemist with classic Hodgkin’s lymphoma diagnosed only recently. She has received radiotherapy to the mediastinum and six cycles of ABVD chemotherapy with a good response demonstrated on CT. She is accompanied by her husband, who is somewhat older than her.

Mrs Hanley gives a history (in between gasps) of 10 days increasing fatigue and breathlessness. She denies having a raised temperature or producing any sputum. In fact she is strangely cavalier about it all. ‘Oh, I’m fine . . . I’ll be heading . . . home later on. I just wanted a doctor . . . to check that I was OK.’ She’s a bit vague when you ask her about her regular prophylactic antifungal medication and you get the feeling she has not been getting them. She mainly seems worried about her husband.

On examination she clearly has respiratory distress, with a respiratory rate of 35/min and use of accessory muscles. But on listening to her chest, instead of the rip-roaring bilateral crackles that you are expecting, she just has a few crepitations at her left base. The chest X-ray tells a different story: widespread bilateral mid- and upper zone shadowing.

There is a discrepancy between the severe X-ray findings and marked breathlessness on the one hand, and the lack of florid sounds on auscultation on the other. This points towards a picture of atypical pneumonia and given Mrs Hanley’s immunocompromised status and your concerns about her antifungal medication, you are also thinking of more unusual diagnoses such as pneumocystis pneumonia (PCP) and Aspergillus.

That she needs to be admitted is obvious; however, Mrs Hanley needs to be persuaded to stay. No one has realized until today that her elderly husband has hitherto undiagnosed dementia and that she is his main carer. You notice how aggressive he gets during her brief disappearance for a chest X-ray, even accusing staff of kidnapping her. This explains Mrs Hanley’s delayed presentation and her seemingly cheerful and off-hand demeanour, evidently trying to pretend to her husband—and maybe herself—that everything is going to be all right.
Everything is not all right. You transfer Mrs Hanley to a side room in the haematology high-dependency unit and commence her on high-dose co-trimoxazole and high-dose steroids for PCP, and clarithromycin and piperacillin-tazobactam to cover for atypical pneumonia. She is by this point on a Venturi oxygen mask saturating uncomfortably at 94% on 8 L of oxygen. Her husband is clearly upset and confused, and does not have the capacity for full understanding of the gravity of the situation, although he recognizes that she is not quite well. He refuses to leave her bedside until a neighbour comes to take him home. Even then he awakes in the middle of the night terrified that his wife is missing and calls the police.

By the next morning, Mrs Hanley has deteriorated further and is on 10 L of oxygen, although she remains her normal cheerful self, desperate for a chat but clearly unable. The physiotherapist is called to obtain an induced sputum to send for microscopy and culture. Infection control measures are used in the room for several hours afterwards.

Despite the best and most appropriate broad-spectrum treatment, by day 3, Mrs Hanley requires 15 L of oxygen to keep her saturations within acceptable limits. The next step will be intubation and ventilation in the intensive care unit.

A discussion takes place among the consultant, Mrs Hanley, and her son, who has travelled a long distance to see his mother and look after his father. The situation is grave. The consultant thinks that given Mrs Hanley’s background frailty and the severity of the infection she would not be a suitable candidate for escalation. It is agreed that Mrs Hanley will remain on the ward, where she will be cared for whatever the eventual outcome. Over the next 2 days Mrs Hanley becomes less and less responsive and treatment is withdrawn. She passes away peacefully on the fifth day.

Microbiology

The sad case of Mrs Hanley illustrates two problems of respiratory infection—pneumonia in the immunocompromised, and the clinical syndrome of atypical pneumonia.

Atypical pneumonia is an old and commonly used medical term—but its meaning is not always clear. When the term was first used, about a century ago, it meant pneumonia that was not the typical acute lobar pneumonia normally seen with the Pneumococcus (see Case 3.1, Community-acquired pneumonia). Usually, in atypical cases, no cause could be found. Sometimes, atypical pneumonia occurred in large outbreaks in closed communities, for example military camps. Later, in the 1940s, it was realized that those patients with unusual pneumonias tended not to respond to the new penicillin antibiotic.

It was only in the years after the Second World War that scientific advances meant the many other causes could be identified. These were found to include Mycoplasma pneumoniae, Chlamydia pneumoniae, Chlamydia psittaci (acquired from birds, and seen in pet shop owners, etc.—the origin of the phrase ‘sick as a parrot’), and Legionella pneumophila, the cause of Legionnaire’s disease (only identified in the 1970s following a large outbreak among members of the American Legion attending a meeting in a hotel in Philadelphia. Inhalation of contaminated water droplets from ventilation systems, etc., can lead to legionella infection). In addition, influenza and many other viruses can cause atypical pneumonia.

These infections all have some common features—the illness generally has a longer, more gradual course than the very acute onset of pneumococcal pneumonia, there is not usually just one lobe consolidated, and there may be marked systemic features such as headache, confusion, weakness or gastrointestinal upset. X-ray findings are often more dramatic than clinical findings, and full recovery (without specific antibiotics) is the rule.
The other common feature of these varied infections—and this is why the phrase atypical pneumonia still has some clinical value—is that they mostly (except for the viruses) respond to macrolide antibiotics—erythromycin, clarithromycin, or azithromycin. This is the reason that severe acute community-acquired pneumonia is usually treated with a combination of a penicillin (for the \textit{Pneumococcus}) and a macrolide (for everything else) (see also Table A6.1 in Appendix 6).

With regard to \textbf{pneumonia in the immunocompromised}, firstly it is important to note that it can be caused by any of the causes of community-acquired pneumonia—this fact is often overlooked as doctors search for more exotic pathogens. It is also important to remember that common community pathogens seen in healthy adults and children are simply more common in the immunocompromised. The \textit{Pneumococcus} is a good example of this—it may even be an early marker of HIV if infection occurs in an otherwise healthy adult (most pneumonias are seen in children or elderly people). Similarly, TB is more common in those with chronic immunodeficiency, although presentation can be more acute.

However, there are other lung pathogens that tend only to infect the immunodeficient. The most well-known cause is \textit{Pneumocystis jirovecii} (formerly called \textit{Pneumocystis carinii}), 5 µm in size—the cause of PCP (Fig. 3.2.1). This tends to be seen in patients who are profoundly immunosuppressed, including late HIV (AIDS) and cancer patients.

PCP came to prominence as the infection that first alerted the world to the HIV epidemic, when there was an outbreak of cases in gay men in California. The first cases to be recognized,
however, occurred in outbreaks among malnourished children in orphanages in Europe during and after the Second World War.

The organism was long thought to be a protozoan, but it is in fact an unusual fungus. It does not grow on agar, and does not carry any typical fungal antigens, and the only way to detect it is by seeing it in respiratory samples, using either a silver stain, or a special antibody stain that makes it fluoresce under UV light.

Clinically the infection is described as an ‘interstitial pneumonitis’—the alveoli fill up with the organisms, and unlike in pneumococcal pneumonia there is not a great inflammatory response, so there is no production of pus to form sputum, or to cause solidification of the whole lobe of the lung. Therefore the X-ray tends to just show hazy shadowing, rather than obvious consolidation. The patients usually present with fever and a cough, and are often quite hypoxic at rest.

Because the patient does not cough up sputum, it is not easy to get the alveolar fluid to examine. Samples can be obtained by bronchoscopy: saline is injected and sucked back, known as a bronchoalveolar lavage. Alternatively, patients can be asked to inhale nebulized hypertonic saline, which they then cough up, to be collected and examined: an induced sputum. This is the technique the physiotherapist used to collect the sample from Mrs Hanley. This technique became popular soon after the start of the HIV epidemic and was very successful, but unfortunately it was forgotten that patients with HIV and a respiratory infection might also have something else, like TB, and therefore forcing them to cough might make the TB spread more. This led to a number of outbreaks of TB on HIV wards, and nowadays induced sputum samples are only collected under strict isolation precautions as mentioned with Mrs Hanley.

Even with appropriate samples, the diagnosis of PCP is not 100% reliable, and so patients are often treated on clinical suspicion alone. The treatment is high doses of co-trimoxazole, as used here: this is almost the only reason this antibiotic is still widely available. Patients at risk of PCP are also generally given prophylactic co-trimoxazole to prevent illness developing.

Other causes of lung infection in the immunocompromised include Cytomegalovirus, Mycoplasma pneumoniae, a variety of Gram-negative rods including Pseudomonas, and, seen in very neutropenic patients (typically those with haematological malignancies) invasive fungal infections, most commonly Aspergillus fumigatus.

Further reading
Case 3.3

Exacerbation of chronic obstructive pulmonary disease

Case example

Home visits are always an intense experience and they are time consuming, taking 40–50 minutes instead of the usual 10. A patient’s home can be very interesting, showing how he manages with day-to-day life, but the environment can also be rather distracting, and it’s harder to do good examinations without notes and proper equipment.

You have a message to say there is a request for a home visit. You know the name well: Mr Arthur Thompson. He is a bony looking, drawn looking man, very thin, 78 years old. He has COPD and the message says, ‘Chest is worse’.

You gather your thermometer, stethoscope, and oxygen saturation monitor and wrap yourself up. It is an icy, brisk day, and your hands and cheeks are stiff with cold by the time you are standing by the familiar yellow front door, waiting for him to answer. You stand patiently and soon see him dimly through the glass, inching his way towards you. When he finally opens the door you find yourself towering over his stooped figure. You brace yourself for the embrace of hot air and the strong and frightening smell of unlit gas. You have learnt, however, not to mention this, as on the last two occasions all the fires were properly lit and he told you off for being oversensitive.

‘Hello Mr Thompson, how are you?’ you ask, shutting the door slowly (to give the place a moment to air) and starting to unwind your coat and scarf.

‘I’m getting worse again doctor,’ he says. ‘Since the day before yesterday.’

You know a lot about his COPD already. As he shuffles slowly but steadily back to his sitting room you mentally run through his medications. You know he is on salbutamol prn, Seretide® two puffs bd (salmeterol and fluticasone) and Spiriva® (tiotropium od, a long acting antimuscarinic). He has the standard Evohaler® inhalers, and these are compatible with the Volumatic® spacer. He is seen every year by the nurse practitioner, who checks his weight, exercise tolerance, mood, inhaler technique, and measures his saturations and spirometry in line with NICE guidance. He has had his pneumococcal vaccine some years ago and is given his flu vaccine each year by the district nurses. Sometimes he also sees the specialist COPD nurse.

You also know his home circumstances; he has a sister who helps him with the shopping but otherwise he is self-caring. He can wash, dress, groom, feed himself, and get to the toilet. He can no longer make it up and down the stairs though, so he has a bed downstairs with a commode. He can walk about slowly within the house, limited by his breathing.

He sits down upright with his hands on his knees. ‘I’ve been taking extra puffs of the blue one. About ten a day. Normally I only need one or two.’

‘And are you eating all right?’ you ask, also sitting down.

‘I’m trying. Trying to eat regular. But I don’t always feel like it.’
You sit still and look at him bolt upright on the sofa, wrapped in his dressing gown, breathing away. He purses his lips as he looks back at you. You ask to take his pulse but really you want to count his breathing. So you sit there pressing his bony wrist gently and watching his abdomen move in and out breathing at 24 breaths a minute.

His pulse is regular at 80 and his oxygen saturations at rest, on air, are as usual 92%. His temperature is 37°C.

You listen to his chest. This is quite an undertaking as he has a dressing gown on over his pyjamas. You keep him sitting down and lower the dressing gown and then raise the pyjama jacket up. His chest just sounds crackly and wheezy all over—you don’t get a clear picture in your mind of a focal area; just a confused impression of crackles. Percussion is quite resonant, again as usual.

‘And are you coughing up more phlegm? What colour is it?’

‘Yellow again. Lots of it.’ At this point Mr Thompson unveils a small sterile pot which until this point has been hidden under a tissue on the table. Inside is yellow sputum ready to send to the laboratory for culture. You quickly avert your eyes and sealing it up in a specimen bag, you thank him gravely.

‘I think we ought to give you a course of antibiotics, Mr Thompson.’

‘Thought so. And them prediloan tablets?’

‘Prednisolone. Yes, I think you’re right. I’ll try and get them delivered tonight so you can start them as soon as possible.’

‘I’ll start them tomorrow doctor,’ he says firmly. ‘I like to know where I am with the doses so I remember right.’

You go back to the surgery and write your notes and prescribe a course of amoxicillin three times a day for 7 days. This is in line with the treatment guidelines in your area for an exacerbation of COPD. You also prescribe prednisolone 30 mg once a day for 5 days and add in extra salbutamol. You conscientiously label the sputum pot and send this off to the laboratory.

Four days later you receive the sputum result:

Mucopurulent sample
Culture result: upper respiratory tract flora +

You have told Mr Thompson to ring back if he is getting worse. However, you have seen him for several years with the same problem, each time resolving and each time leaving his bony frame to live on a little longer. As you expected you don’t hear again until 2 months later . . . but this time it is your colleague’s turn for a home visit.

**Microbiology**

Exacerbations of COPD are common, and are a ‘bread-and-butter’ mainstay of general practice and acute medicine. Common causes include both viral and bacterial infections; non-infective factors such as cold or allergens are also thought to play a part in some cases. Viral causes include rhinoviruses, influenza, parainfluenza, coronavirus, adenovirus, and respiratory syncytial virus (see relevant cases).

Bacterial causes include *Streptococcus pneumoniae* (hence the recommendation of pneumococcal vaccination in all patients with COPD), *Haemophilus influenzae* (typically non-capsulate strains in
COPD), Moraxella catarrhalis, Staphylococcus aureus, and lastly Pseudomonas aeruginosa (see Case 9.3, Otitis externa), which tends to be seen in patients with an element of bronchiectasis in their COPD.

In many laboratories sputum is not checked under the microscope or processed for a Gram stain any more, but simply cultured. Microscopy can identify pus cells and epithelial cells, but a Gram stain will simply pick up the typical mixed variety of Gram-positive and Gram-negative bacteria found in the mouth and respiratory tract, and adds no additional information to the culture result. In addition, processing the samples for Gram stains is labour intensive, whereas rapidly plating out 20 sputum samples is fast and effective, and a better use of a laboratory technician’s time.

All of the above-mentioned bacteria may be grown from sputum samples, and since COPD patients often produce copious amounts of sputum, samples are commonly sent to the lab. However, there is an important caveat in interpreting sputum culture results in exacerbations of COPD—all of these bacteria can be part of a COPD patient’s normal respiratory tract flora, and there is no reliable way of deciding which, if any, are playing a pathogenic role in an individual case. Therefore, in the community, sputum samples are generally not recommended for exacerbation of COPD unless the patient has failed to respond to first-line antibiotics.

However, this creates another problem: if the patient takes antibiotics, their normal colonizing bacteria and also any pathogenic bacteria may be suppressed, and the respiratory tract will become colonised with replacement flora—typically Gram-negatives or yeasts—and this will confuse the diagnosis.

A further problem with sputum examination is that samples are often contaminated with saliva, which is full of mouth bacteria, and these bacteria may also include colonising streptococci, Haemophilus, etc. Therefore, sputum results may be misleading, especially in COPD patients, and especially if taken after antibiotics. However, they can be useful if interpreted carefully. Patients with severe COPD or bronchiectasis may have sequential samples taken every few weeks or months, and if an exacerbation coincides with the appearance of a new organism, this is a more reliable guide to that organism being a real pathogen. The sputum result can also be useful to help choose which antibiotic to give.

If an antibiotic is going to be given anyway, as with Mr Thompson, then it is logical to give one that covers the possible pathogens present in the sputum. Usually the sputum result will not be available at the moment when the decision to give antibiotics is made, and empirical choices are necessary. A common first-line antibiotic is amoxicillin, which covers Streptococcus pneumoniae and most Haemophilus influenzae. Alternative first line agents include tetracycline or a macrolide such as clarithromycin. Some patients are even encouraged to keep a course of antibiotics and prednisolone at home ready to treat early (known as a rescue pack), although Mr Thompson prefers not to.

Further reading

Case 3.4

Tuberculosis

Case example

The young man in front of you looks thin and pale. ‘I have this cough,’ he says. ‘It’s not going away so I thought I’d get it checked out again.’ He has a strong South African accent—not unusual in your practice, which has a large South African population. You check the records and see that Mr Jonathan Marais is 27, and only recently registered at your practice. There is no record of a previous attendance with a cough.

‘Tell me about it. When did it start? Who checked it out before?’ you say.

Mr Marais says he came to the UK 3 years previously, after finishing university, and did a postgraduate teacher training course and he has been working as a secondary school teacher since then, recently moving to your city to take up a new position. He developed a slight cough about 9 months ago, and saw his GP at the time. He was given a course of antibiotics, but when the cough persisted he was told it was possibly asthma, and given an inhaler, and told to come back if it didn’t settle. When he moved house he had no GP for several months, but the cough persisted despite the inhaler, and his girlfriend eventually persuaded him to register with your practice and be seen again. They are planning to get married in a few months, and she has threatened to postpone the wedding until he gets the cough sorted. He smiles apologetically, as if to say that he himself would rather not bother you with such trivial complaints. Nonetheless, he follows this with a bout of coughing.

He goes on to tell you that the cough is hardly ever productive of sputum, except sometimes first thing in the morning. He has no allergies and there are no animals in the house; he doesn’t smoke. He thinks he might have lost some weight, but says that is probably due to his new teaching job, which is quite stressful.

You have a listen to his chest and hear crackles on the left side. You take his temperature, which is normal, and also check his oxygen saturations using your pulse oximeter (97%). While this is on his finger you surreptitiously count his respiratory rate (20).

‘What do you think, doctor?’ he says.

He has had the cough well over the 6 weeks of persistent symptoms that usually trigger you to order a CXR. He also has chest signs. You discuss the commonest causes of chronic cough with him, the asthma already mentioned, persistent nasal discharge and gastric reflux, but suggest waiting for the CXR result before deciding what treatment to try. You have in mind his chronic symptoms, country of origin, and weight loss, but are thinking more in terms of excluding TB.

To your surprise, a few days later you receive a phone call from the radiology department of the local hospital; his CXR shows left upper zone shadows, and they are concerned about TB. You contact the patient immediately with a view to urgent referral to the local TB clinic. As you wait for him to pick up the phone you remember his occupation and raise your eyebrows; there is going to be a substantial amount of contact tracing to be done by the TB team and a lot of worry generated for the students and colleagues at his last two schools.
Microbiology

Mr Marais is going to need urgent further testing at the TB clinic, principally for sputum samples; usually three samples are needed on subsequent days. It will be particularly important to establish whether he has ‘open TB’, in which case his classes and colleagues will have been exposed to the infection (historically known as phthisis) or ‘closed TB’, in which case he is not infectious. TB is a notifiable infection, the point being to arrange contact tracing if necessary.

The usual samples for diagnosis of mycobacterial infection are sputum, or sometimes CSF or biopsies. These samples can then be processed for microscopy and culture to look for mycobacteria (Fig. 3.4.1). Microscopy is simple and rapid, the bacilli are of a reasonable size (2–4 µm), but it does require high concentrations of bacteria per sample (1000–10 000 bacilli/mL) compared with culture which is more sensitive, needing 100 times fewer bacteria than for microscopy.

Mycobacteria have an unusual waxy cell wall containing large amounts of lipids called mycolic acids, and do not take up Gram stain like other bacteria, being invisible by this method. In order to be seen, they are stained with carbol–fuchsin, a mixture of phenol and the red dye, fuchsin. Even so, the dye will not stain the cell wall without the addition of heat during the staining process. Since any organism will take up the carbol-fuchsin stain by this technique, a further step needs to be used to distinguish mycobacteria. The slides, once stained, are flooded with acid for 1 minute. In other bacteria, the relatively thin cell wall, and lack of mycolic acid, means that any carbol-fuchsin will be washed out. Organisms that retain the red carbol-fuchsin stain despite the acid treatment are described as ‘acid-fast’, and are likely to be mycobacteria, hence the common

![Image](http://phil.cdc.gov/phil/details_linked.asp?pid=837)

**Fig. 3.4.1** This is a sputum smear stained by the Ziehl–Neelson technique showing *Mycobacterium tuberculosis* as the long dark rod in the exact centre of the figure.

The acronym ‘AFBs’, meaning acid-fast bacilli. The ‘fast’ in this context refers to the dye being stuck fast in the cell wall.

The stain that we have just described is the classic Ziehl–Neelson stain. In fact, many laboratories now use a different acid-fast stain, namely auramine. This has the advantage that no added heat is needed to stain the bacteria, so it is safer. Also, it is a fluorescent stain so any mycobacteria light up brightly under UV light in a fluorescence microscope and this makes the test more sensitive.

The other method for identifying the presence of mycobacteria, culture, also allows the bacteria to be speciated and checked for antibiotic sensitivity. However, again, mycobacteria are found to be awkward customers, and need special conditions to grow. They grow slowly for a start, taking 1–2 weeks or longer (culture may be continued up to 12 weeks before a negative report is sent out). It is of note that the sensitivity of culture is still low: about 40%. Lowensten–Jensen agar is the traditional medium. This contains a dye called malachite green, which inhibits the growth of most bacteria, but not mycobacteria. Lowensten–Jensen agar also contains egg and glycerol as growth supplements (Fig. 3.4.2).

Most laboratories have now switched to automated liquid culture systems for mycobacteria, which have been shown to be quicker and more sensitive. Whichever technique is used, skin samples and biopsies are cultured at two temperatures, 28–30°C and 35–37°C, because the mycobacteria that cause skin infections usually live in the environment rather than in humans or animals, and may be adapted better to grow at lower temperatures—culturing at 37°C alone may not be adequate.
In recent years, molecular tests to detect *M. tuberculosis* (MTB) DNA directly are being more widely used. These can give a quick detection of MTB in samples, and give an early indication of drug resistance—but they have not (yet) replaced the more traditional techniques.

The genus *Mycobacteria* includes about 50 or more bacteria. Most important is the above-mentioned *M. tuberculosis*, the cause of tuberculosis, and *M. bovis*, the cause of bovine TB. All the rest are commonly called **atypical mycobacteria** or **non-tuberculosis mycobacteria** and tend not to be very virulent, generally only causing skin infections following an inoculation event. Examples include, *M. fortuitum*-*chelonae* and *M. kansasii*. More serious non-tuberculous mycobacteria are *M. leprae*, the cause of leprosy, and *M. ulcerans*, the cause of Buruli ulcer, a progressive mutilating skin erosion seen in some tropical areas.

*M. bovis* is the strain that the BCG, the live attenuated vaccine, is based on. Developed in France, it was first used in 1953, not long after effective antibiotic therapy began to be used (1940). It is given intra-dermally and the protection quoted ranges from none at all to 80%, depending on what studies are looked at. In the UK it was initially given as a school-based programme at the age of 14 (the highest incidence of TB was at that time in the age group 14–25), this has now been changed to a neonatal programme. Since 2005 neonates who come from (or whose grandparents or parents come from) a country with an incidence of >40/100 000 per year, have been vaccinated. In the UK the average incidence is 10/100 000, although some boroughs have a high enough incidence that they have opted to immunize all neonates routinely.

About 2.3 billion of the world’s 7 billion population is said to be infected with TB, but there is a distinction between TB **infection** and TB **disease**. In fact in the 1920s, the majority of the population, especially those living in high density areas such as cities, were likely to have been infected by the age of 40. Most of these people did not, and today do not, have active disease, but there are about 9 million new cases of active disease each year. TB is known to be more common in conditions of poverty, overcrowding, and malnutrition: cases in the Western world are commonest in people who have originally come from (or have connections with) high-risk areas such as South Asia, Eastern Europe, and South Africa (Mr Marais’s country of origin).

It is likely that Mr Marais was infected in childhood or as a young adult in South Africa. Transmission is by inhaling the organism in sputum droplets from an open TB case. In most cases the infection resolves spontaneously, but some of the bacteria survive within macrophages in lymph nodes in the mediastinum or elsewhere. In a small number of cases the initial infection does not die down, but either persists as a progressive lung infection, or spreads through the bloodstream to seed elsewhere in the body—for example, leading to TB meningitis, or TB of the spine. More commonly, however, the infection remains latent in macrophages for many years, only to re-emerge later, if the patient’s immune system wanes—through pregnancy, stress, old-age, or some illnesses.

The commonest such illness is HIV. Worldwide, 25% of people with HIV die of TB. It will be important for the TB clinic to screen Mr Marais for HIV and other infections such as hepatitis B and C. Mostly, the re-emerged illness then presents as a chronic respiratory infection as here, typically affecting the upper lobes of the lungs. Eventually, cavitation of lung tissue can be seen and this cavitation leads to the production of large amounts of sputum containing MTB—thus maintaining the cycle of infection.

Mr Marais will need a 6-month course of treatment, usually including a combination of three or four antibiotics (rifampacin, isoniazid, pyrazinamide, and ethambutol). Ensuring that patients follow the tedious treatment course for such a long time can be very challenging, especially as they usually feel better after a few weeks; this is sometimes achieved by using DOT (directly observed therapy): the nurse actually watches the patient take the tablets each day. The danger with incomplete treatment is selection of drug-resistant organisms that require even
longer courses of treatment. The rates of multidrug-resistant TB are rising worldwide, and this, combined with global migration patterns, means that TB is going to remain a big challenge for the foreseeable future.

Further reading


Influenza

Case example

You are working as a locum doctor in a small isolated rural practice in the UK. Three doctors out of seven are off with influenza; they declined their flu jab 3 months ago when it was offered by the nurses at the practice. You have had yours and are perfectly well. You have also had a notification from the health surveillance team saying that flu is circulating.

You have indeed noticed a marked increase of viral illness in patients: with an especially high temperature, typically lasting 5 days instead of a more usual 3 days, aches and pains and a headache and sometimes a slight cough and sore throat, but no marked respiratory symptoms, no runny nose or cough with sputum. With each you have checked they are not in an at-risk group (chronic heart, lung and renal problems, asthma, pregnancy, the obese, diabetics, the immunocompromised, and health care workers). None has been so far, because the at-risk patients have all been immunized; you are impressed with the surgery’s flu vaccination programme. If someone did have what you thought was influenza and were in at-risk group, they would be eligible for oseltamivir—if seen within the first 72 hours. But so far you have not needed to prescribe it.

You do a search on the computer, and find you have seen 18 patients over the past 3 weeks with a flu-like illness; three in the first week (children), seven in the second week (infants and children), and eight in the third week (mainly adults in the 30–40 age range).

The surveillance data from the health protection agency shows a neat spike of influenza that coincides with yours, although the incidence appears to be dropping, which is hopeful. The tests sent by ‘sentinel practices’ show that the rate of influenza has increased from a baseline of 2/100 samples positive to a peak of 28/100 samples positive just last week. This is not quite matching the 40/100 identified during the 2009 swine flu pandemic, but still pretty high.

You read further and find that the samples are mainly influenza A (H3N2) (15%), with some influenza B (2.3%), and a scattering of swine flu.

You present your data to your colleagues but no one seems that interested. They say it’s obvious that flu is circulating. All except one colleague who has diagnosed a series of 15 children with pneumonia on the basis of coughs and high temperatures. Your colleagues haven’t entered ‘flu’ or ‘flu-like illness’, as a diagnosis. One says, ‘Who knows if it is or not?’ This explains why your audit only includes your own patients. You could still have searched the database if they had entered ‘viral illness’. However, most haven’t entered a diagnosis at all as they are not that into documentation at this practice.

Later you try a search for pneumonia; the diagnosis of that many cases has caused consternation among friends of yours with children. But although these diagnoses have been made, they have not been entered properly in the notes, and you are unable to pick any out.

The number of cases of flu-like illness continues for another week before the epidemic starts to subside and passes on with its march across the country.
Microbiology

Influenza is caused by a 100–200-nm spherical virus, of the Orthomyxovirus family (Fig. 3.5.1). These viruses have a lipid envelope through which two sorts of surface antigens poke. These antigens are both important to the virus, as they allow it to dock on to the cell, and are important to us, partly because they allow identification of different subtypes. The two antigens are known as neuraminase (N) and haemagglutinin (H). There are 15 known H-types and nine known N-types. Inside the lipid envelope is the viral core containing segmented –ve ss RNA nucleoprotein and RNA transcriptase. This is the enzyme that allows the virus to replicate once inside the cell.

There are three sorts of influenza, classified on the basis of internal viral proteins. These are influenza A, B, and C. Influenza C causes a mild cold-like illness and does not cause epidemic flu. Influenza A and B both cause the typical influenza symptoms, as mentioned in the case, and they quite often circulate concurrently, just as they do here: influenza B, as usual, at a lower level.

The reverse transcriptase enzyme error rate, of about 2% a year, leads to mutations in the surface antigens. These change over time in an effect called antigenic drift. This effect, seen in influenza A and B, allows influenza epidemics to develop every few years as the human immune system alternately gets left behind and then catches up. In contrast, antigenic shift is an effect seen only in influenza A. Because influenza A exists in animals and in humans, sometimes novel combinations of animal and human virus emerge. This can lead to pandemic flu.

Influenza A and B viruses are both very infectious. This characteristic of influenza virus relies on two important qualities: its transmission and its subclinical infection rate. Transmission is by aerosol: sneezing generates tiny virus-containing particles, less than 5 µm across. One sneeze can spread the virus to a whole room of people. These particles don’t land for many hours: up to 24 hours, allowing anyone who enters to breathe the particles in. With regard to subclinical infections, 30–50% of people have no symptoms at all and this also helps circulate the virus. Incubation is about 2–4 days and those who do experience symptoms are infectious 1 day before, and until 4 days after, symptoms begin.

Fig. 3.5.1 A transmission electron micrograph of swine flu virus.

Influenza particularly circulates in young children, perhaps due to closer contact with each other in schools and nurseries, or less careful hand washing. Young children are a sort of reservoir of influenza virus, and they pass it on to the adults and elderly people who look after them. It is interesting to see this pattern reflected in the small audit here. Flu epidemics usually peak at 3 weeks and then subside after a total of 6 weeks, also reflected in this case. Because of the higher morbidity in children and elderly people, these (and the at-risk groups) are also now selected for influenza immunizations. Vaccination in the over 65s started in 2000 in the UK, and for 2–4 year olds in 2014. Since influenza vaccines were introduced to the over 65s, epidemic flu has markedly reduced, and the last really high rate of influenza was, in fact, the 1999–2000 season.

In the case story, rates are measured as +ve samples per 100 sent by sentinel practices. The test used for these samples is reverse transcriptase polymerase chain reaction (RT–PCR). The RT–PCR can identify the influenza types and subtypes, for example the one mentioned in the case; Influenza A (H3N2). The rates can also be measured by looking at consultation rates of flu-like illness per 100 000 consultations. Epidemic level is counted at >400/100 000 compared with a baseline of 5/100 000, and a brief calculation of the figures in this case (given the doctor sees 60 patients a week) gives a rate of 1000/100 000, well above the epidemic level.

Once a practice has been informed that flu is circulating the positive predictive value of a clinical influenza diagnosis is about 85%, which should give clinicians confidence to document at least ‘flu-like illness’. There are rapid influenza diagnostic tests (RIDTs) available that give a bedside result within 15 minutes. These work by identifying virus antigens using an immunosay. However, although reasonably specific the test is not that sensitive, and if influenza infection was strongly suspected in an at-risk patient in the face of a negative result, an antiviral treatment would be recommended anyway. They should therefore only be used when the result will affect a clinical decision. Most doctors do not have ready access to these tests in any case, although one could argue that it would have been helpful to the doctor freely diagnosing pneumonias.

Influenza has been known about for several hundred years with several pandemics identified in Victorian times, 1889 and 1899, as well as the devastating pandemic of 1918, and the later, less severe ones, in the 1950s and 1960s. Influenza was thought to be caused by ‘Pfeiffer’s bacillus’ (Haemophilus influenzae), before the viral cause was identified by Laidlaw and his team in London in 1933.

The key symptoms are mentioned in the case and there is usually little to find on examination apart from the raised temperature. However, in the 1918 pandemic, we read that

Pneumonic or septicaemic type of influenza presents a very striking picture . . . often starting with symptoms similar to those of the simple form of the disease, it rapidly becomes apparent that the illness is of a grave type. The breathing is rapid and shallow although there is no obvious respiratory distress; cough is frequent and troublesome; the sputum becomes copious and is frothy and haemorrhagic. But perhaps the most striking feature is the colour of the patient which ranges in pink in the milder cases to a characteristic heliotrope, lilac or violet hue in those who are desperately ill . . . Those with the typical heliotrope tint invariably die very rapidly.

(Conybeare 1946: 84).

The colour described, what we would call cyanosis today, is as a result of severe hypoxia in these previously young and fit patients. Today we would treat this with oxygen (see Case 3.8, Viral pneumonia) but in 1918, although oxygen was of course well known, its therapeutic use was not established, and it had only been used inappropriately (such as subcutaneously or in drinking water). After the gassing of the soldiers during the First World War, it was starting to be used for respiratory problems; for example, 5 minutes per hour using a rubber tube going into the mouth, but it was not until 1922 that a doctor called Haldane established the measurement of PaO2, and the use of continuous oxygen using a reservoir bag.
Severe illness is still seen today. For example, during the 2009 pandemic it was noted that of children admitted with influenza, 10% were then admitted to ICU, and 3% intubated, although recovery was usually swift and the admissions usually only 1–2 days.

Treatment is with the antiviral drug oseltamivir, which interferes with virus budding from the cell surface. Because of the mutation rates of influenza, resistance to the drug is an important issue, and careful guidance has been generated by NICE as to when to use, i.e. for treatment purposes or for prophylaxis. The drug reduces symptoms by 1–2 days.

The intramuscular vaccine used annually in the over 65s and at-risk groups is a trivalent inactivated vaccine, grown in hens eggs. Because it is inactivated, patients cannot catch flu from it. It has an 80% protection level that takes 14 days to generate and lasts for 12 months. Each year the WHO selects the three influenza viruses that are most likely to emerge over the coming 12 months to be part of that year’s immunizations; production takes 9 months. Uptake rates are approximately 75%; the immunization of health care workers is particularly critical, as illustrated in the case here. The vaccine refusal levels among the doctors at this practice are especially embarrassing.

The new vaccine used in under fives is a cold-adapted live attenuated quadrivalent vaccine administered nasally, and it will be interesting to follow the rates of influenza consultation change as this routine becomes established.

Further reading


Case example

Mohammed is 10 months old. He is quietly sitting upright in his pushchair holding onto the rail in front of him. He is quite serious and rather grave.

You welcome Mohammed and his mother and as they sit down you shut the door. You sit down too and smile at Mohammed who turns his gaze to you.

You catch his mother’s eye. ‘What’s been happening?’ you ask.

‘Mohammed; he has cough. One day. Breathing very hard.’

‘Oh dear. Any temperature? Any runny nose?’


‘And how is he now?’ you ask. Mohammed sits there apparently quite comfortable, looking around.

‘Still not good.’

‘Let’s have a look at him.’

You take your pulse oximeter and put it on his finger to measure his oxygen levels. But it is an adult one and you can’t get a reading. Mohammed tolerates it for a bit and then wants to wriggle his fingers. You take it off and then get out your thermometer. You show this to him before moving it fairly slowly to his ear. ‘This goes in your ear’ you explain to him. ‘And will make a beep sound . . .’

He suffers you to put it in his ear. His temperature is 36.9°C.

Next you check his ears. ‘Look it’s my torch, to look in your ears. Now, keep really still. It might tickle a little bit.’

He looks at the auroscope and its light beam while his mum steadies his head. He holds still enough for you to check his ears which are both fine.

You now check his throat. You explain to mum how to sit him on her lap facing forwards: one arm round his arms and body and one hand around his forehead. Mohammed doesn’t like the lollipop stick in his mouth (no one does) but you edge it past his front teeth and he opens his mouth long enough for a split-second glimpse of his tonsils. They are both fine.

‘What a good boy. You are a good boy,’ you praise him, for he settles quickly. ‘Now can we look at your tummy? Where is your tummy?’

He looks down at his tummy reflectively. You use the word tummy because children this age don’t really know that they have a chest as yet. Besides you will want to look at his abdomen to see his breathing.

His mum pulls his vest away from his neck and offers you a small tunnel-shaped gap to get to his chest. But you want to see his whole chest not a small portion of it. You hold out for him to have his vest and other clothes removed. She takes off his fleece, his jumper, his t-shirt, and eventually pulls off his vest.
Mohammed is breathing away. What was before entirely hidden under his layers is now obvious in a moment’s glance. He is breathing fast. He has abdominal breathing, costal recession, tracheal tug, and you can even see the little muscles by his clavicles moving too, his accessory muscles. You count his breathing and find a respiratory rate of 60 breaths a minute. You listen and find wheezes throughout.

‘Did he take his bottle this morning?’
‘Yes. A little.’
‘Or was he too breathless?’
‘Yes. He was breathing.’
‘How much did he have?’
‘2 oz. Normally 5 oz milk.’
‘Ok’. You pause. Mohammed is quite composed, but making no wasted movement. The undressing has puffed him out and he is catching his breath.
‘I think he needs to go to hospital.’
The mum nods as if she was expecting this. She gestures to indicate an older child’s height. ‘Other child asthma. This asthma?’
‘I’m not sure. I don’t think so. Did your other child ever have to go to hospital?’
‘No. But breathing bad sometimes.’
‘Mmm. Mohammed needs some help. I think he needs a check to see if his oxygen levels are ok and he might need some oxygen until he gets better. Sometimes children need help to feed as well if they are too out of breath to drink their milk.’ You are thinking of the possibility of nasogastric feeding but you don’t mention it at this stage. ‘Let’s get him dressed. I will write some notes and write you a letter to take with you. How will you get to the hospital?’
‘By bus,’ the mum says.

After he is dressed and put back in his chair Mohammed starts to cry.

‘Have you got any milk for him?’ you ask. His mother rummages in her bag and pulls out a bottle of milk, which she offers to him. He takes it eagerly enough, and holds it himself, but within a moment or two you realize he is not swallowing but just comforted by the teat while he breathes through flared nostrils.

You finish writing and print off a letter, which you put in an envelope and hand to his mother.
‘Thank you very much,’ she says as you open the door for her to manoeuvre the pushchair though.
‘It’s a pleasure. Goodbye for now. Let me know how he does.’

**Microbiology**

Respiratory syncytial virus (RSV) is a –ve ss RNA virus with a bi-lipid envelope of variable size (120–300 nm) (Fig. 3.6.1). This is formed when the virus buds off an infected cell. RSV is from the Paramyxoviridae family and it causes over 90% of cases of bronchiolitis. It is responsible for infections in older children and adults too, causing LRTI, severe colds, otitis media, and croup. Interestingly, having an RSV infection doesn’t leave the patient immune for very long; immunity fades within 2–3 years, allowing reinfection.

Incubation is 4–5 days and the infection lasts 7–21 days. Transmission is by droplet spread but RSV is notoriously difficult to control, as the virus can stay viable on surfaces for over 5 hours.
For this reason it is important to establish early whether an admitted bronchiolitic child has RSV, to allow prompt isolation and therefore reduce transmission to other paediatric patients, particularly children with chronic illnesses or premature babies.

Diagnosis was traditionally done using cell cultures from a nasopharyngeal swab. The cytopathic effect observed with RSV is the fusion of cell membrane leading to the formation of giant syncytial cells, hence the name of the virus. However, this test takes 2 weeks, not quick enough to help inform decisions on isolation and barrier nursing. More rapid tests include ELISA, immunofluorescence and most recently PCR.

There is no routinely used treatment and no immunization available for this virus. The treatment of ribavirin via aerosol for 20 hours a day for high-risk patients is always mentioned at this point, and there is also an RSV monoclonal antibody called palivizumab that can be administered prophylactically every month, in very specific circumstances.

For the majority of children like Mohammed, treatment is supportive and includes oxygen for respiratory distress, and nasogastric feeding if they are too breathless to feed. Sometimes bronchodilators, steroids, or antibiotics are also tried. Very young children are nursed in an oxygen head-box, often in a semi-reclined position such as a car seat or baby bouncer.

Further reading
Case 3.7

Croup

Case example

‘She’s got a cough. Been ill for 3 days. Actually, I think it’s whooping cough.’

You are speaking on the telephone to Tina’s mum. Tina is 16 months old.

You think: I bet it’s croup. Out loud you say, ‘That’s fine. I have an appointment at 16.10 today. Would that suit you all right?’

‘Oh that’s great. That’s fine, yeah.’

‘Ok, I’ll see you then. That’s all booked in.’

Later that afternoon you buzz for Tina. There is a shuffling outside your door and a knock. You get up to open the door as you think Tina will be in a pushchair. She is, and her mum pushes her in, accompanied by two other people.

‘Hello, hello,’ you say to each. ‘Have a seat. You must be Tina’s mum. And this is . . .?’ you pause inviting her to finish the sentence.

‘Yeah. This is me brother who ought to be me son, he’s young enough!’ Her brother smiles hello as you say, ‘Oh yes. You can get big age gaps sometimes in families.’

‘And this is me son.’ The boy on the other side and more or less the same age as his uncle also nods and smiles.

‘And this here is Tina.’ She picks up a quiet-looking pale little girl from the buggy. ‘She’s not normally like this. Normally she’s running round the room. That is, she’s not running yet, but crawling I mean.’

You run through the story with the mum while the two boys take turns at making funny faces at Tina to amuse her.

Tina has been unwell for 3 days, runny nose, raised temperature, off her food but still drinking ok and still got wet nappies all right. ‘But her cough doctor! She’s lying down with it and when she coughs, she sits herself up!’

You check Tina’s ears, throat, and temperature, and then move onto her chest. She coyly studies her tummy when you admire it (and count her respiratory rate which is 44). There is no respiratory distress. She inspects the end of your stethoscope when you offer it to her. You take it back presently and listen to her chest. There is no wheeze or crackle, but you can hear a hoarse inspiratory sensation in her upper chest.

You take the stethoscope out of your ears.

‘Is it whooping cough doctor?’ asks Tina’s mum.

‘Well whooping cough sounds like this.’ You demonstrate a cough-cough-cough-cough-cough-whoooo (you breathe in air at the end making a forced inspiratory noise). ‘But I don’t think it can be whooping cough because she hasn’t had the cough for very long. And I don’t think it’s a wheeze or asthma.’
‘I thought she was wheezy last night,’ she says.

‘So a wheeze sounds like this,’ you breathe out fast and at the end of an expiration demonstrate a wheeze. ‘But what I think she’s got is croup. Croup sounds like a seal barking.’ You again attempt to demonstrate, less successfully (it’s not easy trying to sound like a seal). ‘I could tell easily if we could get her to cry’ you add.

‘I can’t get her to cry,’ says her mum, ‘But you can if you like!’

‘Yeah?’ you ask catching her eye. She nods and shrugs smiling.

You reach out to little Tina’s rib cage with your nice cold doctory hands and hold your fingers around her little bare chest. She doesn’t like this and pouts. But when you go to lift her up a little as if to put her on your own lap her control breaks and she takes in a stridoral breath and cries. She only cries for an instant, but it’s enough to hear the typically hoarse croupy sound. You stop lifting her immediately, resting her back on her mother’s lap and moving back your chair a little to give her a bit of space. She calms quickly again.

‘Yes, it’s croup all right.’

‘What’s it caused by?’ asks her mother.

‘Just a virus. Like a cold virus but sometimes it takes them this way.’

‘Will she be all right?’

‘Oh yes. She’s coping very well. Usually it starts as a normal cold, gets croupy and then changes into a chesty cough. They’re usually worse the first night they have it. Like last night.’

You explain that children get frightened by the noise they are making and this makes them breathe faster, which makes the noise louder and sets up a vicious circle. The first thing to do is to explain to the child that it’s just ‘croup’ and it’s just a noise and it will go. And then distracting the child is essential so that they calm down and this eases their breathing.

‘Children can get very ill with their breathing with croup, but I think Tina will be fine. But if you are worried about her breathing don’t hesitate. Come back or go to A&E. I’m sure she won’t need to, but it’s good to know what to do just in case.’

‘Yeah, just in case, you know what to do. Well thank you doctor. Thanks for seeing us. You wouldn’t think she would give us so much trouble seeing as she’s the fourth one in the family!’

She dresses Tina but understands you have someone waiting and kindly gathers up her coats, jumpers, and blankets to sort outside, shepherding her brother and her son in front of her.

**Microbiology**

Croup can be caused by various viruses, including influenza, respiratory syncytial virus (RSV), adenoviruses, rhinoviruses, and measles, but in particular it is known to be caused by parainfluenza.

**Parainfluenza** is a negative stranded RNA virus 200 nm in size and is one of the paramyxoviruses, along with RSV and measles. There are four types of parainfluenza virus (1, 2, 3, 4). Parainfluenza types 1 and 2 tend to circulate in the autumn (when this consultation takes place) and account for the majority of croup infections.

Parainfluenza viruses are transmitted in droplet form like any viral cold or cough after sneezing or coughing, and can be picked up from fomites on to the hands and transmitted up to the mouth and respiratory tract. The likely point of entry of the infecting virus is the respiratory tract epithelium. Parainfluenzae viruses attach to the epithelial cells and are then internalized. Once the cell
is infected, several morphological changes take place, such as an increase in the size of the cytoplasm and the nucleus. Vacuoles and inclusions can be seen at this stage in the cytoplasm. Later on in the infection, giant cells with many nuclei are formed following fusion. This is a particular characteristic of parainfluenza and the paramyxoviruses and may also be seen with measles.

Samples are not usually taken for diagnosis, which is clinical, but if the child is ill enough to be admitted to hospital a nasopharyngeal aspirate (NPA) can be taken. If it is not possible to obtain an NPA, a combined nose/throat swab for all the main respiratory viruses (influenza, RSV, adenovirus, coronavirus, rhinovirus) can be taken with a view to rapid result PCR.

This can have several advantages in that in the winter many ill children can be admitted to hospitals and diagnostic laboratories can be very busy, also respiratory viruses are very contagious and patients should be nursed in single rooms to reduce transmission to other patients on the ward. Quick laboratory diagnosis to confirm or refute a suspected respiratory viral infection is very helpful in preventing outbreaks in hospitals as it allows for more efficient use of the isolation rooms.

There is no antiviral treatment or vaccine for parainfluenza virus. For the clinical diagnosis of croup, traditionally steam inhalation was and is used, à la Anne of Green Gables (by L.M. Montgomery). Anne also uses a whole bottle of ipecacuanha for her small patient in the story. This is traditionally used as an emetic but also used as an expectorant. (The author was recommended this medication for a cough by a chemist as recently as 1994.)

Steam inhalation doesn’t really make much difference (except to intrigue and distract the child; maybe this is why it is thought to work) and is no longer recommended partly due to the risk of scalding. Ipecacuanha also doesn’t work.

Nebulized budesonide or a one-off dose of oral dexamethasone can also help settle symptoms a bit. The doctor in this case perhaps should have prescribed a dose of oral dexamethasone. When croup is severe children need admission for oxygen support and sometimes even nebulized adrenaline to help open their airway.

Further reading
Case example

You’re in the middle of a meeting, a rather good one on eating disorders. However, you are on-call, and when a receptionist comes up the stairs panting (three flights) and saying there is a very anxious mother on the phone and could you speak to her straight away as her baby doesn’t sound too good, you move promptly to the telephone in the other room. Mothers are frequently anxious but you can often sift through their story and work out how worried they should be and settle them down.

‘Hello, this is the on-call doctor. Who is it?’

‘Oh doctor, it’s Mrs Baley. It’s about my little girl Olivia. She started shaking about 10 minutes ago and she’s breathing fast.’

That doesn’t sound too good, so you say, ‘Is she alert and interacting with you?’

She says, ‘Not really. She’s awake.’ This is confusing, so you say, ‘And how is her colour?’

‘Not that great actually. She’s a bit of a funny colour, sort of mottled.’ You think; doesn’t sound good either. Then ask, ‘And is her breathing all right?’

‘I’m not sure really.’

‘Can you put the phone near her?’ you ask.

Mrs Baley does so and you hear rapid breathing, noisy at a rate of 60 a minute.

At this point, in retrospect, there is a strong case to call an ambulance. However, you don’t do this. You say, ‘Bring her down and I’ll see her straight away. Are you nearby?’

‘About a 10-minute walk’.

‘Bring her down quick OK?’

You know for sure the child’s breathing is laboured but her colour and alertness is harder to determine from the mum’s description: you have heard enough to be concerned. Perhaps some sort of wheeze? Bronchiolitis?

Within 10 minutes (you are a little tense waiting while still listening to your talk), you hear a call up the stairs and rapidly run down into the waiting room.

There is the mum with a double buggy holding one child and struggling with another.

‘Hello, I’m the doctor. We just spoke. Which is the sick one?’

You realize it is the one in her arms; her colour is pale. You lead the other by the hand but then pick her up to hurry her along.

As soon as Mrs Baley sits opposite you in your room you see in a second how ill the child is. Although awake, her eyes keep half closing and rolling up, she is leant back and floppy, her face is pale white and her lips mauve. Both her arms are blue to the elbow. Her respiratory rate is fast. You listen with your stethoscope and then stop, ready to call an ambulance. Then you think, ‘15 seconds, I can spare 15 seconds.’
She has crackles throughout but no wheeze. Her respiratory rate as before is 60, temperature 38.5°C, capillary refill 4 seconds (markedly prolonged).

You pick up the phone to the reception. ‘Get an ambulance. Respiratory. And bring some oxygen.’

Your hands are trembling as you grapple with the drawer and get out a spacer and mask and salbutamol. The child is entirely passive and you give four puffs waiting 6 breaths each time. The oxygen has not been bought up. You run down to the office where it is kept and run back up with the small black bottle. It is all connected with a mask, tube, and reservoir bag. There is a stretching gap while you work out which dials to turn: 10 L put it on 10. No hissing. There is a key and a notch it can turn. At last the hissing; the bag fills up.

After 2 minutes her colour improves slightly around the lips. You are as frightened as you have ever been. The one though that is flashing up in your mind: ‘This girl is going to die.’

You get mum to bring her over to the couch so that you can look at her back and chest for any rashes. You move her head to check for neck stiffness and feel for a fontanelle (it is closed). The mum is crying and your hands are still shaking.

You say, ‘I know how frightened you are and I’m really worried too. So I’m just focusing on Olivia.’

She says, ‘That’s fine that’s what I want.’ Olivia actually starts to cry, which you take as a good sign, but get mum to put her back on her lap so as not to waste energy crying.

The first paramedic arrives. You feel greatly relieved at his support. He is calm and simply gets out a nebulizer of salbutamol, which can be driven by oxygen. He measures the baby’s oxygen saturations, which are 77% at this point.

The main ambulance crew arrives. You handover: ‘This is Olivia. She is . . . How old is she?’

‘Thirteen months.’

‘Thirteen months with a temperature for 2 days. Thirty minutes ago she started shaking. Mum bought her up here. Her respiratory rate is 60 with crackles throughout. She was cyanosed and shut down. I have given her four puffs of salbutamol and 10 litres of oxygen and she is looking a lot better. She has just had nebulized salbutamol as well. I think she has septic pneumonia.’

Olivia is carried off by her mother attended by the ambulance crew. You hold Olivia’s sister’s hand and take her to the ambulance too.

After they have gone you have to pull yourself together. You still have to see 15 patients that afternoon. You start to wonder if you did the right thing; you could have told her to call an ambulance at home. Either way, from the time the mum called you, Olivia would get the oxygen within 10 minutes.

The next day you ring the hospital to check she is still alive. She is. The registrar you speak to seems remarkably laissez-faire about the whole thing. She was given a bolus of fluid on arrival and started on IV antibiotics and oseltamivir. She settled and in the morning was sitting up. Swabs are negative for influenza but picked up adenovirus.

The mother is told the shaking was either a seizure or a rigor.

**Microbiology**

Adenoviruses are large ds DNA viruses, 90–100 nm (Figure 3.8.1). They were first identified in a patient’s adenoids in America in 1953. There are over 50 serotypes recognized, each with a number.

Adenoviruses are known to cause a wide range of clinical presentations. You will note that adenovirus is mentioned in the differential diagnosis for the croup, the bronchiolitis, and the
CasE 3.8

VIRaL PnEumonIa

In common cold cases, as well as the conjunctivitis case, and is the key microbe for Case 8.2, Keratoconjunctivitis. It is mentioned in the more serious pneumonia and COPD cases and is also known as a cause of gastroenteritis and cystitis. Because of the variety of clinical presentations of adenoviruses, transmission is very variable (droplet, aerosol, faecal–oral); however, it is well known to be resistant to desiccation and will survive on surfaces for prolonged periods despite disinfectants.

In Olivia’s case adenovirus is causing a very severe presentation: at first sight not typical for adenoviruses. However, adenovirus serotype 7 has persistently featured in case studies of severe pneumonia and increased mortality in infants and young children ever since adenoviruses were first identified as a cause of illness back in the 1950s. A recent severe adenovirus outbreak in Taiwan, for example, was picked up when it was noted that there was a large increase in paediatric cases being admitted to ICU with pneumonia. It was noted that 50% had serotype 7 and of the 20% of children who died, 70% had serotype 7. So the doctor’s frightening thought in Olivia’s case, that she might well die, is not so far from the truth.

In the case, the doctor finds out the viral results from the hospital. These have clearly come back very quickly, within 24 hours. Most laboratories will now offer diagnosis for upper respiratory viruses using rapid PCR methods. They are very quick and same-day results are now usual. A major advantage of this PCR technique is that, as has obviously been done here, the test can be run as a multiplex assay (Box 3.8.1), testing for several different viruses from a single specimen; including influenza, parainfluenza, respiratory syncytial virus, adenovirus, coronavirus, rhinovirus, and human metapneumovirus.

**Fig. 3.8.1** A transmission electron micrograph of an adenovirus.
Further identification of adenovirus serotypes would need a special laboratory to arrange cell culture and further antigen testing or sequencing for serotype 7 or serotypes 4 and 3, which can also produce severe symptoms.

There is no treatment for adenovirus infection other than supportive measures, but there is a vaccine. This was developed in the USA for the protection of military recruits. It was noticed in 1956 that these groups were suffering large outbreaks of severe respiratory syndromes, initially thought to be caused by influenza. Investigators found that in fact the cause was adenovirus 4. Adenovirus outbreaks in military troops is not a problem confined to American troops, but is found in military recruits all over the world, and it is felt to be due to large numbers of young men brought together in close confinement with the physical and psychological stress of military training.

Although production of the vaccine lapsed in the USA because of funding difficulties, the formulation was reintroduced in 2011 and consists of live attenuated adenovirus serotypes 4 and 7. Unusually, this formulation is taken orally, as tablets with a coating to resist stomach acid, and is given to recruits immediately on arrival at basic training. The vaccine is not generally available.

Further reading

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**Box 3.8.1 PCR**

When processing swabs for PCR, the first stage is to extract the nucleic acid from the sample. This is usually DNA, the well-known double helix. The first stage is to split the double strands into single strands. This is done using heat and is known as DNA melting. Next the DNA primer is added. This DNA primer is a short strand of DNA known to contain the sequence that is being looked for, for example a part of the adenovirus DNA.

Each separated DNA strand is desperate to anneal or join with its opposite pair, so if the DNA primer matches it, they will join instead. Then with the help of DNA polymerase (an enzyme that builds DNA strands) and some nucleic acid building blocks, two new double strands of the targeted area of DNA are formed. This cycle of separation of DNA strands and then doubling up is repeated over 30 times, allowing the targeted DNA section to build up.

In older PCR techniques there would then be a stage at the end of this process where the amplified product would need to be detected using techniques such as gel electrophoresis, often taking a second day of analysis.

Nowadays, there are modern variants to traditional PCR including multiplex PCR, used in this case, where a group of DNA primers is added to check for several viruses at once, and real-time PCR where the DNA being amplified is linked with fluorescent dyes, which can be measured as the cycles of amplification occur. Other variants include RNA PCR for RNA viruses, quantitative PCR to detect viral load, and qualitative PCR to detect viral mutations; all three techniques are important in the management of hepatitis B and HIV (both RNA viruses).
Chapter 4

Central nervous system

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**Bacterial meningitis**

**Case example**

Martha Wickes is a 19-year-old student who has been admitted after being found fitting by her roommate. After she came round she was also complaining of a headache. She is febrile and treatment has been started for meningitis (ceftriaxone and amoxicillin) while further investigations are arranged, including a septic screen, a CT head scan and later an EEG. There is no known history of head injury or past history of epilepsy. She denies taking any street medication.

Martha is not meningitic on examination and has no rash. A CT head scan comes back as normal, as does a coagulation screen. After discussion with your consultant about proceeding to a lumbar puncture, you go into the room to explain to Martha that, as the medical registrar, you need to take a sample of the fluid that surrounds her brain and spinal cord to look for bacteria. At this point you realize that Martha is delirious, and hasn’t really understood, or cannot recall, anything you have just said. This is not a good sign. You arrange for her to have some antipyretic medication and repeat basic observations including a blood glucose, while you contact your consultant again.

Martha’s parents have been called and are on their way down from the far north of Scotland. After further discussion, you complete the ‘Adults with Incapacity’ form so that you can act in her best interests despite not having informed consent. You also arrange for her transfer to the high dependency unit (HDU) and for IV fluids. Following this, and with the assistance of the HDU nurses, you proceed with the lumbar puncture.

You set Martha carefully up on the bed, making sure she’s comfortable, lying in the left lateral position with her back right up to the edge of the bed in front of you, as flexed as possible but still comfortable, so she does not move at the wrong moment. There is plenty of light, the bed is at the right height, and you have the nurse to assist. You palpate Martha’s back to check for her anatomical landmarks, and identify exactly where you want to put the needle in: between lumbar vertebrae 3 and 4.

After washing your hands you put on a surgical gown with a mask and a double set of sterile gloves. You clean Martha’s back with iodine solution, including her waist, just in case you need to double check where to put the needle, and put a drape over her.

You draw up the anaesthetic and then with a small orange needle you infiltrate a small amount of local anaesthetic just under the skin. Next you change to a longer needle and infiltrate the local anaesthetic a little deeper into the tissues, making sure you draw back on the needle first to check you haven’t hit a blood vessel, before you inject it. While the local is taking effect you remove your outer layer of gloves and take a short procedural pause. This is where you can double check that everyone is still all right, and your equipment is all present.

Martha is surprisingly quiet. You were worried that she was going to get agitated during the procedure, but she seems to understand the importance of keeping still. You take a moment to set up the manometer and make sure the tap at the bottom is closed so the CSF will go up the manometer and not onto the floor. With a new set of sterile gloves you double check Martha’s positioning, take a deep breath and begin to advance the lumbar puncture needle. You are aiming
for the imagined position of her umbilicus and you make sure you are perpendicular to her back. You feel through the needle that you are advancing first through skin, then subcutaneous tissue, then into the tougher ligaments around the vertebrae, and, finally, with a very subtle give, into the CSF space. Thankfully, you have not hit bone along the way; this can be painful for the patient and means you are not in the correct place.

You know you are in the CSF space because when you pull out the wire, a pale yellow oily fluid starts to bulge out the end of the needle. You quickly attach the manometer and watch the level rise slowly. Her opening pressure stops within the normal range and you turn the tap to release all that precious CSF into sample pots that are ready and waiting, putting around ten drops in each. Martha is still thankfully still. Has she gone to sleep? You breathe a sigh of relief that you managed to get a sample first time.

Once the samples have been collected you withdraw the needle and put pressure on the area to make sure there is no bleeding or bruising. A simple plaster is applied, and Martha is allowed to lie on her back.

Within hours you have some preliminary results. Her glucose is low, protein is high, and the initial white cell count is high at $93 \times 10^6$, 60% of which are mononuclear.

This result, combined with a Gram-negative diplococcus identified on microscopy confirms your suspicions of meningococcal meningitis. You discuss her further antibiotic treatment with the microbiology consultant, who advises you to keep her on ceftriaxone and amoxicillin for the present until the culture results are back.

**Microbiology**

Meningitis is a feared illness, with good reason, because cases due to bacterial infection often do very badly. Even with appropriate antibiotic treatment, patients may still die or be left with permanent neurological problems. Many cases of meningitis are actually viral (see Case 4.2, Viral meningitis) which are usually milder and self-limiting—but there is no reliable way to distinguish these clinically: even a mild illness with menigism may be early bacterial meningitis.

The main bacterial causes of meningitis to consider are *Neisseria meningitidis* (meningococcus), *Streptococcus pneumoniae*, and *Haemophilus influenzae* capsulate type b (Hib). Meningococcus is seen particularly in children and young adults, especially when adults congregate together—for example, university residences, as here with Martha, military camps, or religious pilgrimages such as the Haj. Each age group, in fact (neonates, elderly), has a slightly different selection of bacteria that typically cause meningitis.

The key sample needed for suspected meningitis is cerebralspinal fluid (CSF) obtained by doing a lumbar puncture, as described in this case. There are two potential problems with doing a lumbar puncture; firstly, the possibility of raised intracranial pressure, in which case a lumbar puncture may precipitate ‘coning’ (herniation of the brain through the foramen magnum, with potentially fatal damage to the brainstem) and, secondly, patients with meningitis may deteriorate rapidly; so delaying treatment while awaiting a lumbar puncture may be detrimental. Therefore, it is advised not to delay antibiotics in suspected meningitis.

The sequence of events in a patient suspected of having meningitis should be to obtain IV access, take blood cultures, and then administer antibiotics immediately, and only then should a lumber puncture be considered. These procedures are followed in Martha’s case; she has had blood cultures, antibiotics, and a CT head scan before proceeding to a lumbar puncture.

If there is likely to be a delay in transfer to hospital, then antibiotics can be given IM while still in the community. The usual empirical antibiotic in the UK is ceftriaxone.
The CSF can be examined in different ways to try to establish if there is really meningitis, and if so what is the cause. Firstly, it should be inspected. This can be done at the bedside, as it is in Martha’s case. If it is cloudy or turbid, then this strongly suggests meningitis, but seemingly clear CSF does not exclude the diagnosis; cloudy CSF would be a very late finding. If it is blood stained, this can indicate either that the patient has an intracranial haemorrhage, or else that the lumbar puncture needle nicked a blood vessel and so there is blood contaminating the sample. To distinguish these possibilities it is advised to take successive CSF samples in different numbered containers, and in the case of a nicked blood vessel the red cell count is likely to decrease with successive samples.

The CSF is then split, and some sent to the biochemistry laboratory for measurement of protein and glucose, and some to microbiology for cell count, Gram stain, culture, and sensitivities. The cell count is performed in a counting chamber (similar to a urine sample, see Case 5.1, Recurrent UTI). A specialized glass slide with a precisely engineered fluid chamber is marked with a grid and the number of cells in each space in the grid can then be used to calculate the number per litre.

The sample is then spun in a centrifuge, and the remaining pellet is Gram stained to identify bacteria, and stained to differentiate white cells into polymorphs and lymphocytes. The remaining sample is then cultured. At this stage, or later, further investigations may be done using other techniques such as antigen-detection kits and PCR tests for pneumococci and meningococci and multiplex PCR for the main viral pathogens of meningitis.

In this case, the organism seen on microscopy was likely to be *Meningococcus*, pending the culture results (Fig. 4.1.1) This organism can cause two syndromes of infection—bacterial meningitis and fulminant (bacteraemic) meningococcal sepsis, although in many cases, patients have a mixed presentation, as here, or the illness evolves from one form to another.

Although the meningitis seen with *Meningococcus* is similar to that caused by other bacteria, the septicemia is severe, with a higher mortality. It is also characterized by a non-blanching petechial rash that can vary in extent. There may be only a few small (1–2 mm) lesions, easily overlooked, or the patient may have a generalized rash, with some petechiae merging into larger areas, which can necrose. Underlying this obvious rash is a process of disseminated intravascular coagulation, platelet consumption, and bleeding. The illness typically develops with frightening speed over several hours and the patient can rapidly become shocked. If they survive, they may develop gangrene and loss of digits.

The normal habitat of the *Meningococcus* is the nasopharynx, and carriage without disease is common. Spread probably occurs by respiratory droplet spread (or by kissing) and needs close

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**Fig. 4.1.1** A photomicrograph of aerobic Gram-negative *Neisseria meningitidis* diplococcal bacteria.

contact. Household contacts of cases of disease are generally given antibiotics to eliminate possible carriage and block further spread, in the hope of reducing further cases.

Neisseria meningitidis is a Gram-negative diplococcus, 1 µm in size. It grows best on chocolate agar, but it needs an atmosphere with added CO₂. It resembles the Gonococcus (see Case 6.2, Urethral discharge) but can be distinguished from this with antibody tests, or by testing sugar utilization: it metabolizes maltose and glucose, whereas the Gonococcus uses glucose only. Because so many patients (for good clinical reasons) get antibiotics before appropriate samples are sent, cultures are often negative. Indeed, the outcome for the patient is usually already determined by the time the result comes back, the main value of culture is to guide subsequent public health measures including vaccination and to help epidemiological surveillance of infections.

Not every strain of the Meningococcus is invasive. Those that are carry a polysaccharide capsule that is recognized by the immune system. This capsule can be of different types, the main ones being A, B, C, Y, and W135. Vaccines have been developed against some of these serogroups and the MenC vaccine is part of the childhood vaccination schedule in the UK.

Further reading

Case 4.2

Viral meningitis

Case example

John Roberts (37) comes in to see you and although you ultimately diagnose meningitis, you spend less time in consultation with him than with the average patient with a cold.

For a start, as he comes in, he just looks ill. He is pale, sallow; he shuffles in, keeping his head still his shoulders hunched. He appears photophobic, wincing at the overhead skylight.

His story is simple. He has had a headache for 2 days, also a raised temperature, and is unable to keep fluids down. He has no other cause for a high temperature: no cough, no cold, no other pains, no abdominal pain, and no dysuria. He feels out of it; his balance is not right; his vision is blurry. Even when he takes a small sip he vomits.

You examine him and note: ‘has rigors, colour bad pale, cap refill prolonged at 3 sec, sore head and neck, no inc. tone in neck, Kernig’s negative, throat fine, ears fine, temp 38.6.’

You think he has meningitis. You want him in hospital right now; you want bloods, blood cultures, urine, and a chest X-ray: in short, a septic screen. You want IV access, IV antibiotics and IV fluids and, in particular, you want a CSF sample sent.

You are lucky; your referring hospital has an infectious diseases team and you phone and get straight through to the medical registrar. She listens to you go through the story without interrupting and then asks you to send him up right away and she will be waiting for him.

‘Should I get an ambulance for him?’ you ask. ‘His brother is waiting just outside with the car.’

She pauses. ‘If his BP is all right then the car is fine.’

His BP is ok (128/76, HR 88) and you send him out to the waiting car with a letter for the registrar and instructions to go straight to A&E and ask for the named registrar. You make a note of his name to look out for any letters about him from the hospital.

Three days later you receive the following:

Diagnosis: Headache, vomiting, fever; likely viral meningitis

Investigation: Faeces*2 negative for salmonella/shigella/campylobacter/E. coli O157/crypto. Ova, cysts and parasites neg. Influenza A/B PCR negative. Blood culture*2 negative. Urinary Legionella and pneumococcal antigens negative. Malaria film negative, HIV negative. LFT deranged, hepatitis screen sent, inflammatory markers not raised. CT brain normal, CXR normal. Lumbar puncture; lymphocytic pleocytosis (363 WCC cells/mm3, 99% lymphocytes, 1% neutrophils) glucose normal, protein slightly raised, no growth. CSF viral multiplex PCR; HSV-1 DNA not detected, HSV-2 DNA not detected, VZV DNA not detected, enterovirus RNA not detected, mumps virus RNA not detected.

Management: Admitted with 24-hour history of severe frontal headache, fevers with rigors and vomiting with all oral intake. Examination temp 38.6, tachycardia of 90–110, no meningism,
no papilloedema, normal full neurological examination. Treated with oseltamivir to cover influenza, stopped after one dose due to negative PCR results. CSF result suggested viral meningitis. Headaches gradually improved on supportive treatment with fluids and analgesia. Discharged back to GP with follow up on ward next week if remains unwell.

**Microbiology**

John Roberts has had a swift assessment and appropriate investigations by the hospital. Importantly (some would say unusually), the hospital has communicated with you very promptly.

Meningitis, as here, is usually investigated with a full septic screen. This should not, however, delay presumptive treatment for assumed bacterial meningitis with IV ceftriaxone.

The CSF—the investigation you were most interested in—has signs of a likely viral infection. The infectious diseases team has excluded influenza A and HIV, and using a PCR multiplex assay (only used routinely in the last 2–3 years) HSV-1 and 2, mumps, VZV and also the non-polio enteroviruses such as echovirus, coxsackie virus, and enterovirus 70 and 71. Other viruses that can cause viral meningitis include EBV and HHV-6 and rarer causes, particularly in returned travellers, are the various arboviruses such as St Louis encephalitis, Murray Valley encephalitis, and the equine fevers.

Since the PCR multiplex assay is a relatively recent technique to be used routinely, research in viral meningitis is still developing.

Treatment, as here, is supportive and full resolution usually expected within 10 days.

**Further reading**

Case 4.3

Neurosyphilis

Case example

Miss Beryl Jameson (75) is an Afro-Caribbean lady who has just had surgery for gallstones. She is neatly dressed in a skirt and blouse and has her handbag with her. You are seeing her with her grandniece Nicola, who looks a lot more modern, with long plaited hair extensions and leggings. Nicola is looking after her great-aunt while she recovers from her operation.

You discuss the surgery and the dressings and how she is. There is a pause and then the grandniece says, ‘The thing is we’re worried about my aunt’s memory. There was this one time she left the oven on and she never knows where her keys are. And like, she was meant to be going to all these appointments; this was before her operation and they were like, important. But she kept missing them.’

You look at Miss Jameson to see how she is taking it. She is looking at her lap.

‘What do you think about it all, Miss Jameson?’ you ask.

‘Well doctor. I not denying it. I do forget these things sometimes.’

‘Would it be ok if I asked you a few questions to check your memory?’ you say. ‘They sound quite easy but sometimes people really don’t know the answers so they are quite important.’

‘Ok doctor. Go ahead,’ she says.

You run through the ten questions of the brief mini-mental health test (name, DOB, address, year, place, who you are, remembering a street name, counting backwards from 20, who is prime minister/on the throne and when the Second World War started). She scores eight out of ten, being unable to name the prime minister or remember the street name.

‘Well that’s pretty good,’ you say. ‘And I’m not worried about you being able to look after yourself.’ The grandniece looks a little dissatisfied (although Miss Jameson appears relieved), so you continue; ‘What I could do is refer you to the memory clinic for them to assess you further, check you over and do a head scan and so on. We should do a set of blood tests first though if that’s all right?’

They both nod and you print off a blood form with a dementia screen of U&E, LFT, TFT, bone screen, VDRL, FBC, B12, folate, and ferritin. You fix for them to ring you a week after having the test and arrange a dressings follow-up with regard to the surgery.

The results come back as follows:

| T. pallidum reagin antibody level positive. Results indicate treponemal infection at some time. |
| Please refer patient to the GUM clinic for assessment. An HIV test should be considered in all patients with a history of treponemal infection. |

The other results are normal. As you are away when they come back, your ‘results buddy’ Christine, a GP colleague, gets to follow her up. You ask Christie what happened.

‘Yeah, I got the result and had a chat with micro who pretty much said the same as what was in the report except they said the result can be cross contaminated with Yaws which is really common in
the Caribbean. Do you think she has Yaws?’ She dashes on. ‘But anyway you can’t tell one from the
other from tests so you have to treat it as syphilis anyway. So I fixed for her to come in and I thought
I better tell her without the grandniece. But when I suggested that her grandniece wait outside she
said no she wanted the grandniece to stay because of her memory and then I had to explain the result
in front of her. She was really shocked and really upset but the grandniece was actually great and said
d they definitely wanted the referral to the GUM clinic and they would sort this out and get on with the
treatment. I said about the possible cross contamination with Yaws and that seemed to help.’

You receive the following letter 2 months later from the GUM clinic.

Thank you for assisting with daily procaine penicillin injections for the above patient. She is
being treated for possible neuro-syphilis.

We are giving her procaine penicillin 4 MU IM daily for 17 days along with probenecid 500 mg qds.
We have administered the first dose today.

Each 1.2-g vial should be mixed with 4 mL of the water in the box and then 5 mL injected into
one buttock, and the same for the other side. This gives an overall dose of 4 MU (or 2.4 g) daily.
If you have any questions about administration please ring our nurses on (telephone number).

The practice assists the GUM clinic with the daily injections until the last dose is given 17 days later.

Microbiology

This case nicely illustrates several aspects of syphilis—its role as a sexually transmitted infection,
the possibility of long-term neurological complications, and the close relationship with other
non-sexual treponemal infections in the Caribbean and Central America. Syphilis is nowadays
regarded as a slightly exotic and unusual sexually transmitted infection, often tested for but sel-
don found, and it is easy to forget that for most of the last 500 years, until the arrival of antibiot-
ics, it was as widespread and feared as HIV.

It was first described in Europe in the early 1500s, and is thought to have been brought back to
Europe from America by Columbus’s sailors. The disease spread rapidly through the continent,
aided by the movement of armies—it seems to have been more serious then than it is now, with
mutilating skin features and many deaths, and was known as the great pox (to distinguish it
from smallpox). It was also named after everyone’s favourite enemy—so the Italians called it the
French disease, the Dutch called it the Spanish disease, and so on.

The organism is a spiral rod Treponema pallidum, 15 by 0.2 µm in size (Fig. 4.3.1). The untreat-
ed infection begins with a sexual exposure, followed a few days or weeks later by a painless nodule
that ulcerates—the chancre of primary syphilis. This heals spontaneously, but meanwhile
the organism spreads through the bloodstream to cause a variety of skin and other features—
secondary syphilis. Such features include varied rashes (which can be macular, papular, or even
pustular, and can also involve the palms); fleshy warty lesions can develop on the genitalia and in
skin folds, known as condylomata lata; mucous membranes may develop ulceration, often linear
and described as ‘snailtrack ulceration’; many patients have a degree of meningitis (which may be
asymptomatic) and/or neuritis, and most patients have a fever and are systemically unwell. Other
organs—gut, liver, kidneys, or bone—may also be affected.

If the illness is still untreated, this phase usually settles, and many patients clear the infection
entirely. However, a significant number of patients develop a dormant infection (latent syphilis)
and this can relapse with recurrent features of secondary syphilis up to 4 years after infection.
Any time after 5 years, progressive infection/inflammation can occur (seen in less than a third of untreated patients)—this is referred to as ‘late’ or ‘tertiary syphilis’. The typical organs affected are the nervous and cardiovascular systems. Neurosyphilis can be completely asymptomatic, with just minor CSF abnormalities detected, or can present as almost any neurological syndrome, from spinal cord damage (tabes dorsalis) to localized neurological lesions (subtle effects on personality or movement) to features resembling psychosis or dementia. The most extreme form of this was called ‘General Paralysis of the Insane’, although this was rare. It presented 10–20 years after infection, i.e. generally between the ages of 30 and 45 years and most often in men, with progressive dementia linked with slurred speech, reduced vision, spastic paresis, loss of sphincter control, and death after 3–4 years.

The link with dementia-like symptoms is why syphilis testing is always included in a dementia screen as it has been with Miss Jameson.

Cardiovascular syphilis can also occur and typically causes a vasculitis of the aorta, leading to weakening of the aortic wall and aortic aneurysm. Gummas are slow-growing granulomatous lesions that can occur in any part of the body; they may lead to ulceration and secondary bacterial infection, damage of the involved organs, or pressure effects on nearby tissues.

*Treponema pallidum* does not grow in laboratory media, so there are two approaches to confirming the diagnosis: you can aim to see the spirochetes in the lesions of primary or secondary syphilis (see Case 6.7, Genital herpes), or you can look for antibodies in the bloodstream. The spirochetes are too delicate to show up on a Gram stain, and will probably die while being transported to the laboratory, so the usual technique for direct rapid diagnosis is to do dark-ground or phase-contrast microscopy in the GUM clinic of samples from ulcers.

Obviously, in later disease, there is no ulcer to swab, so doctors must send serum to look for antibodies. There are two main types of antibody tests: reagin tests and specific or treponemal antibody tests. Reagin tests were the first to be developed. They were based on the fact that anti-treponemal antibodies will cross-react with certain cardiac lipids—and it is easier to obtain extracts of animal heart than extracts of the impossible-to-cultivate treponemes. The best known of these
tests is the VDRL (from the laboratory where it was developed—the Venereal Diseases Reference Laboratory in the USA). These tests are quick and cheap, and very sensitive—but they suffer from many cross-reactions: false positives can be seen in pregnancy, rheumatoid arthritis, SLE, and many other conditions. Nonetheless, they are still used, as the level of antibody by this method can give an indication of the level of disease activity.

The other tests use specific treponemal antigen, so are much less prone to cross-reaction, and are now available in automated systems. The specific treponemal antibodies are less indicative of disease activity, but can persist for life, even after treatment—so finding them means that the patient has had an infection at some point.

Sometimes the syphilis serology is positive when the result is not really expected—for example in screening for dementia, as with Mrs Jameson, or in antenatal testing (see Case 12.1, Infections in pregnancy). In those situations it is usual to treat presumptively, in case the patient still has live spirochetes causing illness (some old infections may be completely burnt out, but it is impossible to say which). In the case of possible neurosyphilis, it would be common to follow up with a lumbar puncture and scanning, to see if there is evidence of inflammation or damage in the brain.

As we saw with this patient, there are other treponemal infections that are not sexually spread, but can give the same serology test results. These include endemic syphilis (bejel), yaws and pinta—all of these are found in overcrowded tropical areas, and spread by direct contact with infectious skin lesions, and inoculation into abraded skin (or in the case of endemic syphilis, possibly through shared kitchen utensils). They resemble venereal syphilis in that there is a primary lesion at the site of inoculation, followed by haematogenous spread and widespread secondary lesions, with some patients going on to develop destructive tertiary lesions. Pinta is confined to Latin America, and mainly causes skin lesions. Yaws and endemic syphilis are found in the New and Old Worlds, and cause more destructive late lesions. These are caused by different subspecies of *T. pallidum*, and although there are subtle genetic differences, it is not possible to distinguish these strains in a routine laboratory and therefore it will never be clear if Miss Jameson’s test result represents syphilis or yaws. When reporting syphilis serology tests, it is important for laboratories to make it clear that the results indicate a *treponemal infection* (as is done on this report) not necessarily syphilis—otherwise great upset may be caused to individuals who come from areas where the non-venereal treponemes are still common.

Syphilis itself can also be spread from a pregnant woman to the fetus and is known as **congenital syphilis**. The infection spreads across the placenta, and the risk is greatest with secondary syphilis, during the bacteremia. The baby may have no obvious features initially but can then present with failure to thrive. A typical feature after about 6 weeks is a mucopurulent discharge from the nose, known as ‘snuffles’ (direct infection of the nasopharyngeal mucosa), resulting later in the ‘saddle nose’ deformity. Other presentations include a generalized rash, and infection of the bones: osteochondritis. If the child is not treated but still survives, long-term complications are diverse and include deformed bones and cartilage and teeth, blindness due to interstitial keratitis, and deafness due to eighth cranial nerve damage. The severe consequences of congenital infection are the reason that syphilis serology testing is a routine antenatal test.

Further reading

Chapter 5

Urinary

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Case 5.1

Recurrent urinary tract infection

Case example

Mrs Mariya Maksimov (74) is very overweight and very comfortable.
'I tell them, I want to wait for you,' she says in a strong Russian accent. 'I not want to see the other doctors!'

You bask in her warm approval. 'It's very nice to see you again,' you say smiling. 'How can I help you today?'

'I think I got another urine infection,' she explains handing you a sterile container with a sample. 'It never go away. Not really. Not for months and months.'

It's true, you've seen her before with a UTI. Today the urine dip is WCC +++ and RCC ++. You transfer the sample to a boric acid container ready to send it to the laboratory and suggest to her that you wait for the results before treating. Afterwards you are glad you made this suggestion because her urine result comes back as:

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteus sp. &gt;10⁸</td>
<td></td>
</tr>
<tr>
<td>R nitrofurantoin, trimethoprim</td>
<td></td>
</tr>
<tr>
<td>S co-amoxiclav, cefalexin, ciprofloxacin</td>
<td></td>
</tr>
<tr>
<td>WCC 433 (&lt;40)</td>
<td></td>
</tr>
<tr>
<td>RCC 9 (&lt;40)</td>
<td></td>
</tr>
<tr>
<td>Ep cells 11 (&lt;55)</td>
<td></td>
</tr>
</tbody>
</table>

The low epithelial cell number confirms it is a clean sample. The high WCC is consistent with a urine infection. The growth of a single species also increases the test's reliability. You print off a prescription for co-amoxiclav and send a patient note electronically to the receptionist to call Mrs Maksimov and ask her to come in for the prescription. While you are entering her notes and sorting out these details you think about how often you have seen her. It's at least three times with a UTI and so have your colleagues. You decide to review her notes.

You find that in the last 9 months she has had five confirmed infections (by confirmed you mean positive MSU results). The previous year she had two and the year before just one. You decide this is a clear picture of new-onset recurrent infections and refer her to urology. Unfortunately, at this point you make a mistake. You fail to tell Mrs Maksimov that you are referring her. When you see her 3 months later and ask about the referral, she says, 'I wondered what that was! I thought it was a mistake! No one referred me to urology. I should a known it was you looking after me!'

She beams at you.

Again you enjoy her warm approval even though your careful notes review and consequent actions have backfired and the referral has been rather delayed. You are delighted when you receive the following letter 3 months later.
Mr——’s Stone Clinic

Diagnosis left upper pole partial staghorn calculus

I saw this lady with her daughter in the urology clinic today. Her CT has confirmed the presence of a partial staghorn calculus in the upper pole of her left kidney. She had open stone surgery some 40 years ago on that side and the kidney certainly looks small and scarred as a result. I have arranged a DMSA renogram today to establish her split function and also sent routine blood tests including renal function and serum calcium, urate, and phosphate. Given her history of recurrent UTIs, I have sent an MSU although she is asymptomatic at present. She is aware that if she has on-going bacteruria she will need prophylactic antibiotics prior to her procedure.

The follow up letter dated 3 months later reads:

left percutaneous nephrolithotomy under GA. Access via supra 12th rib tract. Full stone clearance achieved.

Mrs Maksimov’s recovery is unremarkable.

Microbiology

UTIs are usually caused by the patient’s own bowel flora, which gain entry to the urinary tract by the ascending route. Escherichia coli is the commonest single causative organism; most of the remainder are caused by coliform bacteria, Gram-negative rods, including Citrobacter, Klebsiella, Enterobacter, Serratia, and Proteus as here.

Mrs Maksimov, having had many urine infections, had obtained a sterile container from reception in which to collect a urine sample. Once obtained, the urine is usually examined with a test strip or dipstick before a decision is taken to send off the sample for ‘microscopy, culture, and sensitivity’ (‘M, C, & S’—not ‘MCNS’ as sometimes written on laboratory request forms—an indication that the requestor does not understand what they are requesting).

Urine dips tend to be oversensitive, with a lower specificity. If they are negative the result is likely to be accurate and a UTI can be excluded on the spot. If they are positive, for example, for nitrite, WCC, and RCC, then it is worth sending the sample on to the laboratory for further tests. Usually at this point the urine is decanted or drawn up into another container, sometimes with boric acid (a white powder preservative, to prevent overgrowth of bacteria during transport) and put into the fridge until transport to the laboratory.

In the laboratory the sample may be dipped again to confirm that further processing is appropriate and then pipetted into a microtitre tray and left to settle for 10 minutes. The settled material (including epithelial cells, white cells, red cells, and microbes) is then counted using an inverted microscope to visualize the bottom of each microtitre well, and the cell count per cubic millimetre is calculated according to the known volume in each well. In practice, as most microbiology laboratories receive many hundreds of samples a day, the cell count may be automated using automated microscopy or flow cytometry.

The usual approach to quantifying the bacteria is to inoculate a known volume using a standard wire loop onto agar (quarter plates may be used, as this significantly reduces the cost of processing many tens of thousands of samples yearly) and the plates are then cultured overnight; the number
of colonies gives the number of bacteria in the original known volume, and simple arithmetic
gives the number per millilitre or per litre.

Identification of the type of bacteria can be done in different ways, and again the intention
is to make it as streamlined and economical as possible. Most laboratories use an agar that dif-
ferentiates between different types of bacteria by giving different colony appearances. One such
agar is CLED, which readily distinguishes lactose fermenters—i.e. likely E. coli—from other
bacteria. A more modern sophisticated option is Chromagar, which shows different coloured
colonies for E. coli, Proteus, Enterococcus, Klebsiella, Enterobacter, Citrobacter, Staphylococcus
aureus, Staphylococcus saprophyticus, and Pseudomonas. This means that a report can be issued
immediately on reading the agar plate, rather than having to spend more time and money doing
further identification.

The laboratory also tests for antibiotic sensitivities, as with Mrs Maksimov, to aid treatment
choices. The usual method is by the disc testing method—the organisms are inoculated on to
specialized sensitivity agar, and up to six filter paper discs containing known concentrations
different antibiotics placed on the agar plate. The plates are cultured overnight, and zones of
growth inhibition may be seen around each disc. For each antibiotic, the zone size is compared
with a set standard to decide if it is greater (i.e. sensitive) or smaller (i.e. resistant). Obviously, if
there is no zone at all, the organism is completely resistant. For some antibiotic–bacteria combi-
nations, there are resistances that are entirely predictable. For example, Proteus is always resistant
to nitrofurantoin, and testing is not even necessary.

There are new automated technologies that are being used more and more frequently and that
can robotically inoculate, incubate, and read agar plates, or even replace agar plates entirely with
liquid-based culture, combined with mass spectrometry analysis and sensitivity testing. This
new technology has been introduced in a small number of laboratories and while it is expensive
to set up, once installed it is quicker than traditional agar plate culture, and in time may replace
it entirely.

Proteus mirabilis, 2 μm in length, is the particular diagnosis in Mrs Maksimov’s case. This
organism gets its name from the Greek god Proteus, who could change his shape at will: this is
because the bacterium contains several thousand flagellae (many more than other bacteria) and
is highly motile. It frequently swims over agar, in addition to forming distinct colonies. This
behaviour is known as swarming, and leads to a film of Proteus bacteria covering the agar plate.
The organism has a distinct pungent foul smell, resembling rotten fish. This, and the swarming,
allows easy recognition in the laboratory.

The swarming tendency of Proteus can be used for deciding if two isolates are actually
the same strain or are different. This involves inoculating the two isolates onto the same
agar plate. If they are the same strain of Proteus, they will swarm into each other and mix
freely, covering the agar. If they are different strains, they will not mix, but form a clear
line where the edges of the two swarms meet, known as Dienes phenomenon (Fig. 5.1.1).
The biochemistry of Proteus too, is actually relevant to its ability to cause renal stone disease,
as it produces urease enzyme, splitting urea into ammonium and CO₂ and increasing the
urinary pH. A high urinary pH favours the growth of the bacteria, and also encourages pre-
cipitation of a chemical called struvite, giving rise to stone formation, just as Mrs Maksimov
experienced.
Further reading

Milo G, Katchman EA, Paul M. Duration of antibacterial treatment for uncomplicated urinary tract infection in women. Cochrane Database Syst Rev 2005;2:CD004682. Assessed as up-to-date: 21 Feb 2005. This Cochrane review has been cited in many guidelines as recommending only 3 days of antibiotics for uncomplicated UTI; however, when the number needed to harm is looked at in the original article it is not at all clear that it is advocating this.
Case 5.2

**Pyelonephritis**

**Case example**

‘Come on in and have a seat. I’m so sorry to keep you waiting.’

‘Yes, well, it’s 50 minutes late. I wouldn’t normally say anything but I’ve never waited so long, and it’s a child, she’s only 10.’

‘I’m very sorry about that.’ You pause.

‘Yes, well, it’s just not on. I know it’s meant to be 10 minutes a person. I’ve never had longer. In fact, often much less.’

You change the subject. ‘Come and sit down. Tell me what’s been happening.’

As they move towards the two chairs, you glance at your screen and read Fern Price (10). Fern sits down, and her father sits down next to her and in the momentary pause you wonder what the problem will be. In fact, though the problem is serious, it is also one that is clear and simple, and you ultimately have them out of the door quicker than many less ill patients.

Fern’s father says, ‘She’s not been right since last week. Then she said it hurt to wee. She’s got tummy pain too, and today she said her back was hurting.’

As he speaks you think: ‘UTI no . . .? pyelonephritis.’ So you ask ‘Is she eating and drinking?’

The little 10 year old nods seriously. ‘I didn’t feel like breakfast this morning,’ she says sounding very articulate for her age. ‘But daddy said I should have a drink, so I’ve been sipping on this.’ She lifts up a bottle of water.

‘Good. That’s good advice. Any vomiting?’ They shake their heads. ‘And is the back pain on one side? Or on both sides?’ You try and phrase the question so that it is not a leading question.

‘Um. This side more.’ Fern reaches round to her right.

‘Can I have a look at you, can you come up on here?’ you ask gesturing to the couch. Fern is very composed and stands up adjusting her top and walks over. Her father remains seated, watching. You ask Fern to lie down on her back with her hands by her side. ‘Does this pull up?’ you ask. She pulls up her top so you can see her tummy. ‘I’m going to press on your tummy like this,’ you press on the couch with your right hand using the flats of your fingers. ‘Is that all right?’ you ask. She nods.

You press with one hand only because she is little and slim; you can get enough pressure this way, and you start off quite slowly so that she gets the feel of it. You watch her face as you go. She is tender suprapubically. You ballot her kidneys, she is uneasy at this. Then you ask her to sit up and tap with a closed fist gently on her back using the ulnar border of your hand. Her back echoes hollowly. The left side she is fine with, the right side she winces and twists away with a jerk. You fetch your thermometer and check her temperature, which is 36.6.

‘Thank you,’ you say. ‘Let’s get you up and dressed while I wash my hands.’ She sits up quite easily and jumps down off the bed.
‘Now,’ you say sitting down again. ‘I think you have a urine infection and I think it is also infecting the kidney. It’s called pyelonephritis. We can treat it very well with antibiotics. What I need now is a urine sample. Can you do that for me?’

Fern looks at her father and nods. You show her where the toilet is and tell her to come straight back in when she has one. ‘We need a really clean sample. If you could wash your front bottom before you do it that can really help. Also we only want the middle bit of urine. So pee the first bit into the toilet and catch the middle bit in the pot, and then pee the rest into the toilet. Ok?’ It is a clean-catch MSU sample that you are requesting.

You don’t hurry her. Her father sits quietly while you get out the form for the urine sample and print off a prescription for co-amoxiclav. When Fern comes back in (acutely embarrassed because she is having to hold a sample of her own urine) you thank her and take it from her. In contrast, you are always delighted to receive a urine specimen so that you can check it. You have had frustrating times in the past where you have wanted a urine specimen from a patient and have not been able to obtain one.

The urine dip test shows:

| WCC +++, RCC +++, nitrates + |

This confirms a likely infection. You send a sample off to the laboratory for microscopy and culture. ‘I need you to carry on drinking water, not too much, just a normal amount. Start taking these antibiotics, they are one tablet three times a day for 7 days. You should start to feel better within 48 hours—often sooner. If you are not better, or if you are worse, then come back. Or, if you aren't able to keep the tablets down, or fluids down. Sometimes people with a kidney infection have a temperature and feel sick. As long as it all gets better, we don't need to do anything more. If it comes back or doesn't get better properly then we’ll look into it more. Probably with an ultrasound scan.’

‘No school then?’ the father says. He is dressed for work and holding a briefcase. Fern looks up alertly. You are not sure if she is pleased or sorry.

‘No, not for a few days until her symptoms are gone. Maybe Friday at the earliest.’

‘Well, thank you. Thank you very much,’ says Fern’s father. Fern smiles shyly and you say not at all, a pleasure, and goodbye for now.

Fern’s first consultation is brief, classic and textbook and so is her MSU result, which comes back 3 days later:

| WCC moderate numbers (200–500/mL) |
| RCC non-significant numbers detected |
| Bacteria significant numbers detected |
| Culture heavy growth of escherichia coli |
| Gent (S) co-amoxiclav (S) trimethoprim (S) amoxicillin (S) ciprofloxacin (S) cefalexin (S) nitrofurantoin (S) |

You rattle through her result and file it, satisfied that she is on the right antibiotic. However, she represents 7 days later, again with her father, with the loin pain still present and the dysuria returned for 3 days, although she feels better in herself. This time, although you are running late again and immediately apologize, Mr Price says, ‘Oh not at all. Thank you for seeing us, we know we have been tacked on to the end of your surgery’.
You repeat her urine dip, which is normal this time, repeat the MSU, and give her an ultrasound form. You advise review or A&E if the symptoms don’t settle. You don’t give her more antibiotics at this point, but unfortunately Fern’s symptoms continue to recur and she represents both to you and to A&E several times and also has, at some point, an urgent US (which is normal).

On her fifth representation you make a decision to refer. ‘I am going to refer Fern to paediatrics because she has had these recurrent infections,’ you explain to her father. ‘I want you to treat the infection she has and then I want her to take a low dose antibiotic every day to stop a further infection until you get the appointment. Appointments are usually quite quick for children maybe 2–3 weeks.’

When they have gone you document the consultation and your plan: recurrent/unresolved UTI. Refer paediatrics with a view to further investigation.

**Microbiology**

Pyelonephritis (infection of the kidney, renal pelvis, and ureters) in common with UTI, is most commonly caused by *Escherichia coli*; Fern’s diagnosis.

*E. coli* was first isolated by a German paediatrician and doctor Theodor Escherisch in 1885; he called it *Bacterium coli commune*, and it was renamed in his honour in 1919.

*E. coli* grows easily in both air and anaerobically; it will grow quickly on most standard laboratory media (including those containing bile, such as MacConkey agar) (Fig. 5.2.1) that are used for examination of urine or abdominal specimens. In a Gram stain, it resembles other coliforms—a ‘chunky’ Gram-negative rod, about 0.5 μm × 2 μm, easier to see than the smaller *Haemophilus*, or the finer *Pseudomonas*. The ease and speed of growth means it is a favourite organism of biological scientists. Much of our understanding of the fundamentals of molecular biology is based on experiments involving *E. coli*.

The cellular structure of *E. coli* is relevant to its role in disease, and the means by which particular strains of *E. coli* (and other Enterobacteriaceae) can be identified. As with other Gram-negative organisms, it has a cell membrane (a lipid bilayer), surrounded by a peptidoglycan cell wall, and this gives the cell support and rigidity. The cell wall is thinner than that of Gram-positive organisms, and this difference is actually the reason why the Gram stain works. Gram positives retain

**Fig. 5.2.1** A scanning electron micrograph of *E. coli* on agar. Reproduced from Centers for Disease Control and Prevention, Public Health Image Library (PHIL), Image ID#8800, Janice Carr, 2006, available from http://phil.cdc.gov/phil/details_linked.asp?pid=8800
the crystal violet Gram stain and Gram negatives lose it when washed with acetone. Outside the
cell wall there is another membrane. This outer membrane can serve as a barrier to antibiotics,
which is one reason why Gram negatives are generally more antibiotic-resistant than Gram posi-
tives. The outer membrane is also a major virulence factor of *E. coli* and other Gram negatives.

The outer membrane contains lipopolysaccharide (LPS). LPS is a molecule that contains a lipid
part inserted into the membrane, and a sugar part that faces externally. The lipid part is a very
potent activator of the immune system, binding to specific receptors on a variety of immune cells
and leading to excessive production of cytokines and inflammatory mediators by the body and
sometimes to septic shock. For this reason, LPS is also called endotoxin (to distinguish it from
other bacterial exotoxins that are actively excreted by the cell). The polysaccharide part of LPS,
sticking out of the membrane, is the part that is actually recognized by the immune system, lead-
ing to the production of antibodies.

Outside the outer membrane, many Enterobacteriaceae, including *E. coli*, have a further layer
of polysaccharide, forming a thick sugary capsule. This may be visible in a Gram stain as a clear
zone around the microbe, and in some bacteria (especially *Klebsiella*) the polysaccharide may be
so profuse as to result in large sticky slimy colonies on the agar plate.

As already noted, UTIs are most commonly caused by *E. coli*, and the most common infection
due to *E. coli* is a UTI (these two things are not necessarily the same). UTIs are almost always
caused by gut bacteria ascending the urethra—the shorter urethra in females is thought to be one
reason why women get more UTIs.

Other infections caused by *E. coli* include peritonitis, abdominal wound infections following
surgery, pneumonia if the patient is ventilated, sepsis, and/or seeding of infection elsewhere in
the body. Thus an unusual infection with *E. coli*, such as a spinal abscess, may be an indirect
consequence of recurrent UTI.

As well as causing disease when it gets outside its normal home in the gut, *E. coli* can also cause
disease within the gut: diarrhoea and gastroenteritis. Such infections are not normally due to our
own strains of *E. coli* (to which we would expect to be well adapted) but to strains which are not
part of our normal flora, and which often secrete exotoxins that contribute to the disease. The
most severe, and fortunately one of the rarest, is that due to *E. coli* O-157.

*E. coli* varies in its susceptibility to antibiotics. It is always resistant to penicillin, but many
strains remain sensitive to a range of common antibiotics including amoxicillin. Amoxicillin
resistance does occur however—probably in 20–30% of cases of UTI and pyelonephritis in the
community, and rates of resistance to trimethoprim are similar.

Historically pyelonephritis was known as pyelitis and the clinical description is very recogniza-
able. However, where we would talk about treatment, a historical textbook talks about the ‘course’;

The course is very variable. The acute stage may subside in a few days or weeks. Chronic pyelitis;
a residual infection of the renal pelvis . . . which may persist for months or years or may be
permanent.

(Conybeare 1946: 729)

Complications nowadays include recurrent infections and unresolved infections. An unre-
solved infection, as is likely in Fern’s case, indicates the need for further investigations, including
an ultrasound, bladder flow tests, and a DMSA. The ultrasound KUB (kidney, ureter, bladder) is
to check for anatomical problems or stones or abscesses (this investigation was normal in Fern).
When she sees the paediatric team, they may also proceed with the bladder flow tests which check
for vesicoureteric reflux (the backwash of urine going up the ureters from the bladder and caus-
ing recurrent infection) and/or a DMSA when radioactively labelled fluid is injected into the
vein to be processed by the kidney and then excreted in the urine. X-rays, taken in real time, light
up the working parts of the kidney and outline the ureters and the bladder, and can highlight any renal scarring or blockages that can occur as a result of pyelonephritis.

Pyelonephritis is a serious infection, so there is more concern to ensure that first-line treatment is effective. For this reason, broader-spectrum agents are more likely to be chosen (UK guidance is to give ciprofloxacin or co-amoxiclav as is used here). Prophylactic antibiotics are sometimes used in children while waiting for investigations, or in those with confirmed recurrent infections to prevent renal damage and scarring.

**Further reading**


Case 5.3

**Schistosomiasis**

**Case example**

Claire Johnson is composed but anxious. She gives you a clear and concise history of recurrent urine infections in the last 6 months. In fact the history is so clear and so concise that you suspect she is a medical professional. When she lets you know her last ‘MSU’ was clear, the use of medical vocabulary confirms your suspicions and you ask, ‘Do you work in a hospital?’

She nods. ‘I’m a fourth year medical student.’

The fact that she is a medical student is important as it will change the way you explain things. She is likely to have a good but patchy understanding of medical matters. Careful explanations will be needed, not assuming she knows all about it already.

‘Sorry,’ you say. ‘Go on; your last MSU was normal.’

‘Yes, even though I’ve been getting bleeding in the urine. It’s not like a normal UTI. I feel ok and when I pass urine it’s ok. And then it hurts and I pass some blood at the end. Like a teaspoon full.’

You look up the last MSU for yourself, which shows normal epithelial cell, white cell and red cell counts and no growth. ‘I see what you mean,’ you say. ‘How many times has this happened?’

‘Like three times, in the last 2 months,’ she says. Then: ‘Could it be something they don’t normally test for? Like TB?’

You look blank. TB is not something you were thinking of. Maybe a bladder stone or something local to the bladder causing inflammation, like a bladder cancer. But that would be strange as she is only 21. You pause indecisively. The urine is clear but she has a very clear description of terminal haematuria.

‘I get a sinking feeling when I see it.’ She carries on. ‘I don’t know what’s causing it but I know something is not right.’

You nod. ‘I think we had better refer you to urology. I’m not sure what's going on but it's most likely to be related to the bladder wall like a bladder stone or a sore or something. Urology will be able to have a look at the bladder using cystoscopy and take samples if they need to, to look under the microscope or check for further infection.’

She nods seriously.

‘Now look. I know you’re going to go home and look up all about it on the internet or symptom sorter. But don’t, because you’ll find something obscure and frighten yourself with it. You seem perfectly well in yourself and that’s the important thing and we’ll just wait for urology to see you.’

You refer her to urology but the urology waiting times are long. You receive letters from the urology department at long intervals. They do an ultrasound and a renal urogram about 12 months later. What they really want to do is a cystoscopy, but the letter says ‘... cystoscopy which the patient has declined for the present.’

Eventually however a cystoscopy is agreed on because you receive another letter from urology, and, to your surprise, the diagnosis is schistosomiasis. She is referred by the urology team to the Hospital for Tropical Diseases and is given a single dose of praziquantel.
At the tropical diseases appointment Dr Claire Johnson is worried. ‘Could my husband have caught it?’ she asks. Dr Andrew is reassuring. ‘No it doesn’t spread between people.’

But Dr Johnson is insistent. ‘But it spreads in water. Sometimes we share baths,’ she says tensely. At this Dr Andrew looks at her a bit quizzically and raises his eyebrows. Then he says, ‘As long as you don’t keep a colony of fresh water snails in your bath, your husband will be perfectly all right.’

You receive a copy of the following letter cc’d to the urology team:

Mr Fines
Consultant Urologist

Dear Mr Fines,

Thank you for referring this lady doctor. It seems that she may have acquired schistosomiasis during her gap year in Malawi 8 years ago, although symptoms of cystitis and later haematuria did not begin until 3 years ago.

Since your treatment with praziquantel she has had no further haematuria.

In this situation there is not much to be done immediately. I have given her a second dose of praziquantel to be sure that the infection is eliminated. I do not think another cystoscopy will add anything unless you had initially been concerned about some mechanical problems such as an obstruction of the urethra.

She was concerned that the schistosomiasis might perhaps affect her fertility but I was able to reassure her that there should be no significant fibrosis from a light infection of this duration.

Yours sincerely,
Dr B Andrew MD FRCPE FRCP DTM&H
Consultant Physician

Following this letter you think seriously about the delay in diagnosis and the travel history which you had not taken. Next time you see a patient with terminal haematuria you will liaise with the microbiology department with a view to sending the urine for schistosomiasis ova.

**Microbiology**

Humans have probably suffered from schistosomiasis for many centuries. Traces of infection have been found in Egyptian mummies and ancient Chinese graves. The cause of the infection was discovered by a German pathologist, Theodore Bilharz, in the mid-nineteenth century, and as a result the disease is sometimes also referred to as Bilharzia. About the same time, in the Katayama region of Japan, the physician Yoshinao Fujii described a febrile illness in farm workers, that he concluded was probably acquired from the water of the rice fields where they worked.

Schistosomiasis is caused by parasite flukes, or trematodes, of the genus *Schistosoma*. There are many species that infect many animals, but humans are infected by three main species—*S. haematobium*, which is found principally in Africa and the Middle East, and causes urinary schistosomiasis; *S. japonicum*, which is found in the Far East and causes hepatic and intestinal schistosomiasis, and *S. mansoni*, which is found in Arabia, Africa, and South America, and also causes hepatic and intestinal disease. *S. japonicum* has actually been eradicated in Japan since the 1970s.

The organism has a complex lifecycle, involving not just the definitive human host, but also freshwater snails as intermediate hosts. The adult pair of worms live in blood vessels in the gut or bladder and feed on the blood of the host. There they produce eggs, hundreds per day. The eggs penetrate into the bladder or gut as appropriate, and are shed in urine or faeces. It is the eggs that
cause the symptoms as they are highly antigenic and induce an intense granulomatous response, which can later lead to fibrosis and organ damage. If the eggs enter freshwater, they develop into a *miracidium*, a free-living ciliated larva about 0.1 mm long. The miracidia penetrate certain species of fresh water snails and reproduce asexually. They then re-enter the water as *cercariae* or mature larvae, which swim around and penetrate the intact skin of someone bathing or wading in the water. The cercariae have to do this quickly; if they do not find a host within 48 hours, they die. Having found a host they then migrate through the skin to the portal veins, where they develop into mature worms. The mature male and female worms pair at this point and then migrate to veins in the bladder or the intestines, where they may remain for many years laying their eggs, as described at the start.

The diagnosis of schistosomiasis is best made by seeing the eggs in urine or faeces (Fig. 5.3.1) (according to the site of infection) or in tissue biopsies from those areas. Eggs will only be present from 6 to 8 weeks after infection—samples taken too soon will be negative. The eggs are oval and large, typically about 60 microns by 140 μm.

An alternative technique is to look for antibodies to *Schistosoma* sp.; serology remains positive for several years. Serology is most useful in a returned traveller from an endemic area; somebody who has grown up in an endemic area may have positive serology without disease.

At the very start of an infestation some patients may develop a short-lived rash (swimmer’s itch) where the parasite has entered the skin; there may also be an acute flu-like illness a few days later (Katayama fever) as the parasites migrate through the body, with fever, diarrhoea, malaise, and urticaria. However, terminal haematuria (blood at the end of passing urine) is the most common presentation of urinary schistosomiasis. Intestinal schistosomiasis, the other common form of schistosomiasis, can cause bloody diarrhoea and abdominal pain, right upper quadrant pain, and abdominal cramps. Complications include anaemia, fibrosis, and scarring of the urinary tract, gut, or liver.

Diagnosis depends firstly on suspecting the infection, on the basis of recognition of clinical features as described and then sending a urine/stool sample as described earlier. Other ways of diagnosis, with the advent of modern investigations, include CT findings of a thickened calcified bladder wall, or a grainy sandy appearance of bladder mucosa picked up on cystoscopy, as in this case.

Globally there are said to be about 200 million cases worldwide in 74 endemic countries, with 20 million severely infected and 100 000 deaths annually. As implied by the life cycle of the para-

![Fig. 5.3.1](http://phil.cdc.gov/phil/details_linked.asp?pid=4843)
site, infections occur where the host snails are endemic, and where people regularly contaminate freshwater with their own faeces or urine, and where they also regularly wade or swim in the same water. Prevention and control in endemic populations is complex, and consists of a combination of education to increase awareness, improved sanitation to break the cycle of eggs entering freshwater, control of snail habitats, the simple measure of providing rubber boots to reduce skin water exposure, and treatment of cases to reduce shedding of eggs.

Prevention for travellers involves pre-travel advice on avoiding paddling, wading, or swimming if in an endemic area. If water is needed for drinking or washing, heating water to 50°C or simply leaving water standing for 48 hours before using are both effective ways of killing the cercariae. Iodine/chlorine water treatment will also kill them.

Further reading

Chapter 6

Genital

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Case example

‘My partner has got a discharge from his penis and he thinks it’s my fault.’
This is said with a faint degree of outrage from the strikingly beautiful 22-year-old, Nsia A., who is sitting in front of you. ‘So we thought we would come to the sexual health clinic together,’ she finishes.

‘What about you? Have you got any symptoms?’ you ask. You are one of the GUM clinic doctors and you have a proforma in front of you that you systematically fill in. You don’t need to look at it any more as you know all the questions off by heart. Starting off with ‘presenting complaint’.

‘Actually I have had a bit of bleeding. Like after sex you know, for about 2 months. It’s a bit painful.’

‘Painful during sex?’

‘Yes.’

‘But no discharge?’

‘No, not really.’

‘A bit?’

‘Well a bit of a sort of yellowy stuff.’

The trio of bleeding, discharge, and dyspareunia makes you think of pelvic inflammatory disease (PID). You move on to the sexual history; however, things are not straightforward here. She says she has been with her current partner for 2 months and that he is male and from the UK. When you ask whether she has had any other partners in the last 3 months she says yes but that this was not a current partner. But then she mentions that she had an encounter with the second partner the previous week. She also has improbable pauses such as when for example you ask, ‘Have you ever used IV drugs?’ or ‘Have you had anal sex with your current partner?’ she answers, ‘Ummmmmm. No,’ as if she doesn’t know without thinking hard.

Eventually you say, ‘Look shall we start again?’ She agrees somewhat confusedly and this time you establish that in fact she has two current partners, each unaware of the other, and she has also had two other casual male partners in the last 3 months. They are all from the UK, vaginal sex only, no anal sex, and she did not use condoms with any. None of them has HIV as far as she knows; she doesn’t know if they use IV drugs. She is on the pill but is otherwise well and on no other medication. She has used IV drugs once or twice; her last HIV test was 2 years ago, just before a miscarriage.

Because she has multiple partners and previous IV drug use, you think it is reasonable to take bloods for HIV and hepatitis B, C, and syphilis, which you do yourself while she is sitting there. You also suggest a pelvic examination and swabs, which she agrees to, and so you ask her to wait outside until the nurse calls her.
Thirty minutes later the nurse calls you and you go through to the examination room and find her on the couch in the lithotomy position undressed but covered with a sheet. After asking permission and removing the sheet, you take a high vaginal dry swab for candida and WCC microscopy, and a wet swab for Trichomonas vaginalis microscopy both to be examined immediately. You then take a low vaginal nucleic acid amplification technology (NAAT) swab for gonorrhoea and chlamydia, plus a gonorrhoeal swab for culture, as you are considering PID as likely. Not all gonorrhoeae are susceptible to the first line of treatment so culture and sensitivities is sometimes needed. You note that her cervix looks normal, with no blood or ectropia or obvious discharge. You then do a bimanual examination and identify tenderness on movement of the cervix.

You ask Nsia to go back to the waiting room while you continue seeing patients in your own room and her slides are checked in the nurse’s laboratory. But the swabs are all negative. The wet swabs show no T. vaginalis (70% sensitive). The dry swabs show no obvious bacterial vaginosis, candida, or gonorrhoea. It could still be chlamydia. The NAAT tests and cultures will take 2–3 days to be processed, and the results will be texted to the patient.

You sit and think for a little before calling the patient back in and initiating the treatment for acute PID. This involves an IM injection of ceftriaxone 500 mg and 14 days of doxycycline po 100 mg bd, plus 14 days of metronidazole po 400 mg bd, the treatment being designed to cover all the common causes of PID including chlamydia, gonorrhoea, Trichomonas vaginalis, and anaerobes. You hand the medications to her directly from the medicines cupboard in your room without a prescription charge; this is routine practice in the GUM clinic to improve compliance. You also give her a leaflet on PID and suggest the use of condoms. You offer her some condoms to take away with her, which she agrees to.

The NAAT test comes back positive for chlamydia. You will need to arrange a review with Nsia to discuss the diagnosis and arrange for contact tracing to allow any sexual partners to be treated as well.

**Microbiology**

PID occurs when an infection (usually sexually transmitted) spreads upwards through the female genital tract. It is usually divided into acute and chronic forms: the acute form when the infection spreads and the patient has symptoms of inflammation of the uterus or fallopian tubes, and the chronic form when persisting or repeated acute attacks leading to scarring and damage of the pelvic organs and consequent infertility, ectopic pregnancy, or chronic pelvic pain.

By the time a patient has chronic PID it is too late to reverse the scarring, so it is important to make an early diagnosis and treat acute PID, or, even better, the STIs that might lead to acute PID. The principal causative infections are Chlamydia and Gonorrhoea—in the developed world most cases are due to Chlamydia. In acute PID, the principal sexually transmitted pathogen is likely to be present, but there may also be secondary organisms involved such as streptococci, anaerobes, and coliforms. Many cases of PID are unrecognized—there is either a mild illness, or it is asymptomatic; few patients have the classic features of pelvic pain/tenderness, discharge or bleeding, and dyspareunia. In addition, there is no single diagnostic test—so the advice is generally to take a two-pronged approach: have a low threshold for starting empirical antibiotic treatment, and screen high-risk patients for the common STIs, as has been done here with Nsia.

Chlamydia is an unusual organism—it is a bacterium, but behaves more like a virus. It cannot grow and reproduce on its own, even with added nutrients—it needs to grow within host cells, either human or another animal. It has two phases in its life cycle: a small inactive hardy form called the elementary body, about 0.3 μm in size, which survives outside cells and spreads infection, and a larger growing form within cells called the reticulate body (Fig. 6.1.1). The reticulate
bodies exist within a large vacuole in the cell called an inclusion body and these inclusion bodies were recognized many years before the cause of Chlamydia infections was discovered. There is a small number of clinically important species. *C. trachomatis* causes urethritis and PID, and also (a different strain) the sexually transmitted genital ulcer known as lymphogranuloma venereum (LGV). It also causes the eye infection known as trachoma (different strain again) and this affects millions of people worldwide causing blindness, and *C. pneumoniae* is a cause of atypical pneumonia (see Case 3.2, Pneumonia in the immunocompromised).

Because *Chlamydia* will only grow within host cells, culture on agar is not possible. Originally, tissue culture was the main diagnostic technique—i.e. growth in a test-tube lined with mammalian cells. This was extremely expensive, slow, and labour intensive—and even with tissue culture, sensitivity was extremely low. Urethral or cervical swabs containing cells were necessary, which means an endocervical swab was needed.

In recent years, PCR and similar technology have taken over chlamydia diagnosis. When used for chlamydia and gonorrhoea testing in GUM clinics this is often referred to as the NAAT test. They are performed on automated machines, and often combine testing for chlamydia and gonorrhoea. These are highly sensitive, and nearly as specific as cell culture. An added advantage is that they seem to be just as reliable when used with urine in men, or low vaginal swabs in women or even self-taken swabs, and are therefore a much less invasive test.

*Chlamydia* does not respond to either the penicillins or the cephalosporins, so treatment is either based on macrolides such as azithromycin, or on the tetracyclines. Treatment of PID usually includes cover for *Chlamydia, N. gonorrhoeae*, and any anaerobes, streptococci, or coliforms that might be present also—as with our case here. The current UK guidance is for a single dose of IM ceftriaxone (to cover gonorrhoea) and 2 weeks of doxycycline (to cover chlamydia) with metronidazole (to cover anaerobes); the ceftriaxone and doxycycline will also cover coliforms and streptococci.

**Further reading**

Case 6.2

Urethral discharge

Case example

Today you are about to see a patient, Mr Sam B. (23) with a genital infection. The last consultation this patient had was with your colleague, and his notes say, 'Runny discharge from penis.' This peculiarly graphic description makes you wince a little and you hope today your patient has a different problem.

When your patient sits down rather tensely and says, 'I was here last week . . .' you know this is not to be.

Your colleague’s history is rather brief and simply says, 'MSU and swabs taken. Treatment with azithromycin 3 days. Bloods.' You check the results.

The urine result shows white cells but no growth. The blood results are negative for HIV, hepatitis B and C, and syphilis. You then check the urethral swab results. One of them says: ‘*Neisseria gonorrhoeae* not isolated. Yeasts not isolated.’

Unfortunately the result for the other swab simply says: ‘Specimen not processed. Technology for CT/GC has changed and requires new swabs. Please repeat using NAAT tubes.’

Your patient explains that he rang your surgery for the swab results. Then because these had not been processed, he took himself off to the GUM clinic. The GUM clinic re-tested him, issued doxycycline od for 7 days and asked him to ring back in a week.

‘So I’ve come today because the other doctor (your colleague) said it would take 3 days for the results to come back and I thought; I can’t wait 7 days. I’m making enough excuses as it is with my girlfriend.’

As an afterthought he adds, ‘The antibiotics haven’t made any difference. I’ve still got a runny discharge from the tip of my penis.’ Your colleague clearly wrote down his presentation verbatim.

You feel sympathetic, and at the same time dismayed, that this patient has had three appointments instead of one. He has had two lots of treatment for chlamydia but what if it wasn’t chlamydia in the first place?

You decide to start again with him. To begin with you apologize about the swabs. Having genital swabs is uncomfortable, so to have had them twice has been a great imposition on this patient. You also tell him that you will speak to the receptionist who re-stocks the rooms and get hold of some of the new tubes as soon as possible.

Next you need a sexual history. This patient is apparently low risk; he has had sex with his girlfriend of 12 months, she is on the pill and had a sexual health screen at the same time as him last week. She is asymptomatic. His only other partner was 6 months before his present relationship, also female; neither partner was from abroad.

You then re-check the history of his presentation. He has had discharge for 10 days. It is yellow and not smelly or itchy. It has not improved with either antibiotic. He has no other symptoms: no rash, no genital sores or warts, no dysuria, no eye symptoms or joint pains. He feels well in himself: normal temperature, normal appetite. He has been going to work as usual.
You say, ‘I think the results from the GUM clinic will come back sooner than 1 week. I wonder if they’ve said that for administration reasons. One thing that is really helpful is if you tell them you are happy for them to communicate with us, then they can send us your results.’ You add, ‘It sounds to me as if you’ve done everything right, you’re avoiding sex until you know where you are with it and you’ve taken the antibiotics. Once you have a diagnosis you may need to tell your girlfriend though in case she needs treatment too . . . Sometimes the cause of a discharge can’t be found, but at least all the important diagnoses will have been checked for using the swabs. Like gonorrhoea and chlamydia.’

‘What else could cause it?’ asks the patient.

You pause and think. You can clearly see gonorrhoea and chlamydia in your mind’s eye, but after that your thoughts are getting a little hazy. ‘I’m reaching the edge of my knowledge,’ you admit. ‘Let’s look up a leaflet.’

You find one and scan it quickly while the patient sits there patiently. You turn back to him. ‘I gather non-infectious causes are rather rare. Things like trauma, say, from having a catheter, or irritation from soaps and bath products. Sometimes its thrush—like a yeast infection but you’re negative for that. One-quarter of the time a cause is not found.’ You add, ‘If you find you are no better and the results don’t show anything, telephone me—we don’t have to drag you in again. We can have another think about what is going on, and I can arrange a referral to a urologist if we need one.’ While you are talking you print out the leaflet for him.

‘OK. So I’ll finish the doxycycline and ring the GUM clinic for the results and call here if I’m no better,’ he says, spontaneously summarizing the consultation.

Once the patient has left you email the receptionist in charge of stocking the store cupboard about the new swabs. Two weeks later she draws you aside and shows you the new tubes. These are not swabs. After studying the cartoon picture instructions carefully you gather in your pipette a small amount of urine to a precise level in the pot and send it off as usual. You take the box of pots to the next meeting and hand them round so that everyone is aware of the change in the sample-taking method.

Sometime later you do receive a letter from the GUM clinic informing you that the NAAT test was positive for gonorrhoea and that Sam B. has been treated with IM ceftriaxone.

**Microbiology**

Urethritis is probably the commonest and certainly the most obvious presentation of a sexually transmitted infection. In much of the world, and for much of history, the commonest cause was gonorrhoea, due to *Neisseria gonorrhoeae*, as is confirmed with Sam B. but in fact in most Western countries, non-gonococcal urethritis accounts for most cases. Of those, most are due to *Chlamydia*; other causes include *Ureaplasma urealyticum*, *Mycoplasma genitalium*, and non-bacterial causes such adenoviruses, herpes simplex, and *Trichomonas vaginalis*. There are also the non-infectious causes as mentioned by the doctor.

The name ‘gonorrhoea’ comes from the Greek, meaning ‘flow of seed’—because ancient physicians assumed the creamy discharge from the penis was leaking semen. It is of course, really pus, due to infection of the genital mucous membranes—in men, this means from the urethra as is seen here, and in women, this usually means the cervix. Male gonorrhoea infections usually present with an obvious discharge—but some may be asymptomatic. Female patients may have a vaginal discharge—but they are more likely to have no symptoms at all. Untreated infections generally resolve in a few weeks—but complications are common, including in women, PID (see
Case 6.1, Pelvic inflammatory disease) or in males, acute epididymitis, and disseminated infection can lead to bacteraemia and septic arthritis. Infection during pregnancy can lead to neonatal infection—typically, a purulent conjunctivitis.

_N. gonorrhoeae_ itself is a Gram-negative coccus, 0.6 μm in size and typically they are arranged in pairs, like two kidney beans side-by-side (Fig. 6.2.1). It is also frequently known (at least, by microbiologists) as the gonococcus. It is a rather fragile organism—it dies easily on swabs or in the laboratory, and does not withstand cold or drying—which is probably why it is only spread sexually: it needs direct mucosal contact to jump from one host to another. Most modern bacterial swabs are transported in a tube containing a nutrient gel with charcoal—this is designed to help protect fragile organisms during transit. Until recently the recommended sample to take in a male was a urethral swab—i.e. from inside the end of the urethra, not just a swab of the end of the penis. This is the test that Sam B. has had, but perhaps because of delay in transport to the laboratory the result is negative (a false negative as it turns out). In females, the infection is actually in the cervix, so the best sample was an endocervical swab.

The swabs can be examined directly by a Gram stain (if in a GUM clinic) revealing presumptive evidence of gonorrhoea—pus cells and numerous Gram-negative diplococci, some of which may be intracellular. This is not definite proof of the diagnosis—sometimes other neisserias may be seen instead—but if there is also a typical clinical story then this allows early treatment.

To grow _N. gonorrhoeae_ several commercial types of agar have been designed just for this organism. The problems of culturing neisserias, apart from the organism’s general delicacy and tendency to die, include a fondness for growing in a CO₂-enhanced atmosphere, precise nutrient requirements, and also a tendency to be overwhelmed by any other bacteria also present in the sample. Therefore, agars for _N. gonorrhoeae_ tend to be rich in nutrients, with antibiotics added to inhibit the growth of any other commensal bacteria. Chocolate agar with added antibiotics (vancomycin, nystatin, colistin, and trimethoprim) is one such medium (‘VNCT’ or Thayer–Martin agar). Another commonly used one is New York City agar, containing the same antibiotics but based on corn starch.

**Fig. 6.2.1** A transmission electron micrograph of a diplococcal pair of Gram-negative _Neisseria gonorrhoeae_ bacteria.

Some GUM clinics take an extra step to maximize culture yield, by actually inoculating the agar plates in the clinic, so that swab transport time is minimized. They can be immediately placed in a candle jar to produce the extra CO$_2$ that the organism needs, while awaiting transport to the laboratory.

Once the organism grows, it needs to be identified and distinguished from all the other bacteria that might grow from a urethral or vaginal swab (or, in the context of a typical GUM clinic, a rectal or throat swab also). The first step is usually to repeat the Gram stain on the colony, to make sure it is a Gram-negative diplococcus, along with an oxidase test (if it is oxidase negative, it cannot be a Neisseria). The next step is to confirm the species—this can be done either with a specific antibody test, detecting $N. gonorrhoeae$ antigens, or with biochemical tests, detecting which sugars are used by the organism.

These traditional techniques may not be around for much longer—automated PCR-based detection of $N. gonorrhoeae$ and Chlamydia (NAAT) is increasingly being used (and is the test Sam B. has at the GUM clinic). Even when culture on agar is still used, other advanced methods of confirming the species such as MALDI-TOF may soon take over.

Treatment is usually given as soon as the diagnosis is suspected, without waiting for proof, especially in GUM clinics where there is concern that patients may not return to get the results of their tests. Many strains of the gonococcus are now penicillin resistant, and ciprofloxacin resistance is increasing (though still rare)—so empirical treatment is usually a single intramuscular injection of ceftriaxone as has been used with Sam B. This is usually combined with a single tablet of azithromycin, not for the Gonorrhoeae, but in case the patient is also infected with Chlamydia.

**Further reading**

Case 6.3

HIV seroconversion

Case example

‘There’s a patient with some slightly odd HIV results,’ your Senior Biomedical Scientist Robert tells you as he pokes his head around the door of your office. ‘I was looking for you earlier in the lab, but I guessed you might have escaped back to your office for a moment or two. The results are ready on the lab results management system for you to have a look at,’ he adds before rushing off to get on with his work in the busy serology laboratory. You enter the laboratory number of the patient into the laboratory computer. It’s a blood specimen from a 19-year-old man, Benedetto Milani, who was seen in A&E. The clinical details that came with the specimen say, ‘At risk, fevers, rash, low platelets.’

During your time as a consultant virologist over the last 3 years in Central London, a new diagnosis of HIV is nothing new, especially given the large population of patients from sub-Saharan Africa who live locally, but in the last few months you’ve noticed quite an increase in new diagnoses in young male patients compared with the normal numbers. It might be another chem-sex-related case, you think.

You check the patient’s clinical details and see that he was in overnight on the medical decisions unit, but appears to have been discharged. You review the results: the fourth-generation HIV test is positive, but the two confirmatory tests using third-generation assays are negative. This will need a bit of extra work in the laboratory, you think, and head off to the laboratory to find Robert in order to discuss what to do next.

A good screening test such as the fourth-generation HIV test used for Benedetto needs to be very sensitive so that you don’t miss patients with infection. The disadvantage of very sensitive tests is that you may sometimes get false-positive results. That’s why for the diagnosis of HIV, you use a testing strategy that employs a sensitive assay followed by more specific confirmatory tests, as well as using tests that look for antibody and/or antigen. The pattern of results in this patient might simply be a false positive, but could also be early HIV infection.

‘Can I have a word Robert?’ You say as you enter the serology laboratory. ‘I don’t know too much about the patient yet, but the clinical details might fit with an HIV seroconversion illness. I’ll need to speak to the doctors looking after him to get another specimen, but could you run the sample again with our other fourth-generation assay, so I can see whether he’s got p24 antigen or not?’

‘I thought you would ask for that,’ says Robert. ‘I’m just printing the result off now. It looks as if it’s all antigen. No antibody detected at all. It’s a shame we don’t use this particular test as our screening assay, but I know it’s too expensive. It’s just a bit annoying that our screening assay just says positive or negative and doesn’t tell you whether it’s the antigen or antibody that is positive.’

‘Thanks Robert. I’ll try to track down the doctors who saw him. We’ll need another specimen obviously, just to confirm the diagnosis. If we wait a few days I’ll expect we’ll see the antibody become detectable in the third-generation assays—and then we can prove without doubt that this is a seroconversion illness.’
You go back to your office and track down the team that saw the patient a few days ago and establish that he’s due to be seen again tomorrow in the review clinic. The medical registrar confirms your suspicions. He’s a young white man from Italy recently arrived in London and into the ‘party and play’ scene. He’s regularly had chem-sex using mephedrone and crystal meth. In some cases he’s been ‘slamming’ the drugs; that is, having them IV. The disinhibition from this results in men having multiple sexual contacts, one after the other, with complete disregard to safe sex.

‘It would be best to get him seen quickly by the HIV team,’ you tell the registrar, ‘In case they want to start anti-retroviral treatment now. But we need to confirm the diagnosis with a second sample first. If you get it up to the lab straight away we can have the results the same day. We’ll test him for hepatitis C and syphilis as well.’

Microbiology

HIV is an enveloped +ve ss RNA virus, 120 nm in size, of the Retrovirus family (Fig. 6.3.1).

Laboratory diagnosis for HIV has evolved significantly over the last three decades since the discovery of the virus. When a person is infected with HIV, the virus has to be present in the patient’s blood for some time before the body starts forming antibodies. The first tests that were developed (1985) detected antibodies only and not viral antigens. This is the reason for the so-called ‘window period’, the period of time where a patient may be infected and be infectious but the test would be negative. With the early tests, the window period was up to 10 weeks. The technology developed such that the so-called third-generation tests (1991), although they still only detected antibody, reduced the window period to about 2–3 weeks.

With the addition of the ability to also detect the HIV-1 p24 antigen, an internal virus protein, the fourth-generation tests (1997) reduced the window further. So a patient with early infection and only antigen in the blood would have a positive fourth-generation test and negative third-generation tests, as with Benedetto. Some more expensive fourth-generation assays can break the results down so that you can see whether the positive result is due to the presence of antibody or the presence of antigen, as has been done here; the presence of antigen confirming early infection.

Fig. 6.3.1 A transmission electron micrograph of HIV.

The early tests used antigens derived from cell culture, whereas later tests use synthetic proteins. Additionally, it is also important to employ tests that will detect both HIV1 and HIV2. This is especially true where the population being investigated may include people from West Africa, where HIV2 is found.

Early testing and early diagnosis of HIV is essential to prevent transmission. To begin with, suggesting the option of HIV testing was sometimes avoided by clinicians. Concerns about insurance companies and the stigma attached to the diagnosis, the fact that there was no effective treatment, and the requirement for time-consuming counselling before having the test, all combined to reduce testing levels. However, concerns about insurance companies were groundless, and effective antiviral treatment has now been around since the mid-1990s, meaning that HIV infection is no longer a terminal diagnosis, so consent for HIV testing is necessary but the need and the requirement for pre-test counselling has been abolished.

Transmission of HIV is via the blood or semen or vertically from mother to fetus either transplacentally, during labour, or through breast feeding. HIV testing should therefore be offered to those patients in high-risk groups such as MSM (anal sex is particularly high risk), sex workers, and IV drug users. HIV screening is also a routine part of antenatal care. Other routes for HIV transmission are following transfusion of blood products (now routinely screened for HIV) and needle stick injuries in health care workers (very rare).

HIV testing should also be considered in less obvious situations, for example the non-specific presentation of tiredness and glandular-fever-like presentation seen with Benedetto. This is to pick up HIV at the viraemic or following on from that the seroconversion illness stage of infection. Recurrent minor illnesses such as molluscum contagiosum, shingles, herpes, and genital warts can also be used as a signal that HIV ought to be excluded as early AIDS can present like this.

Benedetto has been identified as having HIV seroconversion illness. This classically presents with pyrexia, sore throat, myalgia, lymphadenopathy, and truncal rash. These symptoms are very non-specific and it is not easy to identify HIV at this stage.

If Benedetto was left without treatment he would move from the initial viraemia through his seroconversion illness (the stage he has been identified at) over about 4 weeks, and would then progress to the quiescent phase, characterized by antibody formation, low viral loads, and a slow reduction in CD4 cells over the next 4–8 years.

Once his CD4 count was less than 200 and his viral load was increasing after this long time interval, he would then be vulnerable to minor opportunistic infections such as oral candidiasis, recurrent herpes, and the other viruses mentioned. He would then progress on to the major opportunistic infections such as TB and PCP, neurological manifestations such as neuropathy and dementia, cancer such as Kaposi’s sarcoma and lymphoma, and finally death.

The advent of HAART (highly active anti-retroviral treatment) changed the prognosis of patients with HIV dramatically, from 5–10 years to over 20 years and counting. HAART has not only reduced mortality, it has also, by reducing viral load in treated patients, reduced transmission rates. There is constant re-evaluation on when antiviral treatment should be started during the course of a patient’s infection, with some sources suggesting it should be started earlier to improve prognosis and prevent transmission. HAART is also used effectively as post-exposure prophylaxis, for example in needle stick injuries, at-risk sexual encounters, and as treatment during pregnancy, breast feeding, and for at-risk neonates.

Because HIV is an RNA virus, viral mutation is an issue; therefore, the principle of HAART is of combined treatment of up to four anti-retroviral drugs. These drugs include, the nucleoside reverse transcriptase inhibitors (NRTIs), which stop the viral RNA being transcribed to DNA, preventing its insertion into the cell’s genome, for example zidovudine (AZT) rarely
used now. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are similar. Protease inhibitors (PIs) stop the virus from budding off the cell. Fusion inhibitors (FIs) stop the virus attaching to the cell in the first place.

When using drugs for HIV, the synergistic effect of certain combinations should be considered, as should their toxicity. Patient factors, such as commitment to the regime and the need for strict adherence over many years should also be considered. Frequently used combinations of HIV drugs are available combined into one tablet, which helps with compliance.

There is at present no immunization for HIV so the continuing emphasis has to be preventing infection in the first place. As already mentioned, but repeated again here for emphasis, this is helped by having a low threshold to test for HIV. Early diagnosis, early treatment, antenatal screening, blood product screening, and post-exposure prophylaxis are all ways of reducing transmission. Advice to avoid needle sharing for IV drug users and a free needle exchange and avoiding unprotected sex, particularly in MSM and sex workers, is also vital.

**Further reading**


Kuehn BM. Reports: HIV drugs targeted for black market. *JAMA* 2014;312:1086. *Discussing patients in the USA who are doctor shopping and getting HIV drugs when they don’t necessarily have HIV to sell on to others for financial gain.*
Case 6.4

Vaginal thrush

Case example

Estelle Hanson (27) is not a patient who is worried about revealing details of genital symptoms to her doctor.

‘You see I got this itchy discharge about 2 weeks ago. And it was white like white stuff,’ she gestures and grimaces. Then her face clears. ‘But it didn’t smell. So I thought; it must be thrush! And then I got some of that canes . . . that thrush cream which helped. But then the itching came back the next time we had sex, and it was all red—down there. That was about 2 weeks ago. Do you think it could be a condom allergy?’

‘Er,’ you prevaricate. She has put you on the spot, but you are not yet willing to commit yourself. ‘I suppose it’s possible. Tell me a bit more. Is it a new partner?’

You establish that they have been together for a month. She has not had any other partners in the last 6 months. Before that she had a partner but was on the pill at that time and didn’t use condoms.

‘And what contraception have you been using with this partner?’

‘Just condoms. I tried one of the latex free ones and it was a bit better.’

‘Does the itchiness go away or stay?’

‘It’s still there, but there’s no discharge.’

You agree with her that it could well be a condom allergy but that it would be worth taking swabs to check for infection or thrush.

‘Do you want to do it yourself or shall I do the swabs?’ you ask.

‘I can do it myself can’t I? That’s what usually happens. I think I’d prefer that.’

You nod and label up the swabs and a form with a bag. The chlamydia/gonorrhoea swab first and the plain swab second.

‘This one here is for sexual infections, you know, like chlamydia. It’s not that I’ve chosen specially to do it with you, its just part of the normal batch of swabs we do for itchiness and discharge. And this one here will check for thrush and any other infections. You don’t have to put it far into the vagina, just 1–2 cm. Then put the swabs into this bag, seal it up like this, and hand it to reception.’

‘When will the results come back?’

‘About 3–4 days, say Thursday? If you ring then for the result? If you can manage with your symptoms then I suggest we wait for the result and then decide on treatments, or I can prescribe some more clotrimazole now for you.’

Estelle elects for you to prescribe it now, but will hold off using the script until Thursday.

You prescribe clotrimazole in the form of Canesten Duo®; a packet containing both a vaginal pessary and a tube of Canesten® cream.

‘It’s a pessary. Do you know?’
She shakes her head.  
‘Like a sort of tablet but you put it into the vagina. Don’t worry; it comes with instructions about exactly how to do it. Put it in at night so that you’re lying down and it doesn’t start to come out right away, and then use the cream around the vulval area for a few days as you need it. It’s pretty effective.’

‘What about having sex?’ asks Estelle.

‘It’s probably best to avoid having sex until we’ve got the result and done the treatment. If it’s thrush then it’s not a sexual infection exactly because most people will have a few yeasts on their skin and that’s quite normal. But thrush can be caused by having sex. Having sex can upset the normal friendly bacteria in the vagina and then the yeasts, the thrush, can overgrow and cause symptoms.’

She nods. Most people are familiar with the idea of friendly bacteria (maybe because of the bio-yoghurt adverts on telly).

Five days later you get her results:

Swab; self-taking low vaginal: NAAT test Chlamydia negative, Gonorrhoeae negative.

You ring Estelle on her mobile but don’t get through. You leave a brief message for her on her mobile saying that her ‘tests were positive’ and she should go ahead and take the treatment that you had prescribed.

You don’t hear anything further.

**Microbiology**

Vaginal *Candida albicans* (often known colloquially as vaginal thrush) is an example of a mucosal candida infection.  
*C. albicans* forms part of the normal flora of the human body and is routinely found on the skin, the alimentary tract, and female genitalia. However if the epithelial barrier is impaired by abrasion, or if there is a disturbance of the normal balance of flora as often happens following the use of antibiotics, then vaginal candidiasis can be seen. Vaginal candidiasis is relatively common and presents, as here with Estelle, with itchiness, soreness, and a non-smelly, thick, white discharge. Vaginal swabs can be taken and then checked under the microscope for yeast infections using a Gram stain. This can be done on the spot, which is what happens in GUM clinics enabling immediate results, or the swab can be sent to the laboratory for microscopy and culture as in the GP setting in this case (Fig. 6.4.1).

Note that patients are more and more expressing a preference to self-swab for vaginal infections, and where the sexual risk is low, as here, this is often appropriate. The advent of the NAAT (nucleic acid amplification test) test for *Chlamydia* and *Gonorrhoea* has driven this trend and made it practical. It is routine for the GUM clinic to confirm with the patient that they will text the result; however, the doctor here has left a message without confirming with the patient that it is all right to do so, although the message left is deliberately non-specific.

Although the doctor has issued a topical azole, clotrimazole in the form of the combined pessary and cream, oral therapy (fluconazole as a single 150 mg dose) is also effective and has a better compliance.
Oral and particularly oesophageal candidiasis is less common and is seen in those with an impaired or suppressed immune system. For example, patients using inhaled steroids can get oral candidiasis, as can those with diabetes, elderly people, and unwell patients with malignancy. Oral candida presents with white patches that adhere to the palate and can be scraped off leaving a bright red, raw base sometimes with bleeding. Patients with HIV or on immunosuppressant drugs are at risk for the rarer oesophageal candidiasis, diagnosed on endoscopy.

Further reading
Case 6.5

**Bacterial vaginosis**

**Case example**

‘Hello.’ You look at the patient and then back at the computer. ‘You must be Riona Sloan. Oh. We spoke didn’t we? I asked you to come in. It’s about your sore throat isn’t it?’ You look at Riona who is young (21), very slim with dark hair loose around her shoulders. She hesitates, looking down at her lap where she is pulling at her scarf tassels nervously. You recognize the look of someone forcing themselves to be frank about something very private, usually a sexual infection. You wait patiently.

‘Yes, sort of about my throat.’ There is a long pause, and she changes colour. ‘But it’s about a discharge. I’m so embarrassed, it really smells. I’ve had bact . . . That vaginosis thing before and I think it’s that.’

‘Ok,’ you say, wanting to settle her down. You change the subject for a moment to distract her and also to find out a bit more about her before asking a sexual history. ‘And what do you do? Are you studying?’

‘No!’ She draws herself up, smiling. ‘I’m a graduate you know.’ Then she says, ‘But it’s been so dreadful. I was ill with that throat infection on my graduation day ceremony, and then we straightaway went on holiday for a week to celebrate, me and my boyfriend that is, before he had to go back to the barracks (he’s in the army) and then I got this thing during the holiday and we couldn’t, you know…. It’s so embarrassing. And that was 3 weeks ago.’

‘So it’s a watery, smelly discharge?’

She nods. ‘There isn’t anyone else. We’ve been together for 3 years and before that I only knew two other partners.’

‘Ok. I think we better take some swabs so we know exactly what it is. Because before when we took the swabs there wasn’t any bacterial vaginosis, just the normal bacteria in the vagina.’ You stand up and so she stands up. You move over to the couch and draw the curtain. ‘Can you take off your lower things and tell me when you’re ready?’

You go to your trolley and pull out some gloves from the box and then find a normal swab and a chlamydia/gonorrhoea swab. Before, you would have used a speculum and have taken the chlamydia swab from the cervix for the best chance of culture. However, now the swabs are processed by PCR this isn’t necessary. The swabs don’t even have to be kept in the fridge.

Once you are ready and holding the unwrapped swabs you ask if you can come through behind the curtains. Riona is lying on her back with her legs pressed firmly together. You ask her to bend her legs so her feet are near to her bottom and then ask her to let her knees flop to each side. After explaining what you are about to do and asking permission again you proceed to take the swabs from the lower vagina. It takes less than 20 seconds and then you say thank you, and draw the curtains again so that she can get dressed in private. You put the chlamydia swab into the solution and break off the end and then screw on the lid. You push the normal swab into its growth medium, which seals it. While you are outside the curtain you say, ‘I couldn’t smell anything
right now, but I know people are often very careful with hygiene before visiting the doctor.’ Riona agrees and says she went home early from work to allow time for a shower before coming. You sit down and start to label the specimen tubes while you are waiting for her. When she comes out she draws the curtain back for you and sits down.

’Soo do you know much about bacterial vaginosis?’ you ask.

’Not much. A bit.’

’You know it’s not a sexual infection? It’s not something that you catch from a partner. But sometimes having sex can upset the normal balance of the friendly bacteria in the vagina. And then you can get an overgrowth of one particular sort.’

She nods, more settled now.

’I would think you were right and it was to do with how busy you were with graduation and everything, especially if you felt under the weather. It probably wasn’t because of the antibiotics you had before. The other thing is it’s important not to wash too much down below, just once a day is fine.’

’Yes. I read about vaginal douching. I don’t do anything like that.’

’Fine. I’ve got the treatment here for you.’ You issue her with metronidazole tablets one to be taken three times a day, for 7 days and book her in for a telephone consultation for 1 week so that you can go through the results.

Three days later you receive Riona’s results, which do confirm bacterial vaginosis.

**Microbiology**

In the mid-twentieth century it was realized that many women with an abnormal vaginal discharge did not have one of the recognized infective causes, such as candida, trichomoniasis, or gonorrhoea and so this condition was referred to as ‘non-specific vaginitis’.

In 1955 Gardner and Dukes, a microbiologist and obstetrician from Texas, noted that many women complained of a smelly discharge. They also noted the presence of ‘clue cells’ (see Fig 6.5.1) in vaginal samples from most patients (vaginal epithelial cells covered with small rod-shaped bacteria). They inferred that a small Gram-negative rod, which they named *Gardnerella vaginalis*, was somehow implicated as a cause of this condition. In fact, now there is considerable doubt about

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**Fig. 6.5.1** A photomicrograph of a normal epithelial cell and next to it a clue cell with the typical roughened stippled appearance of it being covered with bacteria.

the pathogenic role of *Gardnerella*—many women without symptoms also carry the organisms, and some treatments are effective even though they do not seem to act on this organism.

The current thinking is that this ‘infection’ is actually caused by an *imbalance* of vaginal bacteria, possibly triggered by a particular pathogenic organism (yet to be discovered), or some other non-infectious agent. A key microbiological finding is that the normal vaginal flora of predominant lactobacilli are absent or reduced and are replaced by a mixture of bacterial species, including (possibly) *Gardnerella*, coliforms, and anaerobes. Because of this, there is no simple diagnostic laboratory test, and confirming a diagnosis can be challenging.

One pragmatic approach is to look for a typical clinical presentation as with Riona, while at the same time taking a sexual history and treating blindly.

A more formal approach is to assess three aspects of the discharge: the pH of the vaginal secretions (>4.5 suggests bacterial vaginosis: normally the lactobacilli keep the environment acidic), the presence of clue cells microscopically, and the presence of a fishy odour when potassium hydroxide is added to a drop of vaginal secretions on a glass slide. These are known as Amsel’s criteria, and the presence of all three criteria is regarded as diagnostic. As this approach is laborious, it is probably more suited to a GUM or gynaecology clinic setting than in a GP surgery.

An intermediate approach, possibly more suited to a GP setting, is to send an NAAT to exclude chlamydia and gonorrhoea as here, and a vaginal swab to the Microbiology lab for microscopy and culture. If the Gram stain shows absence of the usual lactobacilli and instead a mixture of bacteria, and also clue cells, then these findings are suggestive of bacterial vaginosis. The same swab can also be used to check for the presence of trichomoniasis, or thrush.

Bacterial vaginosis typically presents with a watery, thin, grey/white discharge. The patients often complain of a fishy odour. There is seldom any pain or itch—if these are present, they suggest a different diagnosis. Although not very serious in itself, bacterial vaginosis can have serious consequences being associated with complications in pregnancy, preterm delivery and an increased risk of postoperative infections in gynaecological surgery.

The treatment for bacterial vaginosis is metronidazole, as is given to Riona. The fact that metronidazole is mainly active against anaerobes, yet *Gardnerella* is not anaerobic, is part of the evidence that *Gardnerella* is unlikely to be the sole cause of this condition.

**Further reading**

Case example

‘Hello! How can I help?’ you ask. You have Rebecca Marden (26) on the telephone, your last and seventeenth call of your phone clinic.

‘Well, I was in France recently and I saw my gynaecologist, and they did an HPV screen and said that it was positive, and that I needed to be seen here by a gynaecologist.’

‘Ah. Ok.’ You pause for a moment. You are not confident about the implications of an isolated human papilloma virus (HPV) result. You look at her name for any clues that she is from France, but can’t see any and her accent is very English. You wonder why she is seeing doctors in France and why she felt she needed to see a gynaecologist.

‘Actually they haven’t given me the whole result yet. There’s another part to come.’

‘Did they do a smear too?’ you ask.

‘Yes, they said the cells had HPV.’

This is a mixed up answer so you try again. ‘Ok. So you said the test for the wart virus is positive. Did they also do a smear to look at the cells on your cervix?’

‘Yes I think so. I’m not sure. They said something about abnormal cells. I don’t think that part of the test is back yet.’

‘Ok. And why did you see a gynaecologist? Had something happened?’

‘Oh. Yes. I had bleeding after sex this one time. The gynaecologist did an examination and said my cervix looked fine. All the swabs were normal too, like for sexual infections and he did an ultrasound and that was fine too. But because of the cells test he said I had to see a gynaecologist for follow-up.’

‘Ok. The thing is, until recently, in this country we didn’t screen for HPV. It was more or less assumed that everyone catches HPV when they first have sex. It was also known that most people then clear it naturally. But a few people don’t, and then after several years a HPV infection can cause changes to the cervical cells and that’s what we are checking for when we do smears. We do smears here for everyone, every 3 years. And just recently there has been a tentative plan to combine the tried and tested 3 yearly smear screening with HPV screening. So to decide about a referral to a gynaecologist in this country I really need a smear result as well as the HPV result.’

‘Oh. But they said I needed a gynaecological referral.’

‘It’s difficult isn’t it? I think that if you’re going with their advice and their tests you would really need to do that in France. We can certainly repeat the smear here and then you can bring in your HPV results.’ There is a pause as Rebecca digests the information. ‘What suits you better then?’ you ask. ‘Shall we wait for the full results from France and then discuss it? Or would you like to do a smear here and then we’ll see what that result shows and decide on referral once we see it?’

‘I think I’ll wait for the full report from France.’
‘Ok. So I’ll wait to hear from you and then we can decide what to do.’

‘Ok. Thank you. Goodbye.’

A few days later you find a plump envelope in your pigeonhole. Inside are three sheets of results and some letters in French with attached translations. You are impressed at Rebecca’s thoroughness. You sit down at your desk and sort the papers by date and then spread them on your desk to read them carefully.

First is a letter with the presenting complaint of a one off episode of post-coital bleeding and the (rather excessive for a single episode) plan of swabs, smear, HPV screen, and ultrasound. Next are the results. The ultrasound is normal, as Rebecca had informed you, as are the swabs.

The smear reads:

<table>
<thead>
<tr>
<th>Table 6.6.1 HPV report for Rebecca Marden</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 DNA not detected 43 not detected 39 not detected</td>
</tr>
<tr>
<td>11 not detected 16 not detected 52 detected</td>
</tr>
<tr>
<td>42 not detected 31 not detected 58 not detected</td>
</tr>
<tr>
<td>1 not detected 33 detected 59 not detected</td>
</tr>
<tr>
<td>45 not detected 66 not detected</td>
</tr>
<tr>
<td>35 not detected 68 not detected</td>
</tr>
</tbody>
</table>

You agree with the last remark. A normal smear in a 26-year-old would usually have a recommendation for a routine repeat screen in 3 years’ time.

You move on to the HPV report (Table 6.6.1).

You know HPV 16 and 18 are the high risk HPV. You are unsure of the usefulness of the other 21 different HPV checked for, or of the implication of the detected HPV 33 and 52.

You telephone microbiology to discuss it with the consultant virologist. Together you discuss the recent changes to HPV and cervical cancer screening following the successful HPV pilot study. A borderline smear now, instead of just a repeat smear in 6 months, is combined with an HPV screen. If the HPV test is negative then the usual 3-yearly screening applies. If the HPV test is positive, then instead of waiting 6 months and repeating the test, immediate referral to colposcopy is suggested. Rebecca’s results of a normal smear combined with positive HPV results don’t quite fit with the formal screening process set up in the UK, but the microbiologist advises you that there are currently 14 high-risk HPVs now identified, not just HPV 16 and 18, so you agree referral to colposcopy is the most sensible course.

Finally, you write a letter to Rebecca to ask her to ring up for a telephone appointment with you to pass on this information.
Microbiology

HPVs are non-enveloped DNA virus, approximately 50 nm in size. Testing in the context of cervical infection is done using PCR on cervical or genital swabs or combined with the endocervical sample taken for cervical screening. Usually cervical infection with HPV is asymptomatic and is only picked up on screening. As is clear from the case there are multiple serotypes. The most important of these are serotypes 16 and 18, and over 70% of cervical cancers are associated with these two. These viruses are transmitted through sexual contact and circulate at a high level in the population.

Because of the oncogenic nature of these viruses, since 2010 a three-dose HPV vaccine schedule has been introduced in the UK for girls aged 11–13, the idea being to administer it before a first sexual encounter, both to allow maximum protection from the vaccine, and to reduce the risk of developing cervical cancer. The vaccine is known to give protection for at least 6 years. For the present, the combined smear and HPV screening regime is still essential. The vaccine consists of HPV capsid protein prepared from yeast cells using recombinant DNA. The viral proteins actually self-assemble into virus-like-particles which are DNA-free empty capsids and are very immunogenic.

There is no antiviral medication for cervical warts. Condoms are recommended to reduce transmission but do not eliminate all transmission.

Further reading

www.cancerscreening.nhs.uk
Case 6.7

Genital herpes

Case example

You pick up the phone. ‘Hello, it’s the GUM registrar, Richard Leo,’ you hear. ‘Is that the on-call microbiology registrar?’ You confirm that it is. ‘Can I ask you about a lady I’m just seeing in the clinic? She’s a 27-year-old woman, Lucy Gomer, first pregnancy, now 33 weeks. She saw her GP 2 weeks ago with some genital ulceration and apparently he sent some specimens to your laboratory and sent her up here today with the positive results. She told me that the result came back as herpes simplex type 2. I’ve looked on the computer, but I can’t see the result. Can you check for me?’

Dr Leo gives you the patient’s demographic details and after a few attempts you eventually find the patient. ‘I’ve got someone here with the right date of birth, with a vulval swab result positive for HSV DNA by PCR test from 10 days ago. The surname is spelled slightly differently from what you told me. Er . . . , actually, it looks as if we entered the name in incorrectly. I’m looking at the scanned copy of the request form. Yes, this must be her. I guess you would like us to do the type specific serology? Do you think it’s a primary infection?’ you ask.

‘Well, it was quite a mild attack by all accounts. Actually the GP didn’t treat her. She says she’s never had vulval ulcers before, but has had cold sores on her lips. She and her partner have been having sex until quite recently. She says her partner’s never had genital herpes. Oh yes, I almost forgot. She said that her GP also sent some blood for serology. Has he already asked for the type specific serology? I gave a talk at that practice a few months ago about herpes simplex. Perhaps he’s doing what I advised.’

You scroll down the results for the patient and come across the blood sample taken 4 days ago.

| PCR result; herpes simplex IgG detected |

‘I’ve got a blood sample here taken 4 days ago. It did come to the lab for herpes simplex serology and it’s positive. He didn’t ask for type specific serology though, so we don’t know whether the antibody is from HSV1 given her history of cold sores, or whether she’s had HSV2 in the past or possibly both. I guess we need to get the type specific serology done as soon as we can so we can plan what to do next in terms of prophylaxis and what to do about the delivery. I’ll get the sample sent off to the reference lab. If we send it off now, we should have it back by the end of the week.’

You can hear Dr Leo talking to the patient in the background and then he comes back onto the phone. ‘That would be great. As soon as possible and then, like you say, we can make some decisions about what to do. She’s quite concerned, as you would expect. I’ll arrange a review with her later this week and contact you again then, if that’s all right. I’ll be liaising with her obstetrics team too so don’t worry about that.’ You agree to the plan and say goodbye for the present to Dr Leo, and then go to the laboratory straightaway to arrange the sample to go urgently to the reference laboratory.
One week later the results come back as follows:

\[
\begin{align*}
\text{HSV-1 antibody} & \text{ +ve} \\
\text{HSV-2 antibody} & \text{ +ve}
\end{align*}
\]

**Microbiology**

The concern here is transmission to the neonate, either during the pregnancy (congenital herpes), although this is rare, or during labour and birth (neonatal herpes), which is much more common and of greater concern. The risk depends on two factors, the pregnancy trimester and whether the infection is a primary infection or a recurrence.

Lucy Gomer, as we know, has a past history of cold sores. Cold sores and genital herpes are caused respectively by HSV-1 and HSV-2. These are enveloped ds DNA viruses of the Herpesvirus family, 120 nm in size (Fig. 6.7.1). HSV-1 is spread by droplet and saliva, often by kissing, HSV-2 by sexual contact. Over 90% of adults are seropositive for HSV-1 and the majority of infections (80%) are subclinical. Typically it is spread in childhood; incubation is 3–7 days. For HSV-2 the seroprevalence rate in adults is slightly less at 20–40%.

In those that do get symptoms like Lucy, HSV-1 causes vesicles on the lips or around the lips and nose, which then burst and become shallow ulcers, before healing over the following 1–3 weeks.

The distinctive property of HSV is that of ‘latency’ in common with other herpesviruses. This is not well understood but it is known that after primary infection the herpes simplex virus travels...
els to the root ganglia via the sensory nerve and lies dormant there; the trigeminal root ganglia if affecting the mouth, the lumbosacral dorsal root ganglia if affecting the genitals.

 Reactivation of the virus is then triggered by a minor illness such as a cold, pyrexia, or ultraviolet light, leading to prodromal symptoms around the mouth/genitals such as burning or tingling, before the vesicles form again. This is known as a recurrence. Recurrences tend to be less severe and last for less time: 5–7 days as opposed to 1–3 weeks.

 A patient may never have a primary episode but still be able to shed virus. Or they may not have a primary episode at infection, but later have a ‘recurrence’. Recurrences may never occur after a primary episode. If recurrences do occur there tends to be three or four in the first year and then less frequently over time.

 HSV-1 can cause ulcers in the genitals but this is more typical of HSV-2. Similarly HSV-2 can cause cold sores, but usually these are caused by HSV-1. Unfortunately, infection with one does not confer protection against the other; hence, the GP’s and Dr Leo’s concern about Lucy Gomer. Although she has known HSV (probably 1) from her history, this does not confer protection to her from contracting HSV-2; from the results it appears that Lucy has a primary infection of HSV-2.

 The GP in this case has taken a PCR swab of the lesion and also requested HSV serology, which is good, before referring her to the GUM clinic after a delay of 2 weeks, which is not so good. Ideally, Lucy Gomer should have been advised to go to the GUM clinic on the same day of her presentation, as genital herpes in pregnancy is a specialist subject. She needs a general sexual health screen, contact tracing and discussion of aciclovir treatment/prophylaxis, as well as symptomatic advice for the lesions such as analgesia, ice packs, local anaesthetic, and advice to avoid sex until healed.

 If she had presented in the first trimester with this primary infection, then there would have been an increased risk of stillbirth, or if the pregnancy progressed of congenital herpes. This can cause growth retardation and preterm labour. Treatment with aciclovir would be advisable.

 If she had presented less than 4 weeks before her due date with this primary infection, then this would have carried the greatest risk of neonatal herpes. Neonatal herpes is transmitted to 40% of babies if vaginal delivery is allowed; hence, a caesarean is usually advised.

 As she has presented after the first trimester, but more than 4 weeks before her due date, there is a good chance the infection will resolve and she will pass her immunity onto the fetus.

 Babies with neonatal herpes can present any time between 2 and 28 days after birth with non-specific symptoms such as lethargy, feeding difficulty, and seizures, sometimes vesicles on their face, jaundice, and hepatosplenomegaly. However, given that 80% of infections are subclinical, for most presentations of neonatal herpes there is no history of maternal infection.

 If, as we hope, Lucy Gomer has a recurrence of HSV-2 rather than a primary infection, transmission is still possible during delivery but much less likely. Oral aciclovir for 4 weeks before the delivery is then advised in this instance (and in the situation of primary infection in the first trimester or primary infection more than 4 weeks before the due date).

 It is important to note that HSV is implicated in several other presentations other than the cold sores, genital herpes, congenital herpes, and neonatal herpes already mentioned. It can cause lesions on the fingers known as herpetic whitlow, as well as widespread severe infection in people with active eczema known as eczema herpeticum, also ophthalmic herpes, encephalitis, and disseminated infection in those with immunodeficiency (particularly seen in HIV).

**Further reading**

Chapter 7

Musculoskeletal

Case 7.1  Chronic osteomyelitis  

135
**Case example**

‘Will it have to come off, doctor?’

Mr Larkin, a 60-year-old man, grins up at you from the bed, and pulls back the covers to show his badly scarred left shin, partly covered with a dressing—but behind the grin he seems worried. You have just introduced yourself and explained that you are the microbiology doctor. You tell him that the orthopaedic surgeons have asked you to see if he is suitable for home treatment with intravenous antibiotics because of the serious infection in the bone of his leg.

You think about how to respond to his question. There is a temptation to respond to a flippant joke in a like manner, but it is more useful to try to address the concerns he is obviously concealing.

‘I think it will be fine—all the metal and dead bone is out, and we are planning to give you a good long course of antibiotics to make sure all the bugs are killed. Let me ask you a few questions, and then I’ll explain what we are hoping to do with you, and how the home IV service works.’

You have already read through his voluminous medical records, and know the background. Twenty years previously he was in a traffic accident—a car skidded on ice and hit him as he was crossing the road, breaking his left tibia and fibula. The fracture took a considerable time to heal, and, eventually, he was left with a deformed and shortened leg. He coped with this, but eventually his limping gait led to damage to his hip joint, so he ended up having a hip replacement about 4 years ago. There was concern that the replacement hip might get damaged in a similar manner, and so about a year ago he was admitted for an elective correction of the tibial deformity. This involved breaking and re-setting the bone, with a metal ‘Taylor frame’ to keep the tibial fragments in place while healing occurred.

About 2 months later, the skin around the pins became a bit red and Mr Larkin was treated with antibiotics, but no swabs were sent, and it healed up. The frame was finally removed 7 months after the surgery, but since then there had been intermittent discharge of pus from the wound. The swabs grew *Staphylococcus aureus*. He was put on long courses of oral antibiotics, but 2 months later he had still not improved, and a decision was taken to operate as it was felt likely that there was deep infection. The sinus tract was excised and he was continued on long-term antibiotics—but the discharge also continued, and X-ray suggested erosion of the bone at the base of the sinus, with a possible piece of dead bone (a sequestrum), in other words, chronic osteomyelitis.

He came into the hospital a week ago for further surgery—this was a year after the first operation to correct the deformity—and a small fragment of sequestrum was removed at the base of the sinus. The sequestrum did not grow any bacteria, but this was not surprising given his prolonged antibiotics. Nonetheless, the surgeons are understandably reluctant to leave him off antibiotics, and you agree with this. After all, another relapse of bone infection might well have serious consequences: impaired mobility, and in extreme cases amputation.

You agree to the surgeon’s request for a 4-week course of intravenous antibiotics, to be given by the Outpatient Parenteral Antibiotic Treatment (OPAT) service, followed by a long course of oral
antibiotic, in the hope of finally eradicating the infection and allowing Mr Larkin to get back to normal life.

You go through the checklist for Mr Larkin. To be suitable for OPAT, he needs to be willing to go on the service, to cooperate with the nurses who come to give the daily injections, and to have a suitably clean space at home for drug preparation and administration. For these reasons, the service is not suitable for all patients, for example those who are homeless, or have very chaotic lifestyles (see Case 10.3, Leg ulcer). The patients also have to be medically stable and fit for discharge. Happily, Mr Larkin appears a very suitable candidate—he is very keen to get out of hospital, has a supportive wife and daughter at home, lives nearby (so he can easily return to hospital if any problems arise), and as a recently retired civil servant he is likely to cooperate and stick to the rules of the OPAT service. You explain the service to him—he will have a PICC (peripherally inserted central cannula) placed, and will be switched to a once-daily antibiotic (teicoplanin) for ease of administration. He will also have a pharmacy-grade fridge delivered to his house, in which to store the antibiotics. When he goes home, which you arrange for the following day, he will be visited by a nurse every day to administer the antibiotics and check up on his progress. If he wants to and is judged competent, it may even be possible to train him (or his wife) to administer the antibiotics themselves, so making it more convenient for him and less costly in nurse time. He will have blood tests weekly and will be reviewed regularly in either an OPAT or orthopaedic clinic.

Mr Larkin agrees to all of this, and you head off to arrange everything, while he phones his wife to say he will be coming home sooner than he had hoped.

**Microbiology**

Mr Larkin’s case is a good example of chronic osteomyelitis, and also of the potential of *S. aureus* to cause a serious deep-seated infection; it is also an example of the growing popularity of home antibiotic services.

Osteomyelitis can in theory involve any bone of the body; it is classically divided into acute and chronic presentations (as always in medicine, there may be some overlapping cases). Acute osteomyelitis is typically due to blood-borne spread of bacteria, and seen mostly in children, affecting the long bones—mainly the femur and tibia. *S. aureus* is the commonest cause, with *Streptococcus pneumoniae* also seen; capsulate *Haemophilus influenzae* used to be common, but is rare since vaccination was introduced.

Although in adults the source is often an infected intravenous line, the dirty syringe of a drug user, or another infection such as endocarditis, usually in children the source of the bacteria that infect the bone is seldom found, and is assumed to be some transient bloodstream infection. Interestingly, acute osteomyelitis in children, even very young, is twice as common in boys. The reason for this has never been proven, but may be due to boys’ preference for rough-and-tumble playing, with more knocks and minor trauma. Growing children’s bones are very vascular, and trauma can cause a haematoma, which may block capillaries and lead to an area of bone necrosis. This necrosis can then be infected during a bacteraemia. The commonest site for osteomyelitis in children is the metaphysis—the highly vascular growing area of bone. The infection in children usually responds to antibiotics alone (they need to be given for at least 3 weeks), but severe or late infections may need surgery also, to remove infected or necrotic tissue.

Inadequately treated acute cases may evolve into chronic osteomyelitis—but nowadays chronic osteomyelitis most often results from orthopaedic surgery (as with Mr Larkin) or from open contaminated fractures. Severe untreated cases may also develop involucra—these are areas of
abnormal new bone formation, around sinus tracts or where periosteum has been lifted by the infection. Unlike with acute osteomyelitis, the patients may be quite well, apart from the annoyance of a recurrently discharging sinus, and these infections may last for decades. If the bone is stable, this may be tolerable for the patient—but in the case of infected open fractures, the infection usually leads to non-union, and needs to be managed actively. Because the infection is protected (from antibiotics and the immune system) within the avascular area, treatment needs surgery as well as antibiotics—foreign bodies and sequestra and infected tissue may need to be removed, followed by long courses of antibiotics, possibly several months.

The need for long antibiotic courses means that these patients are commonly considered for home IV treatment, as with Mr Larkin. OPAT services have expanded a lot in recent years, and are now almost a subspecialization of microbiology or infectious diseases. OPAT is popular with patients—you only have to spend a few sleepless nights on a hospital ward to see why. It is also popular with hospital managers, and hospital doctors, as it eases pressure on their limited beds and allows them to admit more inpatients, shorten waiting lists, etc. As we saw with Mr Larkin, it is important to select and screen patients carefully—they need to be safe to go home, and willing and able to cooperate with the service. It helps if a once-daily antibiotic can be chosen, and of course it is important to check that IVs are really necessary, and no oral antibiotic options are available.

**Further reading**

Chapter 8

Eye

Case 8.1  Conjunctivitis  141
Case 8.2  Keratoconjunctivitis  144
Case example

The first thing you notice about Tamsin (7 months) is her beautiful raspberry coloured hand-knitted dress. You also notice in passing that both of her eyes are slightly pink and she has yellow discharge in the corners of her eyes. She leans against her mother, perfectly calm and relaxed.

Her mother squeezes her on her lap affectionately. 'Yes. That was knitted for her by her grandmother as soon as we knew the sex of the baby. Hence the bright colour and . . . ' she shows you one of the heart shaped buttons.

'They’re beautiful! Well. Tamsin looks very well?' This is good because it’s the end of the day and you are frankly tired. You establish that Tamsin has no cold, cough, or temperature, and no diarrhoea or vomiting. She has had pus in her eyes for 1 day. She has not had this before. With these questions you have eliminated adenoviruses and indeed most viruses from the differential. Also chlamydia infection (usually congenital symptoms from birth) and delayed opening of the eye duct.

'Well, not having any other symptoms makes it less likely to be a viral eye infection, although it still could be. But I think it reasonable to try antibiotic eye drops.'

'Yes, ok,' says her mum. 'I tried in the chemist but they only let you buy antibiotic eye drops if they are over one year, and they told me to see my GP.'

You nod and lean forward to look at Tamsin’s eyes more closely. The conjunctivas are both uniformly pink. There is no redness or swelling of the eyelid. There is pus actually on the surface of one eye, not an uncommon sight in conjunctivitis. ‘Let’s take a swab,’ you suggest. You get up to wash your hands and put on some gloves and sitting back down again, with mum holding Tamsin’s head steady, you slowly approach again and gently take a swab of the yellow pus from the corner of one eye.

You are now reasonably comfortable that this is a straightforward infectious conjunctivitis. At this stage you can slip into a partially automatic explanation.

‘Do you know about cleaning the eyes?’

‘Sort of,’ she says.

‘First of all you need to be careful about hand hygiene because eye infections are quite infectious. You can spread it by touching near her eye and then touching a surface or your own eye. So do wash your hands more than usual.’

She nods.

‘It’s ok for her to go to nursery. Although it’s quite infectious, conjunctivitis counts as a mild illness; bothersome but ok to mix with other children.’ You pause. ‘Sometimes nurseries have their own rules so probably best to check.’

‘Ok.’

‘So cleaning the eye. You need to wash your hands. Then get some water that has been boiled up in the kettle and then left to cool down. Then it’s sterile. Then use cotton wool balls, a new one
each time. Dip them into the water, clean the eye and then discard each time.’ You pause again to make sure you have her attention. ‘It’s quite good to take some water and cotton wool in a sterilized container out and about with you. It’s so tempting when you’re out to quickly swipe the eye with whatever you’ve got to hand.’

She nods again.

‘So we could get rid of the infection just by cleaning. That’s what they used to do in the old days before antibiotics. Sometimes infections get better very quickly that way, within a day or two. You could just try cleaning for 24 hours before starting the antibiotics, to see if it will go away by itself. Or you could start antibiotics tonight. Either option is reasonable. Sometimes it’s nice to avoid antibiotics, the kids don’t like the drops either.’

‘So wait 24 hours?’

‘Yes. I think that might be worthwhile.’

You turn to the computer and print off a script for chloramphenicol eye drops: one drop, four times a day for 7 days and hand it over. Tamsin’s mum stands up holding her around her middle facing outward, and holds the pram with the other hand.

‘Well thank you for seeing us last minute. Have you got any more patients to see?’

‘No. You’re the last one today. Thank you, see you soon.’ You wave goodbye.

The swab result comes back 3 days later.

<table>
<thead>
<tr>
<th>Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scanty growth of \textit{Haemophilus influenzae}</td>
</tr>
<tr>
<td>Fusidic acid (Resistant)</td>
</tr>
<tr>
<td>Amoxicillin (Sensitive)</td>
</tr>
<tr>
<td>Chloramphenicol (Sensitive)</td>
</tr>
</tbody>
</table>

Your instincts were correct; it was a bacterial infection.

**Microbiology**

There are many infectious and viral causes of conjunctivitis, for viral causes see Case 8.2, Keratoconjunctivitis; common bacterial causes include \textit{Haemophilus influenzae} (as in this case), \textit{Streptococcus pneumoniae}, \textit{Staphylococcus aureus}, and \textit{Streptococcus pyogenes}; rarer but important causes include \textit{Chlamydia trachomatis} and \textit{Neisseria gonorrhoeae}, especially in neonates. This discussion will focus on the important organism \textit{H. influenzae}.

\textit{H. influenzae} was first described by Pfeiffer in 1892—he claimed it was the cause of influenza, hence the name; this claim has long since been disproved, but the name persists. The first part of the name comes from its need for extra nutrients for growth, which can be obtained from blood cells, hence ‘haem’ and ‘philus’—‘blood-loving’ in Greek (Fig. 8.1.1).

There are other species of \textit{Haemophilus} too, including \textit{H. parainfluenzae}, which is similar but less virulent than \textit{H. influenzae}, \textit{H. haemolyticus}, which causes URTI and LRTI and \textit{H. ducreyi}, which causes chancroid (see Case 6.7, Genital herpes).

\textit{H. influenzae} is a small (0.1 × 0.3 µm) Gram-negative rod which produces greyish colonies (with a strong smell) on chocolate agar (Fig. 8.1.1). Chocolate agar is a brown coloured agar containing haemolysed red blood cells (no chocolate is contained unfortunately). Haemolysing the red blood cells releases the same chemicals (haemia and nicotinamide)
that are equivalent to the special nutrients that *Haemophilus* species need to thrive, known as X and V factors.

Molecular or advanced biochemical testing such as MALDI-TOF is being increasingly used to differentiate *H. influenzae* from the other species of *Haemophilus*, but many laboratories still use the more traditional method of X- and V-factor dependence to differentiate them. This test is done by culturing the suspect colonies on nutrient agar, and adding three filter paper discs: one with X-factor, one with V-factor and one with both. If the organism needs both factors, there will only be growth around the combined disc and it is likely to be *H. influenzae*. If it needs only one factor it may be another *Haemophilus* sp. and if neither, there will be growth all over the plate, and it is probably not a *Haemophilus*.

Two forms of *H. influenza* have to be further differentiated by the laboratory: capsulate and non-capsulate. The capsulate forms are the invasive species and account for the more severe infectious illnesses, the capsule helping the organism invade tissues and avoid phagocytosis. Capsulate strains are further divided by serological tests into different capsular (sub)types a, b, c, d, e, and f. The most common capsulate strain is type b, *H. influenzae* b, and the Hib vaccine is designed to target this strain.

The *non*-capsulated form is much commoner and is not protected for by the Hib vaccine. It is a less harmful organism and tends to cause conjunctivitis, as with Tamsin, also otitis media, sinusitis, and exacerbating COPD. It is commonly carried in the nose and throat and is spread by droplet transmission.

Before the Hib vaccine was introduced in 1992 in the UK, the capsulated *H. influenzae* b accounted for the majority of cases of meningitis in children under 2 with a very high mortality rate. It also caused epiglottitis and neonatal sepsis, and in adults septic arthritis, pneumonia, and cellulitis. Following the introduction of the Hib vaccine, notifications dropped from 892 per year in the UK to 37 in 1998, and in the last 5 years there have been only 12 confirmed cases of *H. influenzae*.

**Further reading**

Case 8.2

Keratoconjunctivitis

Case example

The notation next to the patient’s name you have just buzzed for says *fat in eye*. This sounds strange. But you assume it to mean *hot fat* in eye. Now it sounds a bit intimidating and you wonder what you would do with someone with hot fat in their eye.

At this point there is a tap on the door and two large ladies come in, one of whom is, presumably, your patient, Marcel Bennoi (54).

This, the older of the two ladies, clearly has an eye problem. In fact she has two red eyes. She has neatly parted, brown hair and a headscarf tied around her head. You focus your attention on her and smile and introduce yourself as she sits down. She smiles and seems to understand but doesn’t say anything.

The other lady sits next to her. ‘I am here to translate for her. I am her friend!’ she says loudly and enthusiastically.

‘Thank you so much for coming,’ you say sincerely. Having a translator with the patient is a relief. It makes the consultation easier and quicker and more effective. ‘Where are you from?’

‘We are Spanish. My friend here is working in McDonald’s.’ As you draw breath in order to take a history from the patient, she rushes on saying, ‘I will explain, as I know the story. So. This was 3 days ago! My friend was working at McDonald’s and she splashed hot oil into her eye.’

‘Which eye?’

‘The . . . left. This one.’ They both point at Marcel’s left eye.

Now you look more closely as she rolls her eyes to the left. There is a roughly oval red patch on the nasal side of the left eye, on the conjunctiva, 4 mm across. This is the less red eye of the two.

‘What did she do then?’ you ask.

‘She washed it with cold water. Then the next day it was very sore so she went to the hospital. A-&-E,’ she enunciates clearly. ‘They looked at her eye and say she very lucky; not on black bit.’

You nod, agreeing how lucky it was that the cornea was spared. ‘What about the other eye?’

‘Then, that night her other eye gots red.’

‘Oh. Did they look at the other eye at the hospital?’

‘Yes. They looked. They say it is good. No fat. Then that night it gots red.’

You look now at the other eye, which has that distinctive look of severe infection, not just an ordinary conjunctivitis. This eye has a dull surface all over, somewhat discoloured or yellowish as well as being red, oedematous but with no obvious pus. Marcel blinks slowly.

‘Is it painful? Itchy?’

Her friend translates but Marcel is already nodding. She understands better than she can speak. Her friend translates, ‘Eye is very painful and itchy.’
Having examined the eye, your mind jumps straight on from painful eye and eye looks dull and oedematous to urgent referral ophthalmology. You suspect keratoconjunctivitis, possibly caught from the eye examination equipment at the hospital.

The local hospital has a walk-in eye clinic and you briskly type up your notes and print off a letter. You ask Marcel and her friend to attend the hospital first thing in the morning. You also print off a script for chloramphenicol.

Marcel and her friend are not keen to spend yet another day at a health clinic. This prompts you to explain properly. ‘I am worried this is an infection, maybe from the eye equipment at the hospital. This could be a bad infection. The hospital eye specialists need to check you and give you proper treatment. It might not be this infection, but it needs checking.’ They both nod solemnly and then laboriously get to their feet, Marcel holding your letter and script, and gather their coats up in a big armful.

‘Thank you doctor,’ Marcel speaks for herself as she leaves.

**Microbiology**

Conjunctivitis (inflammation of the conjunctiva) can have all sorts of infective and non-infective causes. Non-infective causes include, most commonly contact lens wear, trauma, foreign bodies, and inflammatory conditions such as blepharitis, rosacea, and Sjögren’s. Certain drugs can cause dryness (timolol), or sensitivity (preservatives in eye drops).

Infective causes include viral, bacterial (see Case 8.1, Conjunctivitis) and also protozoan parasites such as acanthamoeba.

The key microbe here is one of the adenoviruses, but other viral causes include herpes simplex, varicella zoster, and measles. Adenoviruses are non-enveloped icosahedral DNA viruses about 80 nm in size, of which there are over 50 types.

Different adenoviruses cause different types of infection including respiratory tract infections (see Case 3.8, Viral pneumonia, for further discussion of adenoviruses), gastroenteritis, and others. Adenoviruses also affect birds and reptiles as well as mammals but each adenovirus typically stays within one species.

Adenoviruses 8, 19, and 37 can cause keratoconjunctivitis and are transmitted by close contact. For example, virus from an infected eye can get on hands or fomites. When spread in a clinical setting the virus can be transferred to tonometers, slit lamps, and other eye examination equipment, including the clinician’s hands. From here it is then spread directly on to the next patient’s eye leading to epidemic keratoconjunctivitis.

Epidemic keratoconjunctivitis is not notifiable. However, diagnostic laboratories in the UK have a duty to report all significant laboratory results to the relevant public health body. This used to be known as the Health Protection Agency (HPA), but is now known in England as Public Health England. Mostly notification is done automatically by sending an electronic copy of the report. Sometimes a cluster of cases is noted in a health care setting resulting in an outbreak investigation, usually late in the outbreak. Not all cases in a cluster will have had contact with the clinic; approximately 50% of infections will have been passed on and then caught in the community. Diagnosis is usually clinical or done using PCR; however, in the event of an outbreak or for research purposes; it may be preferable to isolate the virus using cell culture (Box 8.2.1).

Having identified an outbreak and characterized the virus involved, infection control measures are then needed. This might include temporarily closing a unit for intensive cleaning. Additionally, discarding re-usable eye drop vials, reprocessing of tonometers, dedicating an examination room to conjunctivitis patients, disinfecting examination room surfaces between patients, and improved staff hand hygiene and glove use. Control of outbreaks is difficult because
of prolonged shedding of virus by patients (up to several weeks after symptoms have gone) and the resistance of the virus to desiccation. The virus can remain viable on disinfected surfaces for over 10 days.

With regard to treatment, in fact there is no antiviral medication for this eye infection. Treatment is simply supportive and includes topical steroids, eye lubricants, and sometimes aciclovir or antibiotic eye drops. Complications can include corneal scarring and reduced vision with some patients needing long-term steroids. In three recent documented outbreaks, 20–50% of patients developed corneal erosions and associated reduced visual acuity.

Further reading

Chapter 9

Ear, nose, and throat

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Case 9.1

Cold/rhinitis

Case example

It is an extremely busy day. One doctor is off sick, the locum has cancelled because of family issues and another doctor is on leave. It is also the week before Christmas and there is flu circulating.

You crack on through the patients. All the patients needing routine reviews for hypertension, asthma, etc., are saving themselves until after Christmas. So almost everyone you see has an acute illness. In fact, it’s got so that if someone comes in who doesn’t have a cough you start to feel a bit confused.

Your next patient is 5-year-old François with ‘cough’. He comes in with his mother, who says hello with an accent. Also present are his two siblings and his grandmother who nods and murmurs a greeting in French.

He looks very well, lively, bouncing on your weighing machine just for fun, until you pick it up and put it on the desk out of the way.

You dash through the history. Cough? 1 week. No raised temperature, eating fine, other symptoms: runny nose, slight sore throat, ears fine.

You beckon him over; he is skittish but agrees after a French aside from his mother. He lets you listen to his chest. You also take his temperature and rapidly check his ears and throat. All is clear; his temperature is 36.7.

‘I think François has a mild viral cough. Children usually have a temperature for 3–5 days and a runny nose and sometimes a sore throat or sore ears but he is clearly coping very well with it. So we are safe to watch and wait for him to get better. He doesn’t need antibiotics. If he does get another temperature then feel free to call back but I don’t think that will happen. I think he will just get better.’

The mum looks a bit put out, however; you smile and say in a suggestive we-are-now-finished kind of way, ‘Ok. Thank you.’

There is a pause while you wonder why she doesn’t get out of the chair and leave.

Instead she pulls over Antoine, her 3-year-old daughter and says, ‘Antoine has an appointment with you too and the receptionist said you would see them together.’

Paging down the screen you find Antoine booked for in 40 minutes time. But obviously you bring up her notes and agree to see her now.

Antoine has had a sore ear for one night. Again you run through the history. Temperature? Off food? Other symptoms? Since Antoine has only had symptoms for 12 hours, there is not much to conclude. But resigned, you go through your routine. Temperature 36.7, throat fine, chest clear, both ears pink, snotty nose. Upper respiratory infection, viral again. ‘I think Antoine also has a mild viral illness like a cold, perhaps caught from François. But again she looks very well and both ears look fine. So it’s safe to wait for her own immune system to fight it off. She doesn’t need antibiotics. Make sure she is drinking and give paracetamol if she needs it; ears can be very painful.'
She may have a temperature for 3–5 days as I said before. If she gets a discharge from the ear or is up all night then do bring her back. But she should just get better by herself.

Even you feel a bit bored by your repetitive speeches.

Then the mother takes the 9-month-old baby Jacques off the grandmother’s lap and says, ‘They said you would see Jacques as well although he doesn’t have an appointment.’

Your face goes stiff with repressed frustration. Even the grandmother shrugs and looks at the ceiling.

So for the third time you run through the history with the mother. By now you are starting to feel that with the old adage ‘See one, do one, teach one,’ she should be able to do it herself by now.

Jacques has had a temperature for 2 days and a cough. His appetite is fine. His ears are fine, temperature fine, throat fine, chest clear. This time because he is a baby you count his respiratory rate: 36. No respiratory distress.

You start to go through the viral cold advice again and your voice peters out. You just can’t bear to say all the same things again.

The mother gets the message that all three children have colds. She gathers up her things and the baby abruptly, clearly annoyed; perhaps she is fed up about the lack of forthcoming prescriptions. The grandmother is last out of the door and gives you a wry smile and a nod as she leaves.

**Microbiology**

These three children almost certainly have the same illness starting with François (aged 5) 1 week ago (cough) perhaps caught from school, then Jacques (aged 9 months) 2 days ago (cough), and then Antoine (aged 3) 1 day ago (ear).

The illness is likely to be viral, firstly because it is causing mild symptoms, and secondly because each child has multiple symptoms including runny nose, sore throat, sore ear, and cough. These are sometimes collectively known as upper respiratory tract infections (URTIs).

Each child has slightly different symptoms and this is also typical of these viruses. Symptoms vary according to the person’s immune reaction and also their age.

Common viral causes for colds and URTI include *rhinovirus* and *coronavirus*; both of which we will discuss here. Others include adenoviruses, influenza, parainfluenza, and respiratory syncytial virus.

*Rhinoviruses* in fact cause the majority of common colds. Three species, human rhinovirus A, B, and C are now recognized. There are over 100 serotypes, which explains why most adults get one to three infections a year. They are icosahedral ss RNA viruses, about 18–30 nm in size.

They are transmitted by aerosol, that is very fine droplets formed when the patient sneezes, and are then breathed into the nose by the next person. If not breathed in, the virus may be airborne for several hours before coming to rest on surfaces and other fomites. There they can be picked up on a hand and wiped onto the nose. Rhinoviruses are very infectious.

Incubation is 2–3 days and patients are infectious while symptoms are present, usually about 1 week.

Viral swabs of the naso-pharynx or pharynx can be taken and the virus can be cultured but in practice this is rarely done as the clinical illness is mild and self-limiting. The virus, if it is to be cultured, is grown at cooler temperature (33°C) which reflects the fact that it has adapted to the cooler airway, the nose.

In general practice it would rarely be necessary to obtain specimens from patients with colds. However, it has become increasingly recognized that rhinoviruses may cause more severe disease
including lower respiratory tract infections such as bronchiolitis and pneumonia. Very severe
disease may be seen in immunocompromised patients. Rapid diagnosis in hospitalized patients
can be made by utilizing real time PCR of nose and throat swabs. Tests for rhinoviruses are often
included in a multiplex PCR, when specimens can be tested for a large variety of respiratory
viruses (also discussed in Case 3.8, Viral pneumonia).

**Coronavirus** is another key microbe causing colds. These viruses account for approximately
10% of common colds. They are large ss RNA viruses, 220 nm in size and have club-shaped gly-
coprotein spikes sticking through their lipid bilayer, giving the virus a crown-like appearance: hence its name.

There are several species of coronavirus, grouped in four different genera. Some of these infect
humans and there are at least 15 others that can cause infections in birds and mammals. Like
rhinoviruses, coronaviruses are also transmitted by aerosol and droplet formation.

Viral swabs for coronaviruses can also be taken from the naso-pharynx; however, coronaviruses-
es are difficult to culture because they need to be grown in human embryo tracheal cells. Again,
diagnosis is usually made by PCR of a respiratory specimen. The newly emerged viral illnesses
SARS and MERS are both caused by coronaviruses with a different, more sinister clinical picture
(see Case 13.3, Middle East respiratory syndrome).

Various experimental antiviral medications have been trialled for the common cold but none
are in common use. Research on vaccines has not yet gone beyond laboratory studies.

Putting the hand or elbow up in front of the mouth when sneezing reduces aerosol transmis-
sion and washing the hands afterwards reduces fomite transmission.

**Further reading**

Sklansky M, Nadkarni N, Ramirez-Avila L. Banning the handshake from the health care setting. *JAMA*
Case example

Stacey Walker (15) walks in and sits down, putting her phone away as she does so. She pulls out her ear phones from her ears and winds the wire around her fingers looking tired and miserable as she waits for you to shut the door behind her and sit down.

‘It’s a sore throat. I’ve been off school for 2 days and I can’t eat. I feel really dreadful. My mum said she would come here with me but she’s late from work. She got me this appointment this morning, but I’ve been on my own all day . . . and then I noticed this weird rash thing on my face and all over my body. I’ve got a headache too.’

She sits there tiredly and you look at her face noticing confluent smooth redness all over her cheeks and face but not around her mouth. You lean forward and ask to look at her tongue, which is white looking. ‘Let me just get my torch,’ you say.

She opens her mouth and lets you shine a torch onto her tonsils, where you see they are both swollen, red, and enlarged but with no pus beds visible. You also feel her cervical glands, which are palpable but not massive. Her temperature is 38.2.

‘Are you drinking all right?’ you ask.

‘Kind of ok. I can drink, just don’t feel like it.’

She rolls up her sleeves and shows you the rash elsewhere on her body. With a fingertip you feel the distinctive raised texture of the rash. It feels like sandpaper.

The enlarged tonsils, lymphadenopathy, and particularly the sandpapery peripheral rash, plus her systemic symptoms of pyrexia, combine in your mind to form the conclusion: not just bacterial tonsillitis, but scarlet fever, which is bacterial tonsillitis with a rash. This is interesting, as you saw another one yesterday—and your colleague also saw one earlier this morning. You haven’t seen a scarlet fever for 2 years.

You take a swab from her tonsils and also arrange a blood test for FBC, LFT, U&E, and ASO titre and monospot to exclude EBV (and of course request HIV at the same time). You then give advice for a tonsillitis throat (fluids, analgesia, rest, and antibiotics). Her mum comes in half way through this, full of concern for Stacey, and sorry that she is late, so you go over things again and explain what tests you have requested.

You also advise that she should come back if she gets any further rash or any new symptoms such as joint pains or funny coloured urine, or if she feels worse, rather than better. You say you don’t think that she will get these symptoms, it’s ‘just in case’ advice, and that you have put her on the right treatment and you expect her to simply gradually get better. You advise about school as well. She should be off school until she has been temperature free for 2 days and is feeling back to normal.

Her results come back as follows:

**FBC:** Total white cell count: $13.6 \times 10^9$ (4.00–11.00)

**Red blood cell count:** $4.44 \times 10^{12}$ (3.95–5.15)
The bloods confirm a bacterial infection and the throat swab a streptococcal throat, consistent with scarlet fever. You do not need to act further as you have treated her in anticipation of this diagnosis with 10 days of penicillin and given her safety net advice.

**Microbiology**

*Streptococcus pyogenes* (see Fig. 9.2.1) is an A-list celebrity among the bacteria, because it causes a diverse range of infections, some very common, some very serious, and some both. It is also commonly known as Group A strep (see Case 12.2, Post-miscarriage infection, for a discussion of the general classification of the streptococci).

The commonest presenting illness is tonsillitis—and Group A strep is the commonest cause (sometimes Groups C and G streps also cause this infection). It is usually seen in children of school age, spread by saliva, by shared drinks or toys or by respiratory droplets. Patients typically have a sore throat and a high fever, and feel systemically unwell; the tonsils and pharynx are red and possibly swollen, and may have an overlying exudate; the cervical nodes may be enlarged. While patients with tonsillitis are typically more ill than those with viral infections, there is a lot of overlap, and in practice it is not easy to distinguish the two reliably. Bacterial tonsillitis does resolve without treatment—but penicillin antibiotics speed recovery and patients usually feel a lot better within 48 hours.

Group A strep tonsillitis (and other Group A strep infections) can be complicated by scarlet fever (scarlatina), as has happened here with Stacey. This is characterized by a generalized rash, usually erythematous and blanching, with occasional petechiae. On the face the forehead and cheeks are affected, sparing the area around the mouth—which looks pale in contrast—this is known as ‘circumoral pallor’. The tongue can also be affected, going first white (known as ‘white strawberry’), and then bright red (known as ‘red strawberry’). Sandpaper-like skin is also sometimes seen, as here, due to sweat gland obstruction. The rash comes on a day or two after the onset of the pharyngitis and fades after a week or so, sometimes followed by peeling of the skin.

Important differentials are rashes due to viruses and also to drugs—especially if antibiotics have been accidentally given to someone who actually has a glandular fever infection (Case 9.4, Glandular fever) and not a tonsillitis (both can present with pus on the tonsils).
Stacey has had swabs and bloods taken; however the doctor should not be waiting for these results before informing public health of Stacey’s illness (and the two other scarlet fever patients mentioned) as this is a notifiable illness.

The ASO blood test mentioned in the case, measures antibody levels to streptolysin O (one of the proteins that lyse red cells)—known as the anti-streptolysin. As with Stacey, the levels may actually be normal in a confirmed Group A strep infection, if measured too early. In this case, the patient has been ill for a few days only, so has probably not yet developed an immune response.

Fortunately, given the seriousness of many of these infections, Group A streps remain penicillin sensitive, so these antibiotics can safely be used for treatment, even before sensitivity results are available.

In the past, a Group A strep infection was a much more severe illness, accounting for many childhood deaths in the nineteenth century (for example, Beth in the well-known novel Little Women by Louisa M. Alcott). The production of a specific toxin—the streptococcal pyogenic exotoxin—by some strains accounts for this.

There are many other presentations of Group A strep infection. It causes a variety of skin infections, including superficial pyoderma (involving the dermis only), erysipelas (a localized area of cellulitis with a very distinct edge) and cellulitis (infection involving the skin and subcutaneous fat and connective tissue).

One feared presentation—thankfully very rare nowadays—is seen in postnatal patients, who develop an endometrial infection with Group A strep. This is known as puerperal sepsis (see also Case 12.2, Post-miscarriage infection). It was the high prevalence of puerperal sepsis, often fatal, in nineteenth-century Vienna that alerted the Hungarian obstetrician Semmelweiss to the role of doctors’ hands in spreading infection in hospitals and the importance of hand washing in order to prevent this. As a result, he is often regarded as the ‘father of infection control’.

As well as ‘direct’ infections and toxin-mediated illness, Group A streps can also cause a range of illnesses mediated by the immune system. After an infection, the body will develop antibodies to the bacterial strain involved—but sometimes these antibodies cross-react with host tissues, and attack them. Such illnesses are known as post-streptococcal sequelae, and include post-strep glomerulonephritis and rheumatic fever.

Rheumatic fever is a generalized illness that often starts with polyarthritis and fever. The patient may develop an unusual rash on the trunk with migrating serpiginous (snake-like)—i.e. wavy) edges and they may also develop subcutaneous nodules. The heart is commonly involved, with carditis, but this is often clinically silent and only detectable by a doctor hearing a murmur or picking up a heart block. Repeated attacks may result in permanent heart damage, with valvular lesions leading to heart failure and a greater risk of infective endocarditis. Late in the illness—sometimes after everything else has resolved, and sometimes as the only finding—the patient may develop Sydenham’s chorea, a strange illness involving emotional lability and uncontrolled writhing movements of the limbs, which may take months to resolve.

Further reading

Case example

You are doing your weekly clinical sessions at a residential home. It’s a well-managed home and there is always a nurse (Rachel) who sits with you throughout the appointments. You like Rachel. She sorts out the computer when it crashes, and she makes a note of any decisions to act on later. She is outside the room right now, bringing in the next, very elderly patient, while you read your own notes.

David Carpenter is 93. You can’t remember anything about him, even when he hobbles in on Rachel’s arm. He is quite tall and thin and sits down very slowly by holding on to your desk. He straightens his trousers over his knees methodically, while he looks expectantly at you, smiling and doddering slightly.

Your notes say

Reason for contact: Discharge from ear. Planning new hearing aid but needs infection cleared before can take mould of ear.

Examination: Wet discharge left ear, right one fine. Plan: swab, eardrops, modify antibiotics when get ear swab back.

Dementia screen requested; FBC, U&E, LFT, ESR, glucose, calcium, phosphate, TFT, Vitamin B12, folate, syphilis, CXR, CT head scan, urine culture.

David Carpenter’s story springs back into your mind all complete; the really, really mucky yellow ear. You check the swab results:


‘Did he get the trimethoprim tablets all right?’ you ask Rachel as an aside. She nods as David says, ‘WHAT WAS THAT?’

‘HOW IS YOUR EAR?’ you ask. David looks questioningly at Rachel who says, ‘Your ear?’ without even raising her voice. He hears her instantly though.

‘It’s fine doctor,’ he says to you.

‘Can I have a look?’ you ask pointing at it.

David nods and slowly reaches up to his left ear, rummages around and deposits his hearing aid on your desk, quite close to your mouse pad.

You wince as you pull on your gloves, because you remember the ear’s previous appearance, and when you look at it again it looks just as sticky and green/yellow as before, with the discharge at
the ear canal opening dribbling into the external ear. Actually, this time it is a slightly different shade; a distinctive bright sea green colour. You take another swab. You then remove your gloves and wash your hands.

‘He needs to keep the hearing aid out or he’ll never clear the infection. And he needs to have the ear cleaned each day. Will that be possible?’

Rachel nods scribbling busily as David reaches for his moist hearing aid and puts it carefully back in. Then he gets up slowly, putting the same hand on your desk to lever himself up, and you stand up too and say good bye and thank you.

You sit back down and turn to the computer, and then stop and wipe down the desk and the chair handles with wet wipes.

You write:

_Ear drops and oral antibiotics not helped much. Kept hearing aid out for 1 week, frustrating for patient. Plan: repeat antibiotics, try gentamicin ear drops, use indefinitely, i.e. 1 m, clean hearing aid daily._

Later on that month Mr Carpenter’s CT head result comes back, which says,

_Marked mucosal induration toward the mastoid air cells on the left and the epitympanic recess. Appearances may be in part due to past surgical changes, this requires clinical correlation. Acute-on-chronic infective, inflammatory changes may be present._

Could this be mastoiditis? Your second swab grows _Pseudomonas aeruginosa_, which is what you suspected from that green discharge. You refer to ENT, who send back the following letter.

_Dear Colleague_

_Thank you for referring David who was complaining of discharge from the left ear._

_On examination he was found to have had a mastoidectomy done some 40–50 years ago. Today the left mastoid cavity was thoroughly cleaned out. I have insufflated boric acid and iodine powder in the ear to dry it out._

_An audiogram was done which showed severe deafness in both ears and a hearing aid in either ear is totally useless and only causes condensation of moisture. He needs to keep the left ear absolutely dry._

_I would be happy to review if further concerns arise._

_Many thanks,_

**Microbiology**

This case shows the practical difficulty in managing ear infections and interpreting ear cultures, as well as showing one of the many situations in which _Pseudomonas_ may cause problems.

When faced with a patient who has a painful and/or discharging ear, there are a number of things to remember. The ear canal is lined with skin as elsewhere, and has a normal flora of staphs (mainly _Staphylococcus epidermidis_) and corynebacteria, but it is narrow and prone to blockage by oedema/pus/earwax, etc., meaning that pressure cannot be relieved (making the pain worse)
and also that eardrops may not get in. While a blocked ear canal is likely to lead to pain and possibly infection, earwax itself is beneficial, and trying to remove it is likely to do more harm than good, especially if cotton buds or other objects are used—they usually push the wax further in, and may damage the thin skin and leave it open to infection. The skin of the eardrum actually grows outwards very slowly (about the speed your fingernails grow) and eventually it will bring wax and everything else out on its own.

Pain and discharge may indicate an external ear infection—otitis externa (OE)—but may also indicate a middle ear infection—otitis media (OM)—with a perforated eardrum.

There are different syndromes of otitis externa, and understanding them helps make sense of the confusing microbiology results you may get. The first is acute localised otitis externa—this is usually due to a *S. aureus* and can follow on from a boil or folliculitis, or to *S. pyogenes*, which can also cause cellulitis and erysipelas, and then spread to the ear. This condition may need systemic antibiotics.

More generalized otitis externa, acute diffuse otitis externa, seen here with Mr Carpenter, is often due to *Pseudomonas*, and may be a result of entry of *Pseudomonas* into the ear canal from swimming or bathing in unchlorinated warm freshwater. If the skin of the ear canal is damaged, the chance of infection is greater.

A feared complication of *Pseudomonas* ear infection is the much more severe malignant otitis externa. This is malignant in the sense of virulent and invasive, rather than cancerous. This is seen mainly in elderly diabetic patients or the immunocompromised. The infection spreads into surrounding tissues and bone, and may involve the mastoid air cells, and may even penetrate the skull and cause meningitis or brain abscess; involvement of the skull may also lead to cranial nerve damage and palsy.

Acute diffuse otitis externa usually responds to gentle cleaning of the ear canal, with eardrops containing anti-pseudomonal antibiotics (usually either an aminoglycoside such as gentamicin, or a quinolone such as ofloxacin, or colistin antibiotic such as polymixin) combined with steroids to reduce inflammation. If treatment is inadequate, or if the patient continues to damage the ear canal (or does not let it dry out, as in the case here, where the hearing aid possibly exacerbated the infection), the infection may persist and develop into chronic otitis externa. In this situation, the ear canal becomes colonized by various other microorganisms including different Gram-negative Enterobacteriaceae (‘Coliforms’), or possibly yeasts or moulds. Chronic otitis externa may also result from a persisting middle ear infection, with pus being discharged through a perforated eardrum. Swabs from these patients are also prone to grow a mixture of different bacteria or occasionally fungi. Clinically, the two situations are hard to distinguish, unless the eardrum is visualized, or the skull and ear are imaged radiologically.

A worrying complication of ear infections is mastoiditis. The mastoid air cells communicate with the middle ear, and can be infected following acute or chronic otitis media. They can also be infected as part of a spreading malignant otitis externa. Mastoiditis in adults tends to be more serious and may require surgical intervention, as in the case of Mr Carpenter. Clinically the infection is similar to acute otitis media, with pain, fever and possibly ear discharge, but there may also be tenderness and swelling over the mastoid bone, and untreated cases may spread (as with malignant otitis externa) to involve the brain.

*P. aeruginosa*, the diagnosis here, is a key microbe involved both in acute and chronic ear infections. *Pseudomonas* is a group of Gram-negative rods, 0.5 × 0.8 μm in size (Fig. 9.3.1), most of which live in the environment—in the soil, in/on plants and animals, or in water. They all need a moist environment to thrive, and don’t withstand drying.

The main pathogenic species is *P. aeruginosa*, but there are many others. Most non-aeruginosa species are less virulent, but still capable of causing infections given the right opportunity—an
immunodeficient host, or a foreign body, or damaged skin or organs. As well as the ear infections described already, *Pseudomonas* can cause pneumonia in hospitalized patients, chronic chest infections in bronchiectasis and cystic fibrosis, and urinary tract infections in patients with urological abnormalities. Cancer patients may also develop a particular form of bacteraemia, with discrete areas of skin necrosis known as ecthyma gangrenosum. It can also infect (or colonize) areas of abnormal skin such as wounds and ulcers (see Case 10.3, Leg ulcer)—or damaged ears as in this particular case.

*Pseudomonas* is fairly easy to identify in the laboratory. It grows vigorously on most laboratory media; it often has a typical metallic blue-green colour (due to pigment production—the same pigment sometimes makes *Pseudomonas* infections very obvious). Unlike the coliform bacteria, it is **oxidase positive**—i.e. it possesses the cytochrome oxidase enzyme, which enables it to use oxygen (or other molecules) as an electron acceptor. This can be tested in a matter of seconds by smearing a colony of bacteria onto filter paper impregnated with a redox indicator, which changes colour when oxidized. Following, this, of course, more sophisticated biochemical tests need to be carried out to identify the precise species. Antibiotic testing is also important—*Pseudomonas* is nearly always resistant to many commonly used antibiotics, but is still usually sensitive to aminoglycosides such as the gentamicin drops used here, also quinolones, anti-pseudomonal penicillins such as piperacillin, and some later cephalosporins (ceftazidime, but not cefotaxime).

**Further reading**

Case 9.4

Glandular fever

Case example

‘Hello,’ you say to the 19-year-old patient opposite you. You confirm her name. ‘Natalie Jarad isn’t it. Is it about your throat?’ She nods. ‘I think you saw my colleague last week? You’d had a sore throat for 4 days, she put you on 7 days of penicillin for a tonsillitis. Have I got that right?’

‘Yes’, she says. ‘But she made this appointment for me in case I didn’t get better. She thought I might have glandular fever because of this,’ and she points to her neck.

Now you look at her, she does seem to be looking at you rather quizzically. She is not confused about something you have said; she has a swelling in her left anterior triangle. It is a large cervical lymph node, visible from where you are sitting. You don’t even need to palpate it to know how big it is.

However, you do ask if you can examine it and she nods. You stand behind her and position her head so she is looking very slightly down. You gently feel both sides of her neck at once, so that you can compare the swellings on each side. With your left hand you palpate a 5 cm × 2 cm oval swelling, firm, not fluctuant, and not fixed. The skin overlying it is smooth and mobile.

When palpating this lesion with your fingertips you see it in your mind’s eye. For some reason you visualize the lesions in black and white, like a grainy, fuzzy ultrasound image. The large oval swelling floats, as it were, in front of you. Next to it other smaller ovals join it, palpated by your right hand: a 2-cm lesion from under her right jaw, and another from her right anterior triangle.

You come round to face her again so that you can look in her throat and inspect her tonsils. These are large and inflamed, but the beds of pus are healing.

‘And how are you feeling?’ you ask seated once again. You reach over and take her temperature with an aural thermometer (37.9). She pauses and waits for you to finish and then says, ‘Better but only in the last day. I’ve felt less sweaty and felt like eating again. I took my last antibiotic this morning.’

Normally tonsillitis improves within 48 hours of antibiotics, so you think your colleague’s plan of checking for glandular fever a good one. You explain this to the patient and ask her to have the monospot blood test. Because you are checking for glandular fever you also check for HIV, as these tests go together as a bundle (see Case 6.3, HIV seroconversion), after getting consent from Natalie. You suggest that she call for the results in 3 days but that you will ring her if they show anything.

Three days later a blood test result arrives on your computer that reads ‘Marked atypical mononuclear cells, monospot test positive.’ The HIV test and other tests are normal. You flick into the notes attached and remember the girl with the neck gland.

Before telephoning her you review glandular fever on your favourite information website. You can print her off a leaflet from here if she wishes it.

On the telephone you explain the result. She wants to know how long she will be ill for and how long she is infectious for. She also wants to know whether she will get it again, because a friend of hers had glandular fever and says she gets it recurrently.
You answer that is usual to feel unwell for 1–2 weeks altogether. Most people aren’t ill for ages and ages but just get better. You are not sure how long she is infectious for but explain that it is spread by saliva, so she should avoid mouth to mouth kissing or sharing cups and glasses. You advise her that glandular fever is caused by Epstein–Barr virus (EBV) and is not a recurrent illness. However (although you don’t go into this on the phone), in common with the other herpesviruses, you know that it displays the quality of ‘latency’. In the case of EBV, the virus stays quiescent in the lymphocytes and can manifest again if the patient becomes immunodeficient. The reactivation though, is not as glandular fever, but something more serious, such as nasopharyngeal carcinoma or an EBV driven haematological malignancy, either Burkitt’s lymphoma or Hodgkin’s lymphoma.

You explain to Natalie that she should not play contact sports for 8 weeks because of the risk of a blow to the abdomen. This is because the spleen can be more delicate than usual when someone has had glandular fever, and is more at risk of rupture. She should also avoid alcohol.

She doesn’t want to come in for the leaflet but would rather look up the information herself, so you pass her the website details. She thanks you very much for calling her. Later you send a message attached to the patient’s notes to your colleague, who has been feeling down about a recent complaint letter. You say, ‘Thought you’d like to know your instincts were correct. Blood test confirmed glandular fever. I have informed the patient.’

**Microbiology**

Glandular fever is caused by EBV, a ds DNA virus, 150 nm across, of the Herpesvirus family. About 50% of people acquire the virus asymptptomatically as children. In common with CMV there is a second wave of infection among teenagers and young adults, who more often present with the classic triad of fever, pharyngitis, and lymphadenopathy. There is no treatment.

Diagnosis is by the monospot blood test. This measures the non-specific antibodies produced by the B cells that have been transformed by the virus. These non-specific antibodies typically agglutinate sheep red blood cells. The blood film appearance also aids the diagnosis, typically with atypical mononuclear cells (T cells)—hence the term infectious mononucleosis.

More specific antibody tests can be done, but in the presence of a typical illness and lymphocytosis there is little advantage over the monospot test. These antibody tests are usually reserved for atypical or severely ill cases, as there are occasional reports of false-positive monospot tests. Atypical monocytes may also be caused by a number of different viruses as well as EBV, including CMV, HIV, and toxoplasmosis.

The doctor in this case, appropriately checks the patient’s throat and glands. However, complications of glandular fever include hepatitis and splenomegaly and it would have been good to have examined the patient’s abdomen and requested LFTs and an FBC, as well as monospot, on the blood form. Some patients also develop a rash (5%), but if given amoxicillin, over 90% develop a rash. This is why penicillin is always given first line (if used) for tonsillitis, rather than amoxicillin. Rare complications of EBV infection include jaundice and encephalitis.

EBV as mentioned above can also trigger malignant diseases such as nasopharyngeal cancer (seen particularly in southern China), Burkitt’s lymphoma, a tumour of the jaw in children seen in areas with endemic malaria, and Hodgkin’s disease, also a lymphoma.

**Further reading**

Chapter 10

Skin

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Case 10.1

Abscess

Case example

There will be occasions when everyone in the room knows the correct procedure to follow, except yourself. However, as long as you are willing to ask advice, and to take it, then all will be well and you will simply have had a golden opportunity to improve your knowledge.

Conrad Simpson (24) enters your room looking tired and embarrassed. He is accompanied by his girlfriend, who although young, looks resolve and serious. He sits down a little awkwardly. When you ask him how you can help, he says, ‘I’ve got this boil on my right buttock. Well, it’s like a very big boil actually. I had it for about 3 days and then I went to the walk-in centre and they gave me some antibiotics, and, well it’s gone down a bit but it’s not going.’

You envisage the infected boil, perhaps with a bit of surrounding redness, and mentally start thinking of a change of oral antibiotics. He will have been started on flucloxacillin; you could switch him to co-amoxiclav.

You nod encouragingly, but here the girlfriend jumps in hotly. ‘It’s as big as a grapefruit,’ she says. ‘And yesterday he was crying with the pain.’

Your mental image shifts jarringly and you glance at Conrad who looks away. You ask about his temperature, which he says has been normal, and his appetite, which he agrees is reduced. His blood pressure is 130/88, his pulse 82, and his temperature is 37.4. You ask if you can examine him and as you draw the curtains you explain that you would like him to lie on his left side facing the wall and to lower his trousers and pants. As you wait outside, pulling on some disposable gloves, you look at his girlfriend who is unhappy, but controlled.

‘May I come through?’ you ask, hearing that the rustling has stopped and all is still. You hear an inarticulate ‘Yes,’ and leave the girlfriend outside the curtain.

On examination, he has a large swelling 15 cm across with redness surrounding it, coming to a point near the centre with a small amount of discharge. There is a warmth and a thickening to the surrounding skin and you can feel a collection of pus. You remember the classical teaching that you learnt, not as a medical student, but as a 16-year-old work experience student: ‘tumor, rubor, dolor, calor’ (swelling, redness, pain, and heat). If all four elements are present this is consistent with infection.

‘That looks very painful,’ you say to Conrad as you take a swab of the discharge.

Although the swelling is large you still think that it may clear up with a course of antibiotics, especially as it is starting to discharge by itself. Conrad’s basic observations are ok so he should be able to manage with oral antibiotics at home. You will add in some analgesia. The alternative is to refer him for incision and drainage but you feel that this would be a big deal and that he would end up with a large wound and then a scar.

After he is dressed and sitting down again, obviously favouring his right side, you explain your thoughts and prescribe him co-amoxiclav (after checking he is not allergic to penicillin).
You advise him to take it three times a day for 7 days and that you can extend the course if it is improving but not yet better. You also say that if it is not improving at all by 48 hours or even getting worse, then he should come back. At the girlfriend’s prompting you book him into a follow-up appointment with yourself for 2 days time. The girlfriend looks rather tense at this conclusion, although Conrad is smiling and nodding hopefully.

Because you wish to confirm that the antibiotics you have prescribed are the right ones, you explain that after your clinic you will speak to the on-call microbiology team, and that you will telephone Conrad if there are any changes.

While seeing your last three patients your mind drifts back to the abscess. You envisage the abscess with the antibiotics not quite penetrating to the pus, just hovering around the periphery of the cavity.

The microbiology registrar on call has a friendly approachable voice. When he hears about the size of the lesion his liveliness becomes a little more serious and he says, ‘It’s up to you of course, and I’ve not see the lesion, but it sounds as if it really needs draining.’

‘But won’t that leave a big hole and a wound?’ you ask. ‘No,’ he says. ‘It’s usually a cross-shaped incision, only about 2–3 cm across. If I were you I would send him up to the surgeons. He’ll get better a lot quicker once the pus is drained. He won’t have to stay in hospital.’

You thank him for his advice, and turn it over in your mind briefly before reaching for the phone to speak to the on-call surgeons.

You arrange his admission, write a letter to fax to the hospital and then telephone the patient. The phone is answered by his girlfriend. When you explain the new plan she is very relieved, although still very precise. ‘Yes I think that’s a much better plan. I think he really needs it,’ she says.

One week later the nurse tells you she is dressing Conrad’s wound and asks you if you would like to inspect it. You enter the nurse’s room and nod and smile to Conrad’s girlfriend who is leaning against the wall, one arm on the radiator. You say ‘Can I come through?’ to Conrad, who twists his head and nods as you come behind the curtain.

As before he is lying on his left side on the examining couch with the curtain drawn, but this time surrounded by the paraphernalia of wound dressing; the dressing pack laid out, the saline in its little plastic dish, swabs and tweezers, packing tape, and padded white dressings ready to apply.

His colour is much better and his movements more enlivened. The wound looks terrific. There is a small neat plus mark 2 cm across over his buttock, there is no swelling and no redness, and just a small amount of discharge.

‘That’s fantastic,’ you say. ‘You look much better. And do you feel better?’

‘Yes,’ says Conrad. ‘It’s not nearly so painful. I can sit down again.’

You pop your head out of the curtains and look at his girlfriend. ‘Have you seen it?’

‘No, I haven’t dared’ she says grimacing slightly.

‘You should, honestly, it looks so much better.’

She peers round the curtain and breathes a sigh of relief when she sees the improvement. She catches Conrad’s eye.

The swab you had sent comes back as

\[ \text{Staphylococcus aureus scanty. Resistant: penicillin. Sensitive: erythromycin, flucloxacillin.} \]

\[ \text{Anaerobes not isolated.} \]
Conrad is kept on the co-amoxiclav you originally prescribed for 10 days. He comes back every 2–3 days for dressings with the nurse for several weeks and is finally discharged exactly 1 month later.

**Microbiology**

Abscesses are caused by many different bacteria including *Staphylococcus aureus*, *Streptococcus pyogenes* (also known, confusingly, as Group A strep, or Group A beta-haemolytic strep), *Escherichia coli*, and anaerobes. The commonest of these is *S. aureus*.

A swab, as in this case, or more ideally a sample of the pus, can be sent to the laboratory for microscopy, culture, and sensitivity. In this instance, unfortunately, no pus was sent by the surgeons for analysis. Pus samples give a better yield of bacteria, especially fastidious organisms or anaerobes, which may die on a swab before they reach the laboratory.

A pus sample would be first centrifuged to concentrate the small numbers of pathogens in the sample. A sterile pipette or sterile loop would then be used to transfer about 10 μm of the inoculum to each culture plate. The specimen is then spread out across the plates, again using the sterile loop. This allows mixed cultures to be identified, in this instance *S. aureus* (0.6 μm in diameter) (Fig. 10.1.1) and individual colonies can then be picked out later to test for antibiotic sensitivity.

The first line antibiotic for the blind treatment (i.e. before the microbiology results are back) of a skin infection, such as impetigo, small boils, or cellulitis, would be flucloxacillin (erythromycin if penicillin allergic).

Flucloxacillin is used because most staphylococci are resistant to penicillin and amoxicillin. These bacteria produce beta-lactamases, which are enzymes that inactivate penicillin. However, flucloxacillin is not inactivated by these enzymes. It is also acid stable and well absorbed from the gut, so can therefore be given orally.

Co-amoxiclav is usually recommended as a second-line treatment, for example if there was no improvement. This medication consists of amoxicillin combined with clavulanic acid. It is the clavulanic acid which inactivates the beta-lactamases and thus protects the amoxicillin from being degraded. This makes co-amoxiclav a suitable treatment for staphylococcal skin infection.

However, in this instance it may be particularly suitable, as a perianal abscess is more likely to have Gram-negative organisms present, which this antibiotic also covers.

It is important to realize that the first and preferred treatment of any abscesses is to drain the pus—antibiotics play a secondary role. If the pus is drained completely, and the patient is not systemically unwell, antibiotics may not be necessary at all. Small abscesses may sometimes improve with antibiotics, but antibiotics do not penetrate pus well, and will have a limited effect. Incision and drainage is then necessary and the wound must be allowed to heal ‘by first intention’, that is from the bottom up, by inserting a dressing into the wound (not by packing the wound) and by regular dressing changes.

In this instance, the doctor initially decided on the less effective (or one might even say inappropriate) oral antibiotic treatment, but saves the situation by arranging proper follow-up, safety netting, and also seeking advice. The patient’s girlfriend appears from the start to have known that incision and drainage was the more appropriate treatment; however, although her boyfriend was in a lot of pain and she was clearly acting as his advocate, it is noticeable that she did not contradict the doctor.

**Further reading**

Case 10.2

**Impetigo**

**Case example**

‘Jonathon Williams (29); rash on chest.’ You read these brief remarks as you dial the patient’s number.

‘Hello this is Jonathon,’ you hear a deep voice radiating the confidence of someone who works in the city.

You introduce yourself.

‘Ah. Thank you for calling,’ the voice says. ‘Actually I’ve had this rash for 5 weeks. I went to a walk-in centre 3 weeks ago and they gave me antibiotics. It went and then came back. Yes, it’s been back for about a week. It’s got a sort of liquid that keeps leaking from it, which I try and wipe off. I think they called it impetigo at the walk-in centre. Does that sound right?’

‘Yes it could be. It would be good to have a look to make sure that is what it really is. I have an appointment at 11.10.’

‘Oh great. That’s perfect. I’ll be there.’

As you sign off you flick into his letters on the screen and find a document from the walk-in centre prescribing flucloxacillin.

Jonathon Williams, when he comes in, is tall and blonde. He sits himself down comfortably and confidently (over-confidently?) and having checked his name and introduced yourself you ask to look at the rash and he begins the complicated process of undoing his tie, shirt, and cuffs. When he lifts up his shirt, you stare in horrid fascination at the patches of yellow crusting overlying and clotting up his chest hair. Under the crusting are raw areas. Why, oh why has Jonathon not cleaned the crusting off?

However, you nod professionally and say, ‘I agree, this *is* impetigo.’

‘What is impetigo exactly?’ asks Jonathon.

‘It’s simply a skin infection. Usually caused by a bacteria called *Staphylococcus aureus*; aureus means gold and this bacteria causes this typical yellow gold discharge that you’ve got on your chest.’

He nods un-self-consciously.

You pull out a sterile swab from the drawer and with his permission you swab one of the patches and then return the swab to its container ready for labelling.

You then move for a swift conclusion.

‘Ok. We’ll try a week of a stronger antibiotic. But also you need to be very thorough on cleaning the area. You need to clean it at least two times a day, ideally three times. Wash your hands before then use cotton wool balls dipped in saline or water with a few drops of Dettol. Is very important to wash your hands again if you touch the area at all as it’s very infectious and can spread to other people as well as to other parts of you.’
You turn to the computer to print off flucloxacillin and say, ‘You’re probably already trying to avoid touching it but I know that’s difficult.’

He nods. ‘It’s terrifically itchy.’

‘Mmm,’ you agree. ‘But it’s really important. The little cells are doing their best to heal up but they won’t be able to do it so well if you rub them or reintroduce infection . . . I tell you what. We’ll add in an antibiotics cream for you to put on during the day if at any point it gets itchy.’

He nods and you print off the second prescription and stand up signing it. He stands up too.

‘It should improve pretty well with the cleaning and the antibiotics but if it comes back or gets worse do contact us again.’

You pass him the script but he shakes your hand firmly instead and says thank you very much. ‘It’s a pleasure’ you say. ‘Good bye.’

You move towards the sink to wash your hands as his footsteps recede around the corridor.

Three days later you receive the following report:

Culture; moderate growth of Staph. aureus. Erythromycin (s), Flucloxacillin (s).

Microbiology

*S. aureus* is immensely important in terms of the range of different infections it can cause, and how common it is generally, and in the range of severity—from superficial infection, as with Jonathon, food poisoning (see Case 1.2, Food-borne gastroenteritis), to deeper infections (see Case 10.1, Abscess), chronic infections (see Case 7.1, Chronic osteomyelitis), and life-threatening sepsis (see Case 13.2, Complex intra-abdominal infection). In recent years, it has become even more notorious, because of the emergence of some strains that are multiresistant, including meticillin-resistant *Staphylococcus aureus* (MRSA) (see Case 10.3, Leg ulcer).

*S. aureus* has some intrinsic features that help it cause disease. Many strains have a capsule which helps resist phagocytosis. They contain various surface molecules—adhesins—that help them stick to various host and cell tissues (and intravenous lines). The *coagulase* enzymes that help diagnosis are part of this family of molecules, and possibly aid virulence by coating the organism in fibrin, so it is protected from phagocytosis.

*S. aureus* also secretes many extracellular toxins. The most obvious of these is the haemolysin that makes the organism slightly haemolytic on blood agar. The haemolysin can also lyse other cells, and may play a role in virulence. Another is PVL (Panton-Valentine leukocydin) toxin discovered by Panton and Valentine in 1932, which causes severe recurrent skin infections and sometimes necrotizing pneumonia.

*S. aureus* is one of the staphylococci, so down the microscope it appears as Gram-positive cocci in clusters. The organism grows well on most types of agar used in routine laboratories, and the ‘typical’ appearance is of creamy-yellow colonies after an overnight culture (Fig. 10.2.1). This is the origin of the name—‘aureus’ is the Latin for gold, and refers to this colour, and to the colour of the fluid that Jonathon has noticed on his skin. In fact, in recent years, these attractive golden-coloured colonies are rarely seen, and the growth is more often white—and the colonies are therefore indistinguishable from other staphylococci that live on the skin, but which are less pathogenic.
There are many skin *Staphylococcus* species, the commonest of which is *S. epidermidis* but others include *S. hominis*, *S. capitis*, and *S. haemolyticus*. These other *Staphylococcus* species can sometimes cause real and serious infection, but usually finding them in clinical samples means that the sample is contaminated, for example a blood culture, or that the sample has grown normal colonizing skin organisms, for example a wound swab. A big challenge for laboratory microbiology is to quickly and cheaply distinguish *S. aureus* from all the other staphs—on the assumption that *S. aureus* is (nearly) always significant.

*S. aureus* has a few biochemical differences from the other staphs that can be used to identify it once a colony has been grown on agar. The first step is to confirm that the organism really is a *Staphylococcus*, and not another Gram-positive coccus such as a *Streptococcus*. This should be obvious from the Gram stain—but sometimes Gram stains can be less clear than in textbooks, so further evidence is needed. Staphs all produce catalase enzyme, and streps don’t—so if a colony of the suspect organism is mixed with a drop of hydrogen peroxide on a glass slide, and bubbles of oxygen are produced, then the organism is definitely not a strep.

The next step is to distinguish *S. aureus* from the other staphs. The most useful difference is that *S. aureus* produces different coagulase enzymes (mentioned above) causing serum proteins to clot and coagulate. Most laboratory tests to identify *S. aureus* use these enzymes. One technique is the **tube coagulase test**: the organism is incubated in a test tube with rabbit plasma; if the plasma has clotted after a few hours, it is coagulase-positive, i.e. *S. aureus*. A quicker method is the **slide coagulase test**—a colony of bacteria is mixed with a drop of plasma (or in some commercial kits, sensitized sheep red blood cells, which produce the same effect but are easier to see), and then the slide is gently rocked. After a few seconds, if the organism is coagulase positive, then clumping is observed. The fact that this test—in some form or other—is so commonly used to identify *S. aureus* has led to all the other non-aureus species being collectively referred to as coagulase-negative staphylococci (CoNS). Most laboratories will not routinely identify them any further to species level.

![A culture plate of blood agar with *Staphylococcus aureus* growth. Note the presence of antibiotic discs to check for antibiotic sensitivity. Reproduced from Centers for Disease Control and Prevention, Public Health Image Library (PHIL), Image ID#2642, Don Stalons, 1972, available from http://phil.cdc.gov/phil/details_linked.asp?pid=2642](image-url)
After an organism is confirmed as \textit{S. aureus}, the last step is to test for antibiotic resistance or sensitivity. The usual antibiotics tested include penicillin, erythromycin, fusidic acid, and meticillin. Although the usual antibiotic used in the UK to treat \textit{S. aureus} is flucloxacillin, laboratories rarely test this antibiotic directly. This is partly historical—meticillin was the precursor to flucloxacillin, introduced around 1960 but abandoned a few years later (it is rather toxic and can’t be given orally); however, it is more stable and reproducible in laboratory testing, so even after doctors switched to using flucloxacillin, laboratories continued to test meticillin. Laboratories will usually report the result to the medical team as \textit{flucloxacillin sensitive} just as they have done with Jonathon.

**Further reading**

Case 10.3

**Leg ulcer**

**Case example**

Glenna Frazier (38) is the sort of patient you definitely don’t want to see on your own, late on a Friday evening. The receptionist, however, has slotted her into your surgery last minute, because she is aggressive and says she is desperate.

She is gaunt and unkempt. She has dirty bandages wrapped around her lower leg and she has an intravenous cannula in her arm. She is asking you for **Suboxone®** (which is a combination of buprenorphine and naloxone) given as replacement opioid as treatment for drug dependency.

She is very skinny. ‘I’m in so much pain,’ she says gesturing towards her leg (which smells). ‘I’m desperate for a higher dose of **Suboxone®**. And I just can’t sleep. I really need something to relax me.’ She doesn’t appear perfectly alert and her speech is indistinct; you have to concentrate hard to pick up everything she is saying.

Actually, you have met her once before and didn’t really enjoy the experience that time either. That was about 3 weeks ago; she’d come in demanding assistance with housing plus extra medication. She has known drug dependency, and malnutrition and chronic leg ulcers as a result of her injecting habits. She routinely misses dressings appointments, appears late in the day at unpredictable times, and always demands urgent assistance. She has recently been missing appointments with the drug team.

However, today marks a new episode in her leg ulcer progression. She hands you a printout of a letter from A&E. From this you piece together the information that Glenna has had a DVT in both legs as well as infected ulcers and yet, in spite of her drug dependency, she has been discharged with an IV cannula in place. The district nurses have been contacted to continue her IV teicoplanin and Glenna has been instructed to attend the anticoagulant clinic, which of course she has not done. It was felt, ‘there was no need to keep her in hospital.’

The district nurse team have called for the last 3 days and never found her in. (Hardly surprising; an IV cannula for someone who is drug dependent must be like Christmas Day.) And here she is in front of you holding two phials of teicoplanin, not quite with it and yet holding out for extra analgesia.

It’s quarter to six. You slide back your chair and standing up, excuse yourself for a moment, and rapidly walk down the corridor to the nurse’s room. ‘Please, please help me Lynn. I’ve got Glenna in my room and she needs dressings as usual and she’s got these antibiotics to give IV as well.’

Lynn also knows Glenna. ‘Ok, ok,’ she says. ‘I can see her.’ She has finished for the day and is trying to catch up with cervical smear paperwork.

You dart back to your room and send Glenna down the hall to the nurse with a great feeling of relief that she is out of your room. You prop the door open to air the room. However, you know you are not finished with her yet. The telephone rings; Lynn politely asks you to come and view the ulcers. She has Glenna lying on the couch with the dirty bandages removed and the ulcers
uncovered. There are three over her left leg; a palm sized one about 6 cm × 5 cm, a golf ball sized one about 2 cm × 2 cm and a coin sized one about 1 cm × 2 cm. The smell is strong and the colour of the discharge sea green and sloughy, but Lynn has seen them before and says they are improved from the last time she saw them, less red and inflamed. Glenna seems uninterested as you talk over her leg.

‘That looks like *Pseudomonas,*’ Lynn says taking another swab and then getting saline and cotton wool to clean the ulcers.

‘We need to give her the teicoplanin,’ you say, ‘and fix up for her to finish the course. Can you book her in with a nurse tomorrow for that?’

‘We don’t have any saline handy to flush the cannula and the chemist is closed,’ remarks Lynn. ‘Then let’s take it out and give the antibiotics IM,’ you say. ‘Can I leave all that with you?’ And turning to Glenna, ‘You need to go to the anticoagulation clinic.’

‘It hurts so much,’ she says vaguely.

‘I can’t give you any additional painkillers, apart from paracetamol. They won’t mix with the *Suboxone* you are on.’

‘And doctor, what about my sleeping, I just can’t sleep.’

‘I’m sorry I can’t give you sleeping tablets for the same reason.’ You back out of the room before she makes any other awkward requests.

The next week you discuss the situation with a senior colleague. The question of whether to complain formally to A&E for an inappropriate discharge; the fact that they discharged her with an IV cannula; and what is to be done now about her non-attendance for dressings, anticoagulation and about her pain in spite of the *Suboxone*?

The swab results come back and are similar to the previous 6 months of swabs.

*Culture; heavy growth of meticillin (fluclox.) resistant Staphylococcus aureus as previously isolated. Heavy growth of Pseudomonas aeruginosa. Please consult infection doctor if treatment clinically indicated.*

And the next time she is swabbed, 3 weeks later, her result is ‘Heavy mixed growth including coliforms’.

Glenna continues to attend intermittently. She is switched to methadone and up-titrated for better pain control. The leg ulcers persist.

**Microbiology**

This case illustrates both the challenge of managing chronic ulcers and making sense of the culture results, and the particular problem of MRSA.

Chronic leg or foot ulcers are common, and the causes can vary. Many are due to venous insufficiency; some are due to arterial insufficiency or to neuropathy. Immobile patients may also suffer skin breakdown due to constant pressure on a particular area. Rarely, specific infections may cause ulceration of the skin, for example syphilis and TB. Whatever the cause, skin ulcers, being warm and moist, are a good environment for bacteria to grow, and swiftly become colonized by various, often mixed species of staphylococci, streptococci and Gram-negative bacteria, such as *E. coli* and *Pseudomonas.* Glenna’s swabs are a good example of this, including staphylococci, *Pseudomonas,* and coliforms.
These bacteria in turn may play a role in delaying the healing of the ulcer by producing various toxins and enzymes that attack the growing epithelium. The bacteria may also invade surrounding tissue and cause cellulitis, necrosis, or even gangrene.

However, because of the exposed nature of ulcers, it is impossible to sterilize them completely, and so efforts to eradicate bacteria with antibiotics usually result in either re-colonization by the same bacteria once the antibiotics are stopped, or else colonization by new, more resistant organisms. This is one dilemma in managing ulcers—at what stage do you decide that the benefits of antibiotics outweigh the risks of selection for resistance? The danger here is to be led too much by the microbiology result, and not by the actual condition of the patient and the ulcer itself. If the patient is septic, or if there is surrounding cellulitis, then it is likely the patient needs antibiotics. It is less clear if the patient is relatively well, and there is no cellulitis, but the ulcer seems full of slough and pus. There is a strong temptation to give antibiotics in such situations, especially if a swab has grown bacteria, but what is probably more important is to ensure the ulcer is properly cleaned and debrided. This is difficult in practice, especially if the patient neglects themselves, as here, or does not attend regularly for dressing changes.

If a decision to give antibiotics has been taken, as with Glenna by the A&E staff, then the culture results can be useful in helping to choose which antibiotic to give (Fig. 10.3.1). Glenna’s ulcer has grown MRSA. In the UK, most MRSA strains are hospital-acquired—but a patient such as Glenna may have had many previous spells in hospital, or other contact with the health services. MRSA does exist in the community in the UK, although this is more common in the USA. In fact, in the USA, guidelines for managing sepsis assume that any staphylococcal infection will be MRSA, whereas UK guidance still assumes that most strains will be relatively sensitive.

MRSA causes great anxiety both to patients and clinicians, and there is sometimes confusion about its actual significance. As the name says, it means a S. aureus that is resistant to meticillin. These strains first appeared in the 1960s, soon after meticillin was introduced, and used to treat S. aureus resistant to penicillin. Penicillin resistance is due to beta-lactamases (as discussed in Case 10.1, Abscess) but meticillin resistance is by a different mechanism—a mutated target molecule, known as penicillin-binding protein 2A, found in a mobile genetic element so the antibiotic can no longer bind to the bacteria. It is believed that this ‘cassette’ of genes arose first in a different species of coagulase-negative staph, possibly an animal strain, and jumped the species barrier into S. aureus.

Fig. 10.3.1 Photomicrograph of meticillin-resistant Staphylococcus aureus colonies growing on an agar plate infused with meticillin. Reproduced from Centers for Disease Control and Prevention, Public Health Image Library (PHIL), Image ID#7822, Jeff Hageman, M.H.S./Janice Haney Carr, 2005, available from http://phil.cdc.gov/phil/details_linked.asp?pid=7822
Meticillin is no longer used clinically, but the name has stuck, and the significance lies in the fact that meticillin-resistant strains are also resistant to all the penicillin antibiotics, and all the cephalosporins. They may also be resistant to other antibiotics, including ciprofloxacin and erythromycin; so antibiotic choices are restricted, in a way that is roughly similar to severe penicillin allergy. This is not to say MRSA infections are untreatable however—there are still treatment options, including vancomycin, teicoplanin (as used here), and daptomycin (all intravenous drugs).

Most strains are also sensitive to several oral antibiotics, including doxycycline, rifampicin, fusidic acid, and linezolid. Despite this there are many reports of patients suffering very complex and severe infections with MRSA, often following surgery, sometimes with fatal outcomes. Although in some cases this is due to the reduced antibiotic choice, usually a bad outcome is because of patient factors (age and frailty) or the serious nature of the infection itself, rather than the resistance of the organism.

MRSA infections became notorious in the late 1990s as rates increased greatly. This increase was widely attributed to declining standards of hygiene in hospitals, and was behind a big push to improve hospital infection control in the 2000s, but other factors may also have contributed, including the emergence of new ‘epidemic’ MRSA strains that seemed to spread more easily, and increasing use of new broad-spectrum antibiotics: cephalosporins and quinolones (i.e. ciprofloxacin). These antibiotics were (and still are) popular because they were cheap, safe, and effective, but they also seem to be good at selecting resistant organisms, including MRSA.

The situation has greatly improved, with a better emphasis on hospital hygiene, more restricted antibiotic policies, better care of intravenous lines (infected lines were the main source of MRSA bacteraemias), and more screening of patients, so MRSA carriers can be identified and the organism eradicated (or at least suppressed for a time) by a combination of topical chlorhexidine (a disinfectant) and mupirocin (an anti-staph antibiotic) applied inside the nostrils (the usual habitat of the organism).

For Glenna, her drug dependency and poor compliance with dressings will have a much more severe impact on the outcome of her leg ulcers than the fact the bacterial swab has grown MRSA.

**Further reading**


Case example

‘Well. I wanted to see you because we’d discussed it last time, about starting the antibiotics, but it wasn’t so bad then.’ Michelle Palmer is 32.

‘Oh ok.’ You nod, wondering what you did say to her and when. ‘Nice to see you again.’

‘It’s become such a nightmare. And no one expects someone my age to have acne. It’s like a teenager thing as if I’ve regressed or something. And I can’t afford to look like this. I mean I’ve got to look right for the job . . .’

‘What work do you do?’ you interject in an interested voice, feeling that she is getting upset.

‘Oh. I’m a magazine editor. But it’s a women’s magazine so people are always interested in your appearance.’

Actually you can’t see any spots. Her skin simply looks sort of textured and there are a few larger bumps. She does look very stylish though, with bright green glasses frames matching her jacket. Your eyes keep flicking from the jacket, back to the glasses frames absentmindedly, wondering how tricky it must be to get this look right. She has got it right.

‘So it’s not too bad at the moment?’ you say naively.

‘No it is bad.’ Her lips tremble as she tries to suppress her tears but it’s too late and her eyes fill. She angrily rummages in her green leather bag for, you think, a tissue and you anxiously reach for your own tissue box and touch her briefly on the shoulder.

‘Here,’ you offer inadequately. ‘I’m sorry. I’ve upset you.’ You set the box in front of her as a sort of gesture of sympathy.

‘No, it’s not that. I just wanted to . . .’ she stops and reaches for one of the tissues to dab her eyes. Then she turns back to her bag and finds what she is looking for; a packet of what look like mini wet-wipes, but which turn out to be special make-up removers. ‘Here, I’ll show you.’

She sniffs and wipes her nose with the tissue. Then, pulling out the wipe and with the help of a small hand mirror which she has also taken from her bag, she carefully wipes her cheek. What you took to be normal skin colour comes off onto the wipe revealing it to be make-up perfectly matched colour- and texture-wise to her skin. Now removed, it reveals the pink inflamed bumps and spots and thickened whitened scars of acne. You have seen dermatology graded pictures of acne and this would come under ‘moderate’: pustular, but not too bad. However, telling Michelle that her acne is ‘moderately bad’ is not something that crosses your mind.

‘Oh, I see what you mean. That does look very uncomfortable.’

Michelle points wordlessly at a slightly bigger pink spot and you nod looking at it.

‘I thought it was going to improve now that the weather’s warming. And then that one appeared . . .’
‘Oh dear. Are you on any treatment at all?’ you ask.

‘Just that over the counter remedy. You know.’

‘Benzylperoxide . . . Like Panoxyl® Aquagel 10%?’

‘Mmm.’

‘That is a good treatment. It has been tested in trials. But I think we should go onto the next level of treatment.’

‘You mean stronger?’

You nod. ‘Like antibiotics or going on the pill to treat it hormonally. But none of the treatments work quickly. That’s the first thing to know. It’s really important to understand that all the treatments take about 3–4 months to really start working. And none of them cure acne. They just keep it under control. You take it long term, like for 6 months or a year. At the end of the year you gradually reduce the dose and then stop taking it and we all cross our fingers and hope it doesn’t come back.’

‘Oh. Ok. I guess I can’t take the pill because I get migraines. I’m already on Implanon.’

‘Ok. Antibiotics then? They come either as a tablet or as a gel to put on your face. Which one to use is more of a personal decision rather than a medical decision. It depends on what suits you best.’ You pause.

‘I think I’ll go for the antibiotic tablets then if it’s all right.’

You prescribe her 3 months of oxytetracycline, 2 bd as the cheapest first-line option, and counsel her on contraception and pregnancy. While you do this she repairs her face and by the time you have finished printing off and signing her scripts her cheeks look as neat and as un-inflamed as when she first walked in the door. She blows her nose.

‘I think the thing to do is telephone or come back in 3 months and then we can discuss if it’s suiting you, side effects and that kind of thing and go from there.’

She nods thanking you and you smile and say good bye and hope you’re all right as she leaves for another day at the magazine office.

**Microbiology**

Acne is caused by a combination of factors: the blockage of sebaceous glands, the amount of sebum produced and the presence of a small bacteria called *Propionibacterium acnes*, 1–2 μm in size.

Sebaceous glands are all over the skin but the largest are on the scalp, the face, the neck, and the trunk. These glands share a duct with hair follicles, known as the pilo-sebaceous duct. This system is important in animals for waterproofing the hair, but its function is a little redundant in humans. Although it is worth noting that the sebum produced by the gland is fungi-static (see Case 10.10, Tinea corporis).

Puberty activates the sebaceous glands, increasing the amount of sebum produced; this is why acne is particularly seen at puberty. If a sebaceous gland is active and the duct gets blocked then a sterile collection of sebum results.

*P. acnes* (along with *Staphylococcus epidermidis* and *Pityrosporum ovale*) are skin commensals. *P. acnes* is a slow growing anaerobic Gram-positive rod. It is an opportunistic pathogen and has been implicated in other more severe infections such as endocarditis or septic arthritis post surgically. It thrives on sebum, which is a nutrient for it. *P. acnes* produces various enzymes that
help it break down the sebum, skin, and protein, and these enzymes are immunogenic, leading to destruction of the follicle walls, inflammation, and consequently acne. Diagnosis of acne is clinical and microbiology samples are rarely sent to the laboratory.

Because of acne’s apparent-to-all effect on the skin, the condition can be very upsetting for the patient (not dependent simply on severity), as it is with Michelle, and uncomfortable. Severe acne can cause permanent scarring, so treatment is important to help avoid this.

The treatment for acne is as outlined by the doctor in the case: topical benzylperoxide, topical antibiotics, hormonal treatment, or long-term oral antibiotics. It is important to note the teratogenic effects of the tetracycline antibiotics and patients need to be informed of this and advised carefully on contraception where appropriate.

Further reading


Case example

There is a brisk knock on your door between patients. The nurse pops her head round. ‘Can I ask you to see someone?’ she asks.

As you are both on call and not at all busy you nod affably, ‘Of course, no problem.’

The nurse comes into the room and shuts the door before continuing, sotto voce, ‘Actually I’m a bit worried. It’s an elderly patient with a burn all the way down one side. But he can’t remember how it happened.’ The nurse is clearly concerned about elderly abuse and you agree to see the patient straight away. ‘What’s his name?’ you ask.

‘Glenn. He’s 75,’ the nurse answers. ‘I’ll book him into your clinic list now and bring him over.’

Two minutes later there is a second knock at the door. This time it is Glenn. You stand up and usher him in. ‘Glenn Macalan? Come in and have a seat. How are you?’

You pause while Mr Macalan walks slowly over to the seat using a stick and sits down carefully. He props the stick against the wall and then arranges his shopping on the floor. It tips over immediately so he bends down again and gives it a shake to rearrange it. This time it balances. He looks up again and composes himself. ‘Well doctor. I’ve got these marks on my back, which the nurse says is a burn. But I just can’t remember anything like that happening.’

‘And who’s at home with you normally?’ you ask to get a feel of his usual abilities.

‘Just me and the wife. Course, she’s quite elderly too and stays indoors mostly. I do most of the cooking. I still drive so I can get to the shop all right.’

Mr Macalan looks and moves and sounds very able and independent and not at all like someone with a memory problem. Nor so far has he mentioned anyone except his wife, who sounds more disabled than he. If you wanted to assess his memory further you could ask him a mini-mental test (scored out of 10); his name, date of birth, address, the date, the place, who am/other staff, date of the Second World War, who the prime minister is, count backwards from 20, and remembering a short address. But you don’t: instead you ask to look at the rash.

Mr Macalan stands up, lifts up his polo shirt and turns around and faces the other way. You gaze at his back and see a blistered rash. This is in a neat T6 dermatome distribution on the left hand side. It curves round in a band 2 cm wide, from near his spine, round his ribcage. The blisters are 2 mm across and kind of square shaped; often a hallmark of a viral blister.

‘Ah,’ you say satisfied. This is not a burn but a classic shingles rash. This prompts a change in the direction of your questions. ‘Um, is it painful? How are you feeling?’

‘Very painful doctor. Actually I have felt a bit off colour for the last few days. Not quite my usual self.’

‘When did it come on again?’

‘Two days ago.’
You explain to Mr Macalan that it is a shingles rash and not a burn, and you also explain to the nurse later on. Mr Macalan is relieved that he is not losing his marbles. The nurse is still concerned and not quite convinced.

You prescribe aciclovir as Mr Macalan is within 72 hours of the rash developing and it will reduce the chance of post-herpetic neuralgia, and advise him that he will feel a bit ill for a week or two. ‘The rash will heal up on its own over the next 2–3 weeks and it’s normal for it to be painful. Then once it is crusted over it is no longer infectious. People can’t catch shingles from you, but they can catch chickenpox if they’ve never had it. So if you meet up with any pregnant ladies or children, do tell them in case they haven’t had it.’ You advise him to keep it clean and covered and print him out a leaflet about shingles.

You don’t make a big deal about post-herpetic pain as most people don’t get it. You can cross that bridge if you come to it.

**Microbiology**

Herpes zoster (shingles) is caused by varicella zoster virus, as is chickenpox. The varicella zoster virus is a large 120 nm ds DNA virus of the Herpesvirus family (Fig. 10.5.1). The herpesviruses are well known for their tendency to lie dormant and then reactivate. With regards to chickenpox, the virus can remain dormant in the dorsal ganglia and then become reactive years or even decades later and manifest as a shingles rash, typically in a single dermatome on one side of the body.

![Fig. 10.5.1 A transmission electron micrograph of chickenpox virus.](http://phil.cdc.gov/phil/details_linked.asp?pid=1878)
In Mr Macalan’s case, this was a left thoracic dermatome but it can be any; thoracic, sacral, cervical, or even cranial. One of the most serious manifestations of herpes zoster is when it occurs in the ophthalmic division of the trigeminal cranial nerve; herpes zoster ophthalmicus. This can lead to eye complications such as keratitis and generally needs an ophthalmic referral if suspected.

Shingles tends to emerge in patients with a waning immune system, often as they get older, as with Mr Macalan. It has its highest incidence in patients over the age of 70: overall, approximately 25% of the population will get shingles.

As with Mr Macalan, patients tend to feel unwell for 1–2 days before the onset of the rash. Sometimes pain is felt in the affected dermatome before the rash develops. The development of the rash is very similar to chickenpox, beginning with vesicles, evolving into pustules and finally crust ing over. However, the process takes a lot longer: 2–4 weeks in shingles as opposed to 3–5 days in chickenpox. Histological examination of shingles vesicles compared with chickenpox vesicles reveals there is no difference between the two.

In most people, shingles resolves without further complications. Some will suffer post-herpetic neuralgia, diagnosed if the pain lasts more than 3 months after the onset of the rash. Other complications include palsy (weakness) of the associated muscle group usually resolving spontaneously. In the immunosuppressed, a disseminated varicella zoster infection can occur. This is associated with increased mortality, most frequently due to pneumonia.

In this case the doctor advised the patient to avoid pregnant women and children. This is because the blisters shed varicella zoster virus and people without immunity can contract chickenpox (see Case 11.4, Chickenpox). It is interesting to think that a sort of vintage version of the virus circulating perhaps in the 1950s can now re-emerge and infect the children of today. It is also a very effective viral reproductive strategy.

The link between herpes zoster and varicella has not always been so obvious. Because of the dermatomes being affected, parallels were initially drawn between herpes zoster and polio. With regards to chickenpox, traditionally the main concern was the similarity of the rash to smallpox, especially in adults. Some doctors at the turn of the century (1900) went so far as to say that as chickenpox in adults was so rare, ‘It might be a safe bet in some respects to call any case in an adult smallpox that one feels tempted to diagnose as varicella.’ However it was noticed in the 1920s that, ‘The appearance of herpes-zoster in a family is sometimes followed after an interval of 14 days by a case of chickenpox.’

It is now possible, of course, to confirm the presence of varicella zoster virus in the vesicular fluid of both lesions (the virus obviously named after both) using electron microscopy (see Case 10.8, Orf, which discusses electron microscopy further). Alternatively, culture and immunofluorescence could be done on the vesicular fluid, or nowadays it would be PCR.

The treatment of shingles is with the antiviral aciclovir, which needs to be administered within the first 72 hours of rash onset. Because of the high burden of shingles and its associated morbidity and risk of chronic pain in the over 70s, there is now a universally administered shingles vaccine in the UK. This is given as a single one-off dose at the age of 70, the intention being to boost immunity to the virus and prevent its reactivation. The vaccine reduces the chance of getting shingles by 50%. It is called Zostavax® and is very much related to the chickenpox vaccine Varivax®; both are made from live-attenuated virus of the Oka/Merck strain but Zostavax® is a larger dose.

**Further reading**

Case 10.6

Cutaneous viral warts

Case example

‘The only other thing I was going to ask about was this,’ David Oxon (58) remarks. You have already discussed his blood pressure, his cholesterol results, and what medication he should have, whether diets are worth trying and you have weighed and measured him. You are half way through the motion that will signal to him that it’s time for the consultation to close (passing him a script and getting ready to stand). Instead, you arrest it and politely put the script on the desk while you glance at David’s face to see what he means.

He is holding up his right hand where there is an unfortunate lump on one side. You slide your chair closer for a good look. The lump looks a bit like a wart 2 mm across and sticking out by 2 mm, but its surface is not typical, more pointed and pink than usual. You look for tiny black dots on the surface (coagulated arterioles typical for a wart) and can’t see any. The back of the hand is a common site for sun-related skin lesions and so your first thought is, ‘Is it a wart at all?’

‘Actually I had it frozen off at the dermatologist’s almost a year ago and it went. Completely went. The skin was nice and smooth. But then it came back again, just in the last 2 months.’

You nod and slide your chair back to the desk to look up his notes on the computer. Your fingers know which keys to tap for the past medical history and then for scanned copies of clinical letters. You bring up a list of letters including a dermatology one from 8 months ago and find this helpful letter:

**Diagnosis**

2 mm viral wart on dorsal surface of right hand

**Management**

1. 2*10 seconds of cryotherapy to the above
2. No further follow up

*Many thanks for referring this gentleman to my clinic. He has had a 6 months history of a viral wart on his hand. Today, I have explained the diagnosis for this patient and I have discussed cryotherapy as a suitable treatment option. I have warned him about possible side effects such as localized redness, pain and swelling for a few days and then this will subside. I have also warned him about the blistering and also permanent pigmented changes/scarring and numbness. The patient consented. I have performed two cycles of 10 seconds cryotherapy to the above lesion and I have discharged him back to your care, the patient is happy with that.*

*Yours sincerely*

You scan this very detailed letter rapidly. It confirms that this funny lump is a wart and not a BCC (basal cell carcinoma) or solar keratosis, or some other sun-related lesion.
‘Ok, so it’s definitely a wart isn’t it? That’s the first thing. The letter is very helpful. There’s lots of research on warts that says wart paint is just as good as cryotherapy at getting rid of them. So I wonder if it’s worth trying wart paint now?’

David Oxon nods, listening carefully.

‘Both treatments are meant to cause inflammation and trigger the immune system to get rid of the wart. But some people are just non-responders and then neither treatment works. Eventually the wart will just go on its own. But it can take ages, perhaps a year or two.’

‘Mmm.’

‘Well the good thing about the wart paint is at the very least it chemically removes the surface of the wart and makes it smaller and less bothersome. You have to be persistent though, every night for 3 months.’

‘Oh, ok. I think I can manage that. So just any wart paint?’

‘Yes. They’re all salicylic acid, a weak acid. You put it on at night, then cover it with elastoplast and then the next day when you remove it, it will remove a bit of the wart’s surface too, and that’s how you gradually get rid of it. Will you be able to manage the treatment on your hand?’

‘Oh yes, that sounds fine, my left hand is dextrous enough to cope with that. Well thanks very much. And I’ll see you in 2 months to recheck my blood pressure as you said.’

Mr Oxen summarizes your plan and stands up with the script, signalling himself that the consultation is over, as you say, ‘Great! Thank you. See you soon.’

**Microbiology**

Cutaneous warts like this one are caused by human papilloma virus (HPV), of which there are over 100 types. They are small icosahedral non-enveloped viruses 52 nm in size with circular ds DNA (Fig. 10.6.1). They are sometimes classified as either cutaneous warts or genital warts, but in fact genital warts can affect other parts of the body and it’s not unusual to get cutaneous warts on the genitals.

Common serotypes for cutaneous warts include 1, 2, 3, 4, and 7.

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**Fig. 10.6.1** A negatively stained electron micrograph of a papilloma virus.

HPV only replicates in epithelial cells and since only the basal epithelial cells of the skin replicate, these are the cells that the virus needs to enter. The virus typically enters through any small abrasion either from direct contact from another wart or from a fomite. It can stay quiescent for some time, before replicating and causing hyperkeratosis: large pale vacuolated cells, and this lesion forms the wart.

Common warts are usually diagnosed clinically and samples are not taken. However, PCR of biopsies or swabs can be performed to identify viral DNA.

There is no vaccine for common warts, although a vaccine has been developed for genital and cervical warts (see Case 6.6, Cervical screening) and the treatments as described in the case are physical, that is cryotherapy, curettage, or salicylic acid. Anogenital warts are treated with the gentler podophyllin paint. These treatments can lead to wart resolution about 70% of the time within 3 months.

The multiple recommended treatments for warts lead to the conclusion that no one treatment is particularly effective. A recommendation from the 1920s that, ‘Plantar warts are best treated by the single application of a large dose of x-ray, the surrounding skin being well screened with lead foil,’ can be ignored (with a shudder) and attributed to the enthusiasm of the time to treat everything with X-rays. It is now known to be particularly dangerous to X-ray warts due to the potential of wart viruses to cause cancer (oncogenic).

Further reading

Case 10.7

Molluscum contagiosum

Case example

‘Estela De Juan!’

The packed waiting room stirs hopefully but no one jumps up. You try again this time pronouncing the ‘J’ as a ‘H’. This time there is a rustle of movement, a gathering of bags and a standing up. A very tanned looking girl of about 10 years old threads through the crowded room, followed by a slim black haired lady of about the same height.

You smile and welcome them into your room and introduce yourself. The girl seats herself composedly but it is immediately apparent from her mother’s blank face that she didn’t understand what you said.

‘My mother doesn’t speak English,’ says the girl.

‘Can you tell her what I say?’ you ask. She nods. You introduce yourself and then ask, ‘Can you tell your mum that?’

‘Ok,’ she offers a quick aside to her mother who nods and smiles.

You have got used to using translators recently, and at rapidly training up members of the family. You have found it is essential to speak in short sentences, especially when children are translating, and have learnt to insist on getting them to translate everything and not just nod when they understand themselves.

The girl then explains that she has had a rash for 1 week. She saw another doctor here 3 days ago who recommended an antihistamine for the itch and hydrocortisone, and asked her to come back if she was no better. She is well, has no raised temperature, and her appetite is fine.

You ask to have a look and she stands up in front of you and lifts up her blouse.

She has scattered spots on her trunk, about 30–40 on her front and 20–30 on her back. They are small, about 2–3 mm, although some are smaller, pin head sized, and some are larger, 4 mm. The larger ones are kind of flat but most stick up like tiny button mushrooms. You start to suspect what they are and turn her around for a closer look. Yes, some of them have a characteristic dot or hole in the middle known as an ‘umbilicus’. These are molluscum contagiosum.

But these are funny ones; there are more than usual (usually there are eight to ten), they are spread out more than usual (usually you see them just in the groin, or just on the face, or wherever they happen to start), also the large ones are bigger and flatter than ones you have seen before.

‘Where are you from?’ you ask curiously.

‘Colombia.’

‘Oh wow. Then it must be Spanish you are speaking?’ They nod, smiling.

‘I know what this is,’ you say. ‘Let’s get you dressed.’ You sit down again after washing your hands.

‘Ok. These spots are caused by a virus. A bit like a wart virus. Do you know the word virus?’

The girl hesitates and nods and then rapidly translates.
‘It’s not a wart virus though.’ Translate. ‘It is called molluscum contagiosum.’

‘I don’t know that word,’ she says. ‘I will write it down for you,’ you say. She nods.

Piece by piece you explain. Normally you would give a leaflet but unfortunately you don’t have a Spanish language version. ‘It’s not a dangerous condition, but it is annoying. It goes by itself. The main problem is it takes 1–2 years to go.’ (Here you get a reaction from the mum.) ‘I know, but when it goes there is no scarring. Sometimes they are itchy. If you scratch them they sometimes inflame and then they heal up and go.’

‘Should she stay off school?’ is asked. You advise no, but the lesions should be kept covered, for example in sports lessons. They spread by skin to skin contact. They are very common in children. Here you add a caveat. Because these are more extensive than those you normally see you suggest that if they get worse she should come back and you will refer them to dermatology. Although they are almost always best left alone, sometimes dermatologists do treat them. For example, if they are causing visual difficulties (on the eyelid), or if seen in an adult (typically across the abdomen caught during skin to skin contact during sexual intercourse), when they are treated with cryotherapy or chemical treatments.

‘Should I carry on taking the antihistamines?’ asks the girl on her own account. ‘They made me very sleepy. I was in class, like this!’ and she bends forward as if her head is hitting the desk fast asleep. You smile. ‘Have you stopped them?’ She nods. ‘Yes, stop them and the cream.’ You write down the name on a piece of paper so they can look up about molluscum on the internet and hand it to the mum. Everyone stands up and you say goodbye and thank you and, ‘Thank you for translating,’ to Estela. She nods casually and they smile and leave.

**Microbiology**

Molluscum contagiosum is caused by the molluscum contagiosum virus, one of the Poxvirus family. This family also includes smallpox (variola), cowpox, vaccinia (the smallpox vaccine originally derived from cowpox but eventually only viable in humans), and orf.

Poxviruses are the largest viruses seen, at over 250 nm (bacteria sizes are typically 1 μm or 1000 nm) and have a complex structure, ovoid in the case of molluscum (Figure 10.7.1). They are
linear ds DNA viruses with a lipid membrane bilayer and are distinct from other viruses in that they do not have to replicate in the nucleus, they can replicate in the cell’s cytoplasm.

Molluscum is diagnosed clinically but the virus can be demonstrated from the lesions using electron microscopy (see Case 10.8, Orf).

It is transmitted by close contact and resolves spontaneously, given time.

Further reading

Case example

There is a knock on your door. You are in a rural practice in Wales. It is your colleague, Dr Thomas, looking vaguely anxious. ‘Could you come and have a look at a strange lesion on someone’s arm?’

You smile and agree and walk through with him to the treatment room as he murmurs a concise history in your ear: a 25-year-old veterinary student, well in herself, lesion started 5 days ago, grew, turned black but not painful at all, then the rest of her arm began to get red, swollen and inflamed and feel sore. It sounds strange.

When your colleague draws back the curtain you find the patient is a friend of yours, Maisie Llewellyn, and she greets you by your first name.

You smile and say, ‘Hello Maisie. What are you doing here?’ She looks ok, normal colour, alert and upright on the couch, and yet not quite right. You never normally see her sitting, much less prone. She is usually busy striding about on farms, where you see her man-handling sheep or lifting veterinary equipment around.

You walk a few steps forward asking, ‘Can I have a look?’ She nods, and lifts up her arm a little for you to see as she sits there patiently.

It looks quite shocking. There is a large, mainly circular lesion on her right wrist, 6 cm across and sticking out by 1–2 cm. The surface is heterogeneous, some of it red and some of it black. The blackness of the lesion makes it look very sinister and you are worried about what will happen to Maisie. If it were gangrene or some sort of tumour, the outlook could be very serious indeed. However, this bizarre lesion contrasts with her demeanour, while not well, she is not septic either.

The rest of her arm is also not quite right. It is swollen and red and warm. The lesion itself is cool and completely painless.

You look and look and absorb its appearance, waiting for inspiration to come. You have never seen a lesion like this.

Your colleague has gloves on and is palpating it. ‘I was going to try incision and drainage,’ he says quietly. You nod, agreeing, and step back out of his way.

Your practice nurse is assisting and has arranged a trolley with a dressing pack, iodine solution, swabs, and tweezers. There is also a scalpel blade. Your colleague cleans the lesion using tweezers to hold each swab, dipping them one by one into the solution and then cleaning the lesion before dropping each swab straight into the bin once he has used it.

The nurse drops a needle and syringe out of its sterile packaging onto the sterile top of the trolley and then breaks open a vial of local anaesthetic. She reads out the label and the expiry date and then holds it while Dr Thomas draws out the local anaesthetic using the needle and syringe. He gently injects it superficially over the surface of the lesion.
Everybody waits quietly for a minute or two to give the local a chance to work. Presently, Dr Thomas tests the surface of the skin with the sharp blade of the scalpel to make sure all is numb and looks at Maisie’s face for any expression. Your friend nods, quite contained, tolerating being the patient for once. Dr Thomas then incises a small cut 12 mm across the lesion by simply pressing the scalpel blade into the surface.

The nurse has a swab ready to collect pus, but there is no pus at all, even after your colleague presses the surrounding skin. The nurse swabs the incision site anyway and there is a sort of pause while everyone watches her put the swab carefully into a container.

‘I think it’s orf,’ you say.

‘What?’ says your colleague.

You vanish back into your own room for an illustrated book you own on infectious diseases and flick to the page on orf. There is a picture of a smaller lesion, sort of similar.

You read the description to yourself:

Shepherds are infected at lambing time, but shearers, abattoir workers, and veterinary surgeons can also catch orf. Exposed surfaces such as hands, forearms, or the face are usually affected. An irritating but pain free nodule develops, enlarges and has a gelatinous appearance. It may be incised (wrongly) but no material expressed. Healing takes some weeks but there is no scarring. Secondary bacterial cellulitis . . . may occur.

It fits. She is a vet, you know she deals with sheep.

You walk back to the treatment room. ‘Look, I think it’s orf.’ It’s a strange word and you feel a bit silly saying it. You show your colleague the picture and read out the description to everyone present. There is a lightening of the atmosphere.

Now you, Dr Thomas, the nurse, and Maisie all know what it is and what to expect. You all know it is not dangerous and that Maisie will be ok. That this large lesion will get completely better by itself and Maisie won’t need surgery.

Your colleague is pleased and relieved that a diagnosis has been made. He gives you a big smile. Because the arm is red and swollen and likely to have a secondary bacterial infection you agree that the patient needs antibiotics. You leave Dr Thomas inserting an IV cannula for this purpose and nod and wave goodbye to Maisie, who is already looking better, before getting back to your own patient list.

Microbiology

The differential of lesions on the hands and arms includes herpes simplex virus, hand, foot and mouth disease, cowpox, and orf. With a large lesion like this the differential would also include life-threatening illnesses such as cutaneous anthrax or neoplasm. Prompt diagnosis of orf is essential to prevent unnecessary psychological stress and surgery.

Orf is caused by a poxvirus. Poxviruses tend to be large viruses with complex shapes and orf fits with this being 200 × 300 nm (Figure 10.8.1). This group includes variola (smallpox), cowpox, and molluscum contagiosum (see Case 10.7, Molluscum contagiosum).

Orf is caught by direct contact with an infected sheep or goat. The illness is known in animals as ‘scabby mouth’ or ‘sore mouth’. It can only be caught if the farmer has broken skin and comes into contact with the animal lesions. It is not transmitted from human to human. Neither animals
nor humans have strong immune response to the infection and it is therefore possible to catch the virus more than once.

Infection is avoided by quarantining new animals and avoiding taking animals to public events such as agricultural shows where they can pick up a new infection. Wearing gloves to handle infected animals if the skin is broken is sensible. Good hand hygiene with soap and water between handling animals can also reduce the chance of spreading infection within a flock (important for vets and judges at shows). There is also a scabby mouth vaccine developed for animals (not humans).

Scabby mouth is a common infection in sheep and goats and it is not uncommon for farmers to be inoculated with it. However, farmers familiar with the infection often do not seek advice from their GP and most doctors have not encountered patients with orf.

Diagnosis is usually made clinically. Laboratory confirmation can be obtained using electron microscopy on a smear of vesicle or blister fluid but most hospital microbiology laboratories no longer have electron microscopes so the samples are sent off to reference laboratories such as the Public Health England Virus Reference Laboratory in Colindale or the Rare and Imported Pathogens Laboratory at Porton Down (Box 10.8.1).

![Fig. 10.8.1 A transmission electron micrograph of orf virus showing its large complex shape.](http://phil.cdc.gov/phil/details_linked.asp?pid=8434)
Box 10.8.1 Electron microscopy

In Victorian times microscopists had accepted that it was simply not possible to visualize structures smaller than 500 nm. However in the 1930s, scientists worked out that they could direct a beam of electrons with solenoids in the same way as a beam of light is converged by lenses. Electrons were focused onto a fluorescent screen or a photographic plate forming a *transmission electron micrograph*: a black and white image formed *directly* by the electrons. The more electrons absorbed by the plate, the brighter the image. It was found that the image could be improved by the use of stains that absorbed electrons and sharpened the contrast, for example a metal-based stain from osmium. A working electron microscope was developed by the 1950s that was capable of visualizing a structure of 1 nm.

The beam of electrons is very hot, so any biological sample has to be processed first either by freezing or dehydration and the microscope kept cool with circulating water.

In the case of a sample from a patient with suspected orf, the laboratory would mix the dried fluid from the lesion with the stain and place a drop of this suspension onto a metal grid. The metal grid would then be placed onto a specimen holder and inserted into the electron microscope with the grid in line with the electron beam. The specimen holder can be moved so that different parts of the grid can be visualized.

The sensitivity of electron microscopy depends on a high concentration of viruses per millilitre (at least $10^5$). If the concentration is too low then the microscopist may not be able to find the viruses. Immune electron microscopy can help with this problem, using virus-specific antibody to agglutinate the virus particles together making them easier to spot.

A second form of electron microscopy called scanning electron microscopy also exists that can produce a three-dimensional image. This is used for research rather than for diagnostic purposes.

Electron microscopy can be used for identifying viruses if the virus has a distinctive shape as does orf and the other poxviruses. It is also used to identify viruses that cause gastrointestinal infections such as rotaviruses. However, these days it is being used less and less for diagnosis due to the implementation of nucleic acid amplification tests such as PCR.

Further reading


Case 10.9

Tinea capitis

Case example

You call in Hetel Singh (7) and her mother. Hetel is neatly dressed with smoothly brushed hair and she sits nicely in the chair nearest you. Her mother adjusts her sari and headscarf next to her. When she speaks she has a South London accent. ‘It’s about Hetel’s head; she’s got a bald patch there that I’m worried is ringworm. I’ve been putting on an antifungal cream.’

You look at Hetel again and see the bald patch near her forehead, which you hadn’t noticed at first. You beckon her forward so that you can lift her hair up and look more closely. It is in a neat circle, 3 cm across and a red raised appearance around the outer edge. The scalp is not smoothly bald (so it’s not alopecia areata); there are broken off hair follicles present.

‘Yes it does look like ringworm,’ you say. ‘How long have you been using the cream?’

‘Only 2 days – since I noticed it. I bought her in here as soon as I could, because I thought she would need tablets.’

‘Oh. Let me check,’ you say, because although you have seen lots of ringworm on the body (tinea corporis), athlete’s foot (tinea pedis), and nails (onychomycosis), you haven’t seen it on the head before. As you reach for the BNF she says, ‘I thought it was ringworm. I’m a biology teacher you see, and when I had her hair cut the day before yesterday that’s when the hairdresser pointed it out I knew exactly what she was talking about as I’ve just been teaching about fungi and things at school. I was so embarrassed.’

The BNF concurs with your patient. This is not the moment for creams. Hetel needs a sample sent off and oral treatment for 4 weeks.

You weigh her and calculate a once a day dose per kilogram and then beckon over Hetel again and she stands patiently while you gently brush up some flakes from her head with a plastic brush to send off to the laboratory. Previously you have used a sterile scalpel to scrape flakes but the brush works well too.

‘And what about infection? Does she have to stay off school?’

‘No,’ you say, ‘It’s not that infectious, it needs close contact to spread. If you use the cream topically, as well as the tablets then that should be fine.’

‘What about at home? We’ve got separate towels and hair brushes. Should I and my husband get some antifungal shampoo to prevent our getting it?’

‘You can do. It’s available at the chemist without a prescription, an antifungal shampoo with ketoconazole in it. However I wouldn’t recommend it unless you actually get symptoms (in which case early treatment is ideal). You’re doing everything right, particularly with separate towels, bedding etc.’

‘You’ll have to let your students know what’s happened!’ you suggest as you open the door for them at the same time as handing her the prescription. She smiles and you have a feeling there is no way she would do that. Hetel waves and says goodbye politely and they both leave.
You turn to the computer and document the consultation. Then you look up tinea capitis to see if Hetel should be at school or not because you were not perfectly sure about that advice. Fortunately you read ‘It’s not practical or sensible to keep them off for the full duration of treatment of 4 weeks.’

Several weeks later you receive the microbiology report:

Site: scalp. Microscopy: for culture only. Culture: Trichophyton soudanense—a significant growth. This infection can pass between children that live together.

**Microbiology**

Tinea is the Latin word for worm, and as the rash usually looks like a ring or a disc the commonly used term for this condition is ‘ringworm’, as mentioned by Hetel’s mother. But tinea is not caused by a worm; it is caused by a fungus.

Fungi are eukaryotic cells with stiff cell walls like plants, but no chloroplasts. They get their energy from feeding off living organisms (parasitic fungi) or dead organic matter (saprophytic fungi). The dermatophytes (the name of the fungi that typically cause skin, nail, and hair fungal infections) are saprophytic, and feed off shedding keratin.

Fungi can either exist as oval cells which bud off when they proliferate (e.g. baker’s yeast) or as long filaments called hyphae (e.g. a fluffy looking mould on an orange) which shed spores to proliferate. Mushrooms, which are also fungi of course, consist of lots of hyphae bundled together to make the solid form of the mushroom.

There are five sorts of true fungi. These are basidiomycetes (mushrooms), zygomycetes (bread moulds, not normally a pathogenic group), oomycetes (water moulds, again not a pathogenic group), deutoromycetes (this group includes *Coccidioides* spp., which are rarely seen pathogens), and ascomycetes, the group we are interested in. This group includes many well-known fungi such as baker’s yeast and brewer’s yeast, as well as pathogenic fungi such as *Aspergillus*, *Candida*, and the dermatophytes.

*Trichophyton soudanense* (the dermatophyte infecting Hetel’s head) (Figure 10.9.1) is one of the three main sorts of dermatophytes: the *Trichophyton* spp., *Epidermophyton floccosum*, and *Microsporum* spp.

**Fig. 10.9.1** A photomicrograph of *Trichophyton soudanense* stained with cotton blue, showing hyphae with reflexive branching.

Reproduced from Centers for Disease Control and Prevention, Public Health Image Library (PHIL), Image ID#11008, Dr Libero Ajello, 1974, available from http://phil.cdc.gov/phil/details_linked.asp?pid=11008
Hetel’s infection is on her head and this indicates she needs oral treatment, not just topical treatment. Oral treatment is also indicated for nail infections and for acute infections, and for *Trichophyton rubrum*, even infections of just the skin, because this species is especially infectious.

In the old days, treatments for scalp infections were not very effective and included castellani’s paint plus magenta or potassium permanganate soak (a purple liquid which was painted over the shaved scalp). Even X-rays were used for a time, leaving some children with permanent alopecia.

Some children were simply left until they grew out of the condition at puberty. This is because the sebum that adults produce on their hair is hostile to fungi and therefore the condition would resolve spontaneously. Adults do not suffer from tinea capitis.

The oral medication griseofulvin was approved first (1958) and later terbinafine (1996), which was even more effective (interfering with fungal sterol production, used to make fungal cell membranes) and these are now the recommended oral treatments. Care should be taken with the dose and formulation in children.

**Further reading**

Case 10.10

Tinea corporis

Case example

‘It’s about this rash, doctor. It’s ringworm in’t it. I’ve seen it before on me other kids.’ Daniel Rourke is 8 and his mum pulls him forward firmly and pulls up his sleeve proffering his arm to you over the corner of the desk.

He is a mixed race child so the background tone of his skin is dark but not black, allowing you to see the rash reasonably well. ‘Oh!’ you say. ‘That’s a very distinct one.’

There is a 4-cm circular lesion on his forearm with a raised erythematous edge with marked flakiness, and with central sparing, that is paler skin in the middle as if it has partly resolved. This is a classic ringworm lesion, so classic indeed that it surprises you.

‘They’re not usually as clear as that,’ you say.

‘And it came up so quickly doctor, just a week he’s had it. I knew what it was, ‘cause me older boy had it once but his was more patchy like. It’s itchy too.’ Daniels other hand goes to scratch his forearm at this reminder, and she bats his hand back.

‘Yes,’ you agree. The lesions are usually smaller, less distinct, sometimes just generalized redness and dryness in patches, difficult to tell apart from eczema. In those instances a trial of treatment can sometimes differentiate the two.

‘Is it ok if I take a sample?’ you ask. Daniel’s mum nods and both look intrigued when you come back with a small paper envelope and with what looks like a collapsible tooth brush. Inside the envelope is a square of stiff black paper which you unfold. After putting gloves on you clean the lesion with the alcohol swab to wipe off any residual creams. You then screw the plastic brush together with its handle and rub it firmly over Daniel’s rash. Daniel looks surprised but doesn’t move. Flakes of skin are dislodged, which you then gather up on the brush and tapping the brush over the paper, deposit the flakes in the centre. The light skin flakes show up easily on the black paper.

When you have enough you discard the brush and carefully fold the paper so that the flakes of skin aren’t flipped off, and slip it back into the envelope ready for labelling and sending to the laboratory.

You then turn to the computer and print off a prescription for two tubes of miconazole cream: an antifungal cream. You elect not to use Daktacort® (the antifungal combined with steroid) as the steroid delays healing.

‘Use twice a day for maybe 4–6 weeks. It’s really important to carry on the treatment even once the rash is gone for 10 whole days. Otherwise it tends to come back again. You should notice it improving within a week or two so if it’s not improving or if it’s getting worse just come back again.’

‘Yep all right. I’ll remember that.’

‘I’ve given you plenty of cream but if you need more just ask for it. Or in fact you can buy it over the counter at the pharmacy if you run short at the weekend or something.’

‘Ok. Right come on Daniel; back to school. Or is it all right to go to school?’
Tinea corporis means, of course, a fungal infection of the body. Infections of the groin, the feet, and so on, are all named after the site: tinea cruris, tinea pedis, etc.

Tinea is caused by fungi known as dermatophytes. Of the three main sorts, we have already met the *Trichophyton* species in Case 10.9, Tinea capitis. There is also *Epidermophyton floccosum* (this one often affects the groin and genitals) and *Microsporum* spp., in Daniel’s case a *Microsporum canis*.

The identification of this organism is interesting as it indicates the infection came from an animal (zoophilic), rather than from the environment (geophilic) or from another human (anthropophilic). Infections from other humans don’t make us react so much, as we are used to them. But this infection from a dog or a cat has caused a marked inflammatory response; remarked upon by the mother who has seen less obvious, presumably anthropophilic, infections before, in her other children. It would have been interesting for the doctor to have asked Daniel about any new pets.

The sample once received at the laboratory has been processed systematically using microscopy, culture and then further tests to identify the exact species.

For microscopy the skin flakes are carefully put on a slide with potassium hydroxide. This dissolves the keratin allowing the fungal hyphae (the filaments) to be seen. If the stain calcofluor white is used and the slide viewed under ultraviolet, the hyphae show up even better. Alternatively lactophenol blue can be used (which stains the hyphae a lovely blue) and again makes them easy to pick out. At this stage a preliminary report can be forwarded to the clinician, for example ‘Fungal hyphae seen’.

To culture the sample a medium called Sabouraud’s agar is used, which is both glucose rich and has a low pH. It also contains both an antimicrobial, chlorhexidine, and an antibiotic, chloramphenicol. This enables the fungi to thrive while inhibiting any bacterial contaminants.

Once the colonies have grown (which can take 3–4 weeks) then further biochemical tests, colonial characteristics, and microscopic morphology are used to identify the exact species.

The treatment used for Daniel is an azole called miconazole, although clotrimazole or any azole can be used. These chemicals disrupt the ergosterol membrane of the dermatophytes and are therefore ‘fungostatic’ (they stop the fungi growing but do not kill it).

It should be noted that nystatin, another antifungal medication (not an azole), although good for candida infections, does not work on dermatophytes. Therefore, combination creams including nystatin (e.g. Tri-Adcortyl®: nystatin, fucidic acid, and hydrocortisone) should not be used. Nor should steroid combinations be used, as the azoles are very effective and actively reduce the inflammation rapidly by themselves, whereas an added steroid, which will reduce inflammation as well, will also actively delay healing and promote the growth of the fungus.

**Further reading**

Case 10.11

Fungal nail infection

Case example

Richard Walmsley (29), a new patient, appears to be a nervous or anxious individual. He is complaining of intermittent abdominal pains. Because of the feeling of anxiety you pick up over the phone, you don’t bother taking a detailed history but directly offer him an appointment for that afternoon so that you can interact face to face.

In person, Richard is tall and slim and palpably nervous of you, but clearly more nervous about his symptoms. He has had bloating and abdominal pain coming and going for the last 3–4 months. He’s tried cutting out wheat, which has helped a bit. He works as a junior administrator at the local council.

Bloating is a symptom more frequently seen in women, but is also sometimes seen in men with associated bowel symptoms. You patiently pace him through his history, including red flags (weight loss, change in bowel habit, blood or mucus in stool, constant unmoving abdominal pain, change in appetite or energy).

With this last, he does agree he has been tired recently. You add in tiredness questions, asking about his occupation, family, partner, sleep, and mood.

With regard to sleeping, he says he has difficulty sleeping because of a rash and lifts up his shirt. You can’t see anything. He also mentions he has a male partner triggering you to assess for sexual risk. You are starting to get restless as you know you are now running over for this consultation.

A few minutes later you have examined him (unremarkable abdomen), checked the rash (nothing to see), and a mole that he asks you about, and formulated a plan of blood tests and stool test to exclude both inflammatory bowel problems and medical causes of tiredness and including a sexual screen of HIV, hepatitis B and C, glandular fever and syphilis, with the intention of a telephone review in a week to discuss the results (which you expect to be normal). You hand him a blood form with TFT, LFT, U&E, FBC, Fe, HIV, Hep B, Hep C, ESR, CRP, VDRL; diagnosis ?IBS/?tiredness written on it.

You have been reasonably patient and thorough and he seems a little calmer. You have suggested the possibility of IBS but suggest waiting for the results before discussing if further.

You are ready to move on to the next patient. You have been with him 22 minutes.

‘Could I show you one more thing?’ Richard says, trustingly taking off his shoes. He removes his sock with a flourish, which flicks god-knows-what towards your face. It’s too late to say NO.

He lifts his foot towards you. ‘I’ve got these really dry feet and in the last 6 months the big toe nail on this foot has started to go a really funny colour and last summer I never wore sandals because people kept noticing it and it was embarrassing.’

You hold his right foot (which you caught by the heel just before it landed on your knee) and inspect it. His big toe nail and the one next to it are both yellow and thickened with a crumbling appearance. You lift the foot up and check the sole and then the heel for dryness and then
look between each toe for any signs of athlete’s foot. There is a little dryness on the big toes but nothing else.

‘Is the other foot ok?’ you ask. Sometimes symmetrical big toe nail discoloration is present, which would then fit more with shoe trauma or bruising rather than a fungal infection. But Richard says his other foot is fine.

‘Let’s get you dressed,’ you say. ‘It could be a fungal nail infection. Is that what you were thinking too?’ He nods. ‘What I’ll do is give you a sterile pot and a form,’ you scribble hastily on a pot as you speak, ‘and get you to trim a bit of the affected nail off yourself at home. Then just hand it into reception. The result takes quite a while to come back, usually 6 weeks because it takes that long to grow the fungi. But it’s best to wait for the result because the treatment takes so long, usually 6 months of a daily tablet for toe nails.’

‘Six months?’ He looks surprised.

‘Yes. So it’s worth confirming it really is a fungal infection. Some people want treatment because they are concerned about the way it looks. Other people don’t bother because it doesn’t usually cause any harm or pain. It usually stays just as it is. It’s a personal choice really. We’ll decide when the results come back,’ you say handing him the form and opening the door firmly.

Richard Walmsley stands too, hesitantly and gathers the 3 forms (blood, nail and stool) in his hands. ‘So I’ll speak to you in a week?’ he says uncertainly.

‘Yes. Telephone in a week and we’ll go over all the results together. I think it might be IBS but we’ll wait and see and talk about it then.’ Inside you are jumping up and down with impatience but outside you simply smile and nod. ‘Goodbye. Speak to you soon.’

You document his problems: ‘(1) abd pain, (2) rash, (3) mole, (4) tiredness, (5) sexual health screen, (6) toe nail’ rattling away at the keyboard.

Six weeks later a colleague forwards a document from the mycology department to you that reads:


You send a letter to Richard informing him his result is back and to contact you to discuss if he wants treatment.

**Microbiology**

This is a very typical scenario in that Richard has not presented with his nail problem but merely asked about it almost as an aside at the end of a (long) consultation. This is a common occurrence and it kind of makes sense, as for most people (not all) fungal toe nail infections are a very minor complaint.

*Trichophyton rubrum* is a fungal infection known as a dermatophyte (discussed earlier in Case 10.9, Tinea capitis and Case 10.10, Tinea corporis). It is an anthropophilic (human to human) infection and is therefore generally well tolerated. It tends to be an infection of covered parts of the body, for example, the feet and the groin.

Tinea infections often result from damage to the skin typically caused by increased temperature or moisture, that is sweaty, hot feet. *T. rubrum* is the commonest cause of tinea in this country and is thought to have been imported into the UK from the East, by returning soldiers during the Second World War.
The treatment for a fungal nail infection is oral terbinafine for 4–6 months. (It should be noted that terbinafine doesn’t work for microsporum infections, in which case griseofulvin should be used.) The long treatment time is because the medication only penetrates the growing nail, so treatment must be continued until the nail has completely grown out and replaced itself.

Because it is a minor condition, and a daily tablet for that long is difficult to sustain for most people, the decision to treat should usually be left to the patient. The option not to treat is always worth raising as the doctor did with Richard. If the patient does decide to go ahead with treatment then it is usual to prescribe 2 months at a time, so that if the patient lets the treatment lapse there is less tablet wastage.

Further reading

Case 10.12

Candida intertrigo

Case example

‘I don’t know why my husband is so worried now! I was much worse last week—coughing and
coughing, I couldn’t catch my breath!’ she catches his eye and he looks away sheepishly. ‘Now I’m
feeling a lot better, my appetite is better . . .’

As if to illustrate this, Mrs Verde on the verge of another remark, instead starts coughing and her
husband flicks his eyes back to her again, looking concerned.

‘Oh no. Not again,’ she manages to squeeze out.

You pause what you were about to ask while she coughs for ages, about 15 times, and goes alarm-
ingly red in the face. Then she draws breath and holds still for a moment. Her colour settles. Next
minute she pushes on.

‘But I can’t go out, darling! Otherwise when I cough I, you know, I . . . down there.’

‘Leaking do you mean? Like urine leaking? When you cough?’

‘Yes, darling. I have to wear pads.’

Mrs Verde and her husband are both 72 and Italian. She is tiny, dark haired, and so full of energy
you can’t help but enjoy yourself when with her. Her husband, also short, sits next to her, satisfied
at having hauled her into the surgery to see you.

You establish she has never smoked, has never had asthma, has been coughing for 1 week and that
her appetite is returning. You are satisfied it is not COPD or a serious infection and wonder if you
should give her broad-spectrum antibiotics for an acute bronchitis—partly in the light of her age
and partly in the light of her family’s expectations.

You check her temperature, pulse, respiratory rate, and oxygen saturations (all fine). When you
ask Mrs Verde to stand up to listen to her chest she is hardly taller than you when you are sitting.

‘And I’ve got a rash darling, under here. I never had this before, I’ve been washing it every
day morning and evening. Here, it’s under here. And so itchy! I’ve been putting Vaseline on it every
day.’ Her husband nods in agreement.

You help her lift up an outer jumper then a flowered dress and then two vests, but no bra.

‘No bra darling! Not today! I thought you wouldn’t mind!’ She energetically lifts up all her clothes
in front of you and you see a marked homogenous red rash under both breasts including the
crease marks with a clear delineation ending where the breasts stop overlapping with the skin.
There is no discharge or crusting.

‘Oh yes,’ you say, ‘This is a yeast infection.’ This is what you expected to see after hearing her
description. ‘I can give you a special cream for this to cure the infection. It will get better. Stop
the Vaseline though. But carry on with gentle washing. The washing is good. Make sure to keep
it all clean and dry.’
You move on to listen to her chest, which is unremarkable. Then after helping Mrs Verde rearrange her layers and sit down again you move over to the sink to wash your hands. When you are back at your desk you find Mr Verde has brought out a festively wrapped package for you. He hands it to his wife.

‘To say thank you darling. For seeing me so quickly!’

‘Thank you Mrs Verde, Mr Verde. That’s very kind of you. It’s a pleasure.’ You smile, pleased and surprised.

After you hand her the prescription for clotrimazole cream and amoxicillin capsules and have politely opened the door for them both, you say that you look forward to seeing them both again. You feel you have just said goodbye to a party guest.

**Microbiology**

Intertrigo is the term used for an eruption between two opposing skin surfaces; in this case the breast and the rib cage. Other common sites include the groin (nappy rash if seen in babies), the axilla, and the umbilicus. The opposing skin surfaces become warm and moist, which breaks up the stratum corneum of the skin and allows infection to enter, in this case *Candida*.

*Candida albicans* is the commonest of the many species of candida. Other examples include *C. krusei*, *C. glabrata*, *C. tropicalis*. A *Candida* infection is often described to the patient as a yeast infection, as with Mrs Verde the doctor briefly mentions ‘yeasts’. Unfortunately, patients often interpret this to mean that they have caught it from yeasts in bread or beer and some even cut these foods out of their diet completely. It is important to understand that baker’s yeast and brewer’s yeasts are different species altogether, the *Saccharomyces* spp. For example, *Saccharomyces cerevisiae* is used for making beer.

Yeast is simply a colloquial expression for those forms of fungi that exist as oval cells, 2–3 μm in size, of which both *Candida* and *Saccharomyces* are one (Fig. 10.12.1). Mould is the colloquial expression for those fungi that exist as hyphae (although funnily enough we don’t often tell patients they have a mould when presenting with tinea).

There is a case to be made for the doctor in this instance to have done both a blood glucose test to check for diabetes (a common predisposing condition for candida intertrigo) and a swab

![Fig. 10.12.1](http://phil.cdc.gov/phil/details_linked.asp?pid=2918)
for microscopy and culture. (There is also a discussion to be had about whether antibiotics should have been prescribed at all.) Candida spp. (like the dermatophytes) culture well on Sabourard’s agar. Unlike them, however, it grows much quicker, within 48 hours, and forms white butyrous colonies.

*C. albicans* can be differentiated from the other candida by a special test called a germ tube test. This is where the sample is incubated in human serum for 3 hours to encourage the yeast cell to produce hyphae. If positive, the yeast cell can be viewed under the microscope showing a parallel-walled, long structure (3 times the size of the cell) poking out of the round yeast cell (Fig. 10.12.2). The *C. albicans* hyphae have a characteristic look under the microscope compared with other Candida spp, and can therefore be differentiated. This is an important test to use when the candida infection is not intertrigo or mucosal but invasive. Invasive candida can cause meningitis, septicaemia, and severe gastrointestinal and urinary infections. Because invasive candida infections are not uncommon, fungal infections are routinely checked for on every CSF and blood culture sample sent to the laboratory. Invasive candida infections do not occur so much in normal patients but in those patients who are immunosuppressed. The identification of *C. albicans* is important in these life-threatening instances, because it means the organism is almost always susceptible to fluconazole, whereas germ tube negative yeasts such as *C. glabrata* and *C. krusei* are not susceptible to fluconazole and would need a different antifungal agent prescribed.

**Further reading**

Case 10.13

**Scabies**

**Case example**

You have already met Abigail Chester (42). You saw her a month ago with itchy dry feet, which you treated for eczema, and then 3 weeks ago with a strange, patchy, red, dryness around her breasts: very itchy. You treated this for contact dermatitis. But now you wonder if you were off-track altogether.

She is Afro-Caribbean, which hasn’t made interpreting her rashes easier (rashes look different on different skin tones and are particularly hard to see on black skin). She spreads out her hands in front of you. The backs of her hands show dark with the pink of her palms showing through at the finger webs.

‘Is it scabies doctor?’ she asks. Then she abruptly closes her hands and uses the fingers of one hand to scratch all the webs of the other hand at once, irritably. It makes you wince.

You catch her left hand with your fingertips and look closely at the finger webs, and then turn her hand over to look at her wrists. You are looking for burrows: lines of white just under the surface of the skin, about 4 mm long, and usually curving or wiggling. As usual you fail to find any.

‘My aunt and her friend, and her two children, have been staying at me house, down from Birmingham for 2 months. Then yesterday my aunt called me and say she got an itch and her friend just been diagnosed with scabies by her GP. And all the children!’

‘When did they move out?’ you ask.

‘Just about 4 weeks ago. And I been got this itching for the last few weeks and wondering what it was!’

You review the topic by printing off a leaflet for Mrs Chester, and as you scan through it you think about the time course, which appears to be consistent with scabies.

‘Is there anyone else at home?’ you ask.

‘No, it’s just me and me father at home,’ she answers.

You prescribe enough treatment to treat them both twice. They need 100 mL of lotion to cover their bodies entirely, as instructed, and they need to leave it on for 5–10 hours before washing it off and repeating the treatment after 7 days. You prescribe 400 mL.

‘You know you need to wash bedding and towels and things too?’

‘I’ve been reading about it. It’s a *nightmare!*’ She accepts the leaflet with a chuckle however which indicates she is accepting the diagnosis with good face. ‘Such a lot of work all this. I guess I’ll just have to have a Good Spring Clean!’

‘Now the most important thing is it will continue to feel itchy. The treatment is very good and will kill all the scabies mites straight off. But the itchiness will carry on for at least another 3 weeks before settling down. OK?’

‘Mmmm. OK.’

‘Here you go then.’ You pass her the printout on scabies and go through it with her, underlining the things you’ve talked about with regard to treatment and cleaning, and the prescription. At the
end you check to see if she has any questions. ‘Do the treatment today and then you’re straightaway no longer infectious,’ you conclude.

‘OK doctor.’

**Microbiology**

Scabies in humans is caused by a tiny 0.4 mm eight-legged mite called *Sarcoptes scabiei* var. *hominis* (Fig. 10.13.1). It can’t hop or fly so it is spread only by very close contact, for example by holding hands for long periods (not just shaking hands) or to children young enough to be held for long periods by adults. It is also spread between adults during sexual intercourse. It can spread from bedding, as mites can survive without their host for 36 hours, but this is rare. In experiments done during the Second World War, of 100 people sleeping overnight in infested sleeping bags, only three caught it. Scabies is more common in overcrowded households and is also associated with poverty, poor hygiene, malnutrition, and promiscuity.

The gravid female mite, once it lands on a new host, will burrow into the stratum corneum and lay about two or three eggs a day. These will hatch after 3–4 days and the larvae then take about 10 days to mature into adults. The young adults mate and the males die leaving the females who begin to lay eggs of their own. The mature females then live for about 4–6 weeks.

What is interesting is the ‘incubation period’ in that the human immune system takes at least a month to start to react to the mites. It is quite usual for a patient to have had an infestation for several weeks before presenting with itchiness, although they would have been infectious from the start. However, if someone gets infested for a second time, there is no delay to symptoms, and they start to experience itchiness within 2–3 days.

Although the mite prefers the thickest skin to burrow in (the palms and the soles), they can spread anywhere. Therefore, a patient will not present with just itchy finger webs but with itchy skin *everywhere*. The itch is particularly bad at night or after a warm bath and can disrupt sleeping. They may have an erythematous papular eruption on their trunk, abdomen, and genitals and itching on the fingers, elbows, buttocks, axillae, thighs, nipples, and genitals. The itching can be so bad that bruising can be seen as well as excoriation.

Fig. 10.13.1 A light micrograph of the human ectoparasite *Sarcoptes scabiei*. Reproduced from Centers for Disease Control and Prevention, Public Health Image Library (PHIL), Image ID#6301, Donated by the World Health Organization, Geneva, Switzerland, 1976, available from http://phil.cdc.gov/phil/details_linked.asp?pid=6301
Because of the non-specific presentation, the differential is wide and can include insect bites, eczema, tinea, and contact dermatitis. Eczema and contact dermatitis were both mistakenly diagnosed here with Mrs Chester.

Scabies is typically diagnosed clinically but can also be diagnosed microscopically by taking skin scrapings or biopsies. The skin scrapings are combined with potassium hydroxide to dissolve the keratin and then examined under the microscope for mites and ova.

During the First World War there were accounts of a very high incidence of scabies among the soldiers, presenting uniformly with genital papules. Indeed, in one article the writer asserts that one-quarter of patients presenting to a London dermatology outpatients department appeared to have had scabies, including secondary complications such as impetigo and secondary bacterial infection. The treatment at the time consisted of isolation and admission on the first day for, ‘a warm bath with plenty of soap’. (Washing is known to reduce the mite load although not to altogether cure the condition.) Then, ‘A sulphur Vaseline ointment should be rubbed in vigorously all over for the following 3 days and on the 5th day another warm bath with soap should be administered, and in addition clean clothes.’ This advice was still being quoted following the Second World War when again a large increase in scabies infestation was noted, although the sulphur ointment had been switched to a benzyl benzoate one.

The treatment recommended today is an insecticide, either permethrin 5% (first line) or malathion (second line) left on for 10 hours and then washed off. The insecticide lotion has to be applied all over; including difficult areas such as under the nails, between the buttocks, between the toes and fingers, and also over the soles and palms. The treatment is repeated after 7 days. All household members need to be treated, and at the same time all bedding, towels and clothes need to be washed at >50°C, or alternatively put into plastic bags for 72 hours to allow the mites to die.

Anti-itch therapies may also be needed following treatment, for example crotamiton cream (Eurax®) can be helpful, and the use of sedating antihistamines at night. Eczema can sometimes be triggered by scabies and need further attention. Some patients may become very fixated on the diagnosis and repeatedly re-treat themselves, and even avoid family and friends for weeks or months because of beliefs of persistent parasitosis.

Further reading

Case 10.14

Head lice

Case example

‘I think I might have head lice.’

Jane Purley in front of you is young (24) and has her hair down loose. It is shoulder length and a bright copper colour, not perfectly straight but wavy. You stare at it speculatively.

Of course, it doesn’t take more than a second for you to feel an itch in your own head.

‘I work in a school,’ she continues. ‘A primary school. I’m a teacher and some of the children have got nits. One of the mums found them in her daughter’s hair and came and told us. Of course we sent out letters to the rest of the class to get all the other mums to check their kids. Quite a few of them turned out to have them and I started feeling itchy a few days ago.’ You nod sympathetically.

‘Well, so I was wondering how you diagnose it. Can you diagnose me and tell me if I have nits?’ She’s very anxious and obviously desperate. Normally a head lice problem doesn’t get as far as the GP. The majority of people self-diagnose and then self-treat with the aid of the pharmacist.

Some people you know try to diagnose it by looking for nits. Nits are the empty white egg shells that are left stuck on the hair shaft. When the eggs have not hatched yet, they are grey looking, hard to see and very hard to detach. So, in a way, there is no point trying to remove the nits, as they are empty, and it’s not practical to try and remove the grey un-hatched eggs. The best method of diagnosing a head lice infection is wet combing for the lice.

So when Miss Purley asks you to diagnose her on the spot, you have a vision of you personally wet combing her hair with conditioner on your hands and a bowl of hot water next to you and rinsing a fine toothed white plastic nit comb of suspicious little black dots, and you say—perhaps more firmly than is necessary, ‘No. No. You have to do it yourself.’

You hasten to explain. ‘The best way of diagnosing nits is wet combing with a head-lice comb. You put conditioner on your wet hair because that stops the lice from wriggling away, and you comb through from scalp to the end of the hair shaft doing each square inch of scalp slowly and steadily. It should take at least 30 minutes.’

‘You can’t diagnose it now?’ she asks.

‘No, I’m sorry, it’s just not practical. The good news is head lice don’t carry any kind of infection. All they are trying to do is live their little lives.’ You are trying to reframe her possible head lice infestation from revolting and horrific down to slightly annoying problem.

You explain that the head lice wake up and feed by biting every 4 hours, which is why her head is not itchy all day, just every few hours. Some people can have a head lice infestation for 2–3 weeks before even noticing any itching. The eggs take 7 days to hatch and hatched lice take 7 days before they can lay eggs, which means it’s possible to clear an infestation by wet combing every 3–4 days for 3 weeks, removing newly hatched lice before they can lay more eggs.

The chemical treatments are also effective, for example malathion or dimeticone 4% (Hedrin*). Dimeticone is the newer silicone treatment that has the advantage of being non-toxic (to humans).
It works by physically coating the insect and interfering with the water balance in the lice, preventing the excretion of water. This method of killing means the lice are less likely to develop resistance. Either treatment is left on for 12 hours and given twice, 7 days apart.

Miss Purley is still really unhappy. You do feel sorry for her because it is difficult to wet comb one’s own hair effectively and it is an extremely tedious job as well.

You hand her a prescription and wish her luck with the clearance.

Microbiology

Head lice (*Pediculus humanus capitis*) are wingless insects. They can range from the size of a full stop, to 3–4 mm and are a black-brown colour. They are transmitted by close contact usually between children. The lice simply crawl from one head to another via the hair shafts (Fig. 10.14.1). They do not fly or jump and they are not transmitted in bedding. Head lice are one example of an ectoparasite: parasites that live on the skin or hair of their hosts. This group includes both insects (six legged, including fleas, lice, and bedbugs) and acarina (eight legged, including scabies-mites and ticks).

There are three species of lice that affect humans: head lice (*Pediculus humanus capitis*), body lice (*Pediculus humanus corporis*), and pubic lice (crabs or *Phthirus pubis*).

Head lice are not vectors for disease, but body lice are. Typhus fever caused by *Rickettsia prowazekii* is transmitted by the bite of the body louse and these ectoparasites have been very important throughout history, causing outbreaks and epidemics wherever there was poverty,

![Fig. 10.14.1 A light micrograph of a head louse.](http://phil.cdc.gov/phil/details_linked.asp?pid=19067)
overcrowding, and undernourishment. Such outbreaks were seen in prisons (gaol fever) and during war and famine. In the First World War typhus was common on the Eastern Front, but rarer on the Western Front, possibly due to a combination of better nutrition and delousing of the troops. The Western Front did however see many cases of another louse-borne disease, namely trench fever (due to the bacterium *Bartonella quintana*).

The female louse lays about eight eggs a day. These take 7–10 days to hatch and they then take 6–10 days to mature into adults. They live for 30 days. Head lice are endemic in the UK usually in children aged 4–11 with a peak age of 7–8. The presence of nits (the empty egg shell cases) is not proof of active infestation—this can only be confirmed by seeing live lice, recovered as described above by wet combing, or dry combing (less reliable but quicker). Sometimes samples from the head are sent to the laboratory in specimen bottles for identification. This isn’t usually for an infestation (which is usually obvious) but for someone who has an *idée fixe* that they have an infestation. In this instance microscopy usually reveals a skin particle or other debris.

Head lice (or the belief of having head lice) may cause great anxiety and distress for the patient and family. Other complications of head lice infection include an itchy rash on the back of the neck, excoriation, and difficulty sleeping.

**Further reading**

Chapter 11

Children

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Case example

The little 5-year-old boy in front of you is called Kelly and he is quite overweight. He has had a cough for 3 weeks and sometimes after coughing he vomits. He is leaning against his overweight mother's very plump knees. He is otherwise well, doesn’t wheeze, and his appetite is fine. If you were in the UK you would advise that this was likely a viral infection, that on average coughs do last 3 weeks, but sometimes up to 6 weeks, but that as long as he was coping, his appetite and breathing ok then it would be fine to watch and wait for him to get better. Obviously if he were to get worse or to get any new symptoms, or if were not better by 6 weeks, then to come back and see you.

However, this not being the UK, you have had to modify your prepared script. First you draw the little boy towards you to examine his chest. You get him to turn around and face his mother. He rests his hands on his mother’s knees while you lift up his t-shirt at the back and listen with your stethoscope for any crackles or wheezes. His chest is clear. You turn him round and lift up his t-shirt at the front to look at his chest and abdomen. His breathing is relaxed and slow.

You say, ‘I think this is a likely chest infection, but as it has gone on for 3 weeks I think it would be reasonable to make sure this not whooping cough. Did he have all his immunizations?’ The mum nods.

‘So his baby vaccines at 2 months, 3 months and 4 months, and the ones before school?’ you say. She nods again.

You stand up and reach behind the mum and her son to the trolley (it’s a cramped room), where after a brief rummage you find the right swab. This is a small swab on the end of a very thin wire with a liquid filled container to insert it into, seal, and send to the lab.

You ask mum to sit Kelly on her lap facing frontwards and to cuddle him tightly around his middle and arms with one hand, and over the forehead with the other hand. This will steady him while you take the swab. There is a bit of a struggle for Kelly to get onto his mother’s lap, as Kelly is so big because he is overweight, and the lap is so small because mum is overweight. For a moment you wonder if they are going to manage it, but they do; Kelly is balanced at the tip of his mum’s knees.

‘I’m going to put this little swab in your nose. It will feel kind of funny like you want to sneeze but just keep really still and then I can do it in two seconds!’ You make these remarks directly to Kelly after getting to his eye level.

You kneel in front of him and then, when they are ready, you push the swab into his nose, not upwards but horizontally aiming at a point towards the back of his head. The swab easily passes from the nose to the nasal pharynx. You twist it 360 degrees and quickly withdraw it. Kelly doesn’t hold still, he is too strong for his mother, and the feeling is too weird, but you are finished so quickly that he is simply left rubbing his nose with a surprised look on his face. ‘It tickles,’ he says.

Previously a pertussis swab would have been cultured. Culture had a low sensitivity and swabbing for pertussis was rarely done. Because of this, as far as you know, you have never seen a case
of pertussis. However, recent advances in testing for pertussis have changed the situation and pertussis can be reliably and sensitively diagnosed using PCR on a nasopharyngeal swab, as you are doing now.

Kelly’s swab does come back as positive. You phone the microbiology laboratory for advice. They suggest a course of antibiotics for Kelly: clarithromycin, twice a day, for 7 days. Transmission is by droplet, spread by coughing and sneezing, rather than aerosol, so only close household contacts need treatment, and they recommend an antibiotic course for him and a course for his mother and older brother. They advise that family members do not need swabs. Kelly should no longer be infectious (it is over 21 days since the start of the illness). In addition, the antibiotics, although they won’t affect the course of the illness, will reduce infectivity and the microbiology team advises that Kelly can go back to school after completing the course.

You ring Kelly’s mother and pass on the advice and leave out the scripts for her to pick up. However, Kelly’s mother doesn’t leave it at that and takes things into her own hands. You find that she has booked two emergency slots for the following day for herself and her other son to have nasopharyngeal swabs with you too.

Microbiology

Whooping cough, or pertussis, is caused by a small (0.8 × 0.4 μm) Gram-negative coccobaccillus (short with rounded ends) discovered by Bordet and Gengou in 1906, called *Bordetella pertussis*. There is another similar bacterium, *Bordetella parapertussis*, which occasionally causes a similar but milder illness.

As mentioned in the case, the organism is delicate and often died on the swab before processing for culture; furthermore, the infectivity (i.e. the amount of bacteria present in secretions) decreases as the illness progresses, so the sensitivity of culture was low (probably no greater than 50%), and decreased with time. The traditional medium for culturing *B. pertussis* was Bordet–Gengou agar, containing sheep blood, glycerol, and potato extract as nutrients, also the antibiotic cefalexin to prevent the growth of ordinary respiratory flora. Alternatively, charcoal–blood–cefalexin can be used. The agars are incubated for 7 days as *Bordetella* grows quite slowly.

Detection of *B. pertussis* using PCR offers greater sensitivity than culture. This test has been available in reference laboratories in the UK since 2001, but it is reserved for acutely unwell infants who have been admitted to hospital.

The other method of diagnosing pertussis is serological, examining for IgG antibody levels. This test can be used from 2 weeks after the onset of the illness and is particularly useful after 4 weeks, when PCR or culture becomes unreliable.

Whooping cough typically presents as a persistent cough for over 3 weeks, vomiting after coughing and coughing fits. A description of the cough from a medical textbook written in 1929 (from the eighth edition 1946) provides a clear description of what seems to be an eyewitness account:

> The paroxysm may be divided into 3 stages: (i) a short inspiration (not constant), (ii) a series of short sharp coughs which appear to gather speed and violence; and, finally, (iii) a long drawn inspiration; the sudden entry of air into the emptied lungs through a partially closed glottis gives rise to the characteristic whoop. During the paroxysm which, once started, nothing avails to stop, there is intense venous congestion of the face, which assumes an almost bloated appearance, with conjunctival suffusion and sometimes epistaxis. When the paroxysm ends, the child rapidly recovers its ordinary appearance and its equanimity.

(Conybeare 1946: 41)
Complications can include nosebleeds and sub-conjunctival haemorrhages and even petechiae, all due to the high pressure in the thorax induced by coughing fits. Rare complications include secondary pneumonia, seizures due to hypoxia during a coughing fit, and death.

The doctor asks Kelly’s mum about immunization and Kelly has had the full course so it seems surprising that he has got a confirmed pertussis infection. However, it is known that the vaccine, an acellular vaccine made from purified components of the bacterial cells, is known to protect at high levels in the first few years of life when the child is most vulnerable to infections and complications and then to wane. Pertussis routinely circulates in older children and adults; hence, any unvaccinated infants are personally vulnerable to infection. In some countries (including the UK) pregnant women are now advised to get revaccinated to protect the neonate right from birth.

Increased pertussis notification rates have been noted across the developed world over the last decade. Whether this is due to the more sensitive PCR tests, increased awareness of adult pertussis among doctors, or a real increase in cases, is difficult to determine.

Further reading


Case example

‘I got a letter from the health protection team,’ the mother of 4-year-old Allyn Mayur starts off quite reasonably over the telephone.

Allyn Mayur’s name is by now perfectly familiar to you. You bring up his notes and immediately a series of warnings on one corner of the screen pop up: ‘1st DTP overdue, 2nd DTP overdue, 3rd DTP overdue, MMR overdue, Preschool boosters overdue.’

However, you know all this, as Allyn’s mother is well known to the surgery having declined vaccines for all four of her children, of which Allyn is the youngest.

The reason Allyn’s name is familiar to you is that he has caused waves at the surgery by being a very rare example of a measles case. He was picked up by your colleague Dr Blaise, surprisingly quickly given that none of you have ever seen a case before. Following his second presentation within 5 days of a febrile illness, Dr Blaise, (who saw him both times) raised the case during a clinical meeting as being ‘funny looking’ and querying scarlet fever or adenovirus. On mentioning the surname, the family was recognized by one of the team as a vaccine decliner and someone mentioned the possibility of measles, so Dr Blaise was asked to go through the story in more detail.

Initially, Allyn simply had a typical non-specific presentation of a high temperature and cough for 1 day. On the second presentation 5 days later, his mum brought him in again because of a rash for 2 days, and Dr Blaise then also noticed a bilateral conjunctivitis.

A patient leaflet on measles is then brought up on the computer and everybody sits quietly reading for a few minutes and agree it is a possibility. ‘Better notify it and get some advice,’ you suggest to Dr Blaise. ‘It would be interesting to bring Allyn back to see if he has those Koplick spot things. I thought I had a case once a few years ago and they sent me a kit for doing a saliva swab (it came back as negative though). You should do a throat swab as well if you’re thinking of scarlet fever.’

‘What about the other children?’ someone asks. You all sift through the leaflet again. The incubation is 2–18 days and Allyn would have been infectious from 4 days before the rash until 4 days after. ‘They could well catch it; airborne droplet spread and highly infectious,’ you remark. ‘You better mention it when you ring. I wonder where he caught it?’

You leave it to Dr Blaise to liaise with the health protection team and communicate further with the mother.

It happened that you were the on-call doctor when a call from the health protection team came through 2 days later informing you that Allyn’s illness was measles and asking for lists of patients in clinic for each morning Allyn had been seen, with a view to sending each patient a letter informing them of the measles exposure and asking about vaccination history. In addition, they asked about high-risk individuals present, for example unimmunized pregnant women or babies and patients with reduced immunity. The health protection team confirmed...
that they had written to the patient directly and would be in further contact with the family by telephone.

At this point you had sent Dr Blaise a screen message to inform him of the result and he had rung you back straightaway with great interest, saying, ‘I can’t help feeling that it is a kind of just reward for declining to immunize these children. I mean I wouldn’t wish measles on anybody, but now he’s better I do think the mum ought to sit up and take notice.’

In short then you are reasonably up to date with the story and the phone call from Allyn’s mum is not at all unexpected.

‘Yes. Oh, thank you for calling. How is Allyn?’ you ask, wanting to establish that Allyn is ok in the first instance.

‘He’s much better and the other children are ok. I wasn’t too impressed to be badgered by this health protection thing though this morning.’

‘Oh?’ you begin before you are rapidly interrupted with, ‘Why are they calling me and not you? I’m not quite sure why they are involved.’

‘Well, measles is a notif . . .’ you begin apologetically before she continues with, ‘I made it clear to them that I was not satisfied with the treatment I received at your surgery. Nobody mentioned the possibility of measles when I first came in with him. It was only because I brought him back and said that there was an issue that anyone took me seriously.’

‘Well, initially the very non-specific . . .’
‘I told the health protection team that I was intending to complain about your practice to the Ombudsman . . .’

It is at this point that you realize that simple clear explanations are not working and that your own pulse rate is going up. Reflecting on Allyn’s presentation you feel that this patient has had a surprisingly early pick-up of measles and conspicuously good care. You feel for the mother as her decision has led to harm to her child, but on the other hand you are not prepared to tolerate her passing on the blame in this way and wilfully ignoring the consequences of not immunizing her child.

‘Mrs Mayur, I’m going to interrupt you at this point.’ You pause, having achieved a temporary silence over the phone. ‘I’m very sorry indeed that Allyn has had measles, and I am very pleased indeed that he is now better. But it’s really important for you to take on board that he probably would not have caught this illness if he had been vaccinated.’ You stop again and then say, ‘You obviously have some serious concerns about vaccines, can you give me an idea about what they are?’

‘I’m not prepared to talk about them with you,’ she says fluently.

‘Because it’s not too late. He will still benefit from all the vaccines. For example, the meningitis one?’

‘No. I’m not interested.’

‘Well ok. Shall we leave it at that?’ There is silence, and then the phone goes dead.

Twenty minutes later you hear loud shouting at the reception desk. After clinic is finished, the head receptionist lets you know that that was Mrs Mayur complaining. ‘She says she is moving practice. She says she didn’t like the way you spoke to her.’ You review the conversation mentally and hotly recount it to the receptionist, who listens patiently. You later also discuss it with a colleague. You feel that it was right to address the issue with the mum, but you are not perfectly sure you handled things correctly. Your main hope is that the complaint doesn’t go any further.
Microbiology

Measles is a highly infectious notifiable disease caused by measles virus. Measles virus is of the Paramyxovirus family and is a ss RNA enveloped virus 200 nm in diameter.

The Koplick spots mentioned in the case are pathognomic for measles, and are worth emphasizing. In the past, diagnosis often rested on identifying these lesions. These are small white spots on the inner cheek, like grains of salt with a raised erythematous base. They appear 2 days before the rash appears, and may sometimes be seen for up to 1–2 days afterwards. The differential mentioned by Dr Blaise and his colleagues includes adenovirus and scarlet fever but could also include rubella, parvovirus, enterovirus, and roseola infantum. Minor complications of measles infection include otitis media, pneumonia, and diarrhoea. Major complications include encephalitis and sub-acute sclerosing pan-encephalitis (SSPE), but SSPE has not been seen in the UK since 2004.

Before the measles vaccination was introduced in 1968, annual notifications in the UK were between 160 000 and 800 000 a year. There was a slight reduction of measles notification of about 100 000 a year following the vaccine, but measles transmission was not properly interrupted until the introduction of MMR in 1988 (see Appendix 4 for information on immunization schedules in the UK). The two-dose schedule introduced in 1996 has led to annual notifications in the UK now, of only a few hundred cases each year.

The MMR controversy linking MMR with autism has now largely settled; the data for this being based originally on a very weak case study, based on only 14 patients, since withdrawn from the *Lancet* where it was originally published.

The diagnostic test mentioned by the doctor in Allyn’s case is a salivary swab for measles-specific IgM or measles virus RNA detection. These can be taken up to 6 weeks after the onset of the illness. Note that Dr Blaise is notifying the illness as a case of clinical suspicion; he is not waiting until the diagnosis is confirmed. This will give the communicable diseases team more time to intervene if necessary.

The older children in Allyn’s family, as has been noted, are at high risk of being infected. Post-exposure MMR vaccination can be effective if given within 72 hours of exposure (too late for his siblings). Passive human normal immunoglobulin can also be effective if given within 6 days of exposure but is only used in non-immune pregnant patients, or high-risk patients, for example with HIV or malignant disease. The public health team will need to do contact tracing and immunize unvaccinated individuals as soon as possible. Measles is one of the most infectious viruses known and it is possible for one person to infect 17 others ($R_0$ 17) (Box 11.2.1).

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**Box 11.2.1 $R_0$: The basic reproductive ratio**

$R_0$, the basic reproductive ratio, denotes the number of cases that one case generates (on average, over the course of its infectious period and in an otherwise uninfected population). Where $R_0$ is less than 1, the infection would be expected to die out in a population, and where $R_0$ is over 1, the infection would be expected to spread.

The $R_0$ value is affected by the duration of the infectivity, and the infectiousness of the agent (tending to be higher for pathogens spread by aerosol such as measles and lower for those with droplet spread such as Ebola).

Although different $R_0$ values can be quoted for each pathogen, in reality the number varies considerably for any one pathogen depending on additional factors such as overcrowding, hygiene measures, personal protection equipment, immunization rate, and population susceptibility.
The MMR vaccine is a combination of live attenuated virus from measles, mumps, and rubella. **Mumps virus** is a ss RNA virus from the Paramyxovirus family and causes fever, headache, and myalgia before inflammation of the parotid glands develops, ‘parotitis’. Complications include orchitis in men (25%) with subsequent subfertility in 50% of men affected, and oophoritis in women (5%). Other complications include meningitis, pancreatitis, and deafness.

**Rubella virus** is from the Togavirus family and causes a non-specific viral illness with a fleeting rash on the neck and face. It is important because of the consequences of catching it during pregnancy and the subsequent, very serious, congenital rubella syndrome (CRS). CRS (deafness, microcephaly, cataracts, and mental retardation) is mostly only seen in pregnant women born outside the UK who acquired the infection overseas.

Although Allyn’s mother has declined vaccination for her children, actually coverage for the MMR is now very good, over 90%, high enough to maintain herd immunity. Measles is still a major infectious disease worldwide in South-east Asia and sub-Saharan Africa in particular, with intensive efforts by WHO to improve vaccine coverage in these areas.

**Further reading**


Case 11.3

Post-polio syndrome

Case example

Sam Gale is a short, fairly thin 62-year-old man and he walks slowly in with a marked limp. It is a warm day and he is wearing shorts and sandals so you can see his movements quite clearly. The limp affects his left leg, right up to a tilting pelvis and compensating arm movement, to keep his balance. He thumps down into the seat in front of you and then tucks his left leg behind his right, so that sitting it’s hard to notice any physical problem at all. Except you notice his left foot is a mauve colour whereas his right foot is a normal pink.

‘Hello. How can I help you?’ you ask. There is a pause while you look at each other.

‘You asked me to come back,’ says Sam at last.

‘Oh yes,’ you prevaricate. ‘Just bear with me.’ You read your own notes. Infectious exacerbation of COPD you treated with antibiotics, steroids, and asked for a CXR because of his long smoking history. ‘Are you better? The CXR came back as normal.’

He nods and then veers off the chest discussion. ‘I went and saw that polio exhaustion specialist.’

‘Oh. How did it go?’

‘Pretty pointless actually. He was too busy chatting with the receptionist about some photos or other. I just felt I was in the way really. I don’t know what I was expecting. Some help I suppose.’

He reaches awkwardly for his rucksack, which is on the floor, and rummages around to pull out a printout. ‘Look. Everything I’ve learnt about post-polio syndrome I’ve worked out for myself. It says here about tiredness and a vitamin D check.’

You shuffle through the printouts, noting the blood checks page, which he has highlighted, but really looking for a prognosis. ‘I suppose it’s a long-term kind of issue,’ you say. ‘I would think it’s all about how you are coping. You know, quite pragmatic things like help with the stairs, walking aids. Do you work?’

‘Yes. I work at the leisure centre as a receptionist. They wouldn’t give me the time of day about all these symptoms there—like I’m making it up. I thought I was just a moany old git getting old. Now I know why I’m so exhausted. And all they’ve done is sent me to occupational health. I think I’ll just chuck it in. I’m through with working. I’ve been working since the age of 15. Now I’m 62.’

‘Oh don’t say that! Working can be quite a good thing; gets you out of the house, meeting people. I think an occupational health referral is the right thing to do. They’re doing the right thing. How are you managing? Is it just you at home?’

‘Yes, just me. Well I bought my own toilet seat raiser and I have a stick. But the physio says try not to use it, that I will be stronger if I keep using all my muscles. I see the physio every month.’

‘There you are then. I bet the consultant thought you were coping so well you didn’t need any help. After all it’s like a 20–30-year kind of plan isn’t it? Gradually adding in extra help as you need it.’

‘I suppose so.’

You ask curiously, ‘Were you abroad or did you catch polio in this country?’
‘Here,’ he says. ‘I don’t really remember. I was one of a big family. I guess they noticed that I hadn’t got up. I was only 3 years old. It was during the polio epidemics of the 50s. Then they put me in an iron lung.’

‘You were in one of those?’

‘Yes, I still remember—it had a mirror so you could see people. Or maybe I don’t remember and it was just the photos, you know. I was in it 3 years. After that they took me out and I went to a convalescence home where I wore callipers on my legs. Later on, when I was bigger, they put screws into the growth plate of my good leg to slow its growth. Then when I was 14 they said, bye bye; that was all they could do for me, and that’s been it really. I’ve just got on with things until now.’

You arrange plans for the vitamin D test and blood tests for tiredness and future follow-up. He laboriously gets up and swings on his rucksack before limping to the door, which you hold open for him. You briefly watch him make his way down the corridor, without a stick, steadying himself against the wall once or twice before he turns the corner.

You document:

Post-polio exhaustion. Seen specialist. Mainly practical things, has aids in house, and walking aids, is seeing occupational health. Has physio. Works at gym, may cut down hours. Bloods to check vit D. Review to discuss results as nec.

**Microbiology**

Poliovirus is of the Picornavirus family. It is a small icosahedral +ve ss RNA virus 20–30 nm across (Fig. 11.3.1).

There are three serotypes of poliovirus, 1, 2, and 3, as well as the three oral polio vaccine types (attenuated versions of the wild-type viruses) that also circulate.
Once a cell is infected with poliovirus, it takes 4 hours for newly synthesized virus to be produced and to exit the cell. The virus initially replicates in the lymphoid tissue in the throat (tonsils) and the gut (Peyer’s patches). It was noticed children having a tonsillectomy were at marked increased risk of polio paralysis. This viraemic phase is then followed by a CNS phase where the virus spreads along nerve axons, infects the neurons, and kills them (lysis). This causes an inflammatory reaction in the CNS that causes oedema. The nerve cells worst affected are the anterior horn cells of the spinal cord. These are the cells that supply the muscles, which is why there is the lower motor neurone type of limb paralysis seen (floppy weakness and absent reflexes).

The virus is excreted in nasal secretions initially but then mainly via the faecal-oral route; a fact that was only dawning on medical practitioners as late as the 1940s. Incubation is 5–12 days and patients are infective for 2–3 weeks.

Although polio is traditionally diagnosed clinically, these days it is necessary to demonstrate actual presence of the virus by PCR on stool samples. If poliovirus is detected further analysis is needed to establish whether it is the wild type, or the vaccine virus.

Polio used to be endemic to most countries and most children would have been infected by all three serotypes by the age of 5, hence the name infantile paralysis. Most infections would have been completely sub-clinical; a few would have had a febrile illness. Only maybe 1/1000 would get paralysis.

In some countries sanitation then improved and children began to acquire the infection later (over the age of 5), allowing an epidemic pattern to emerge. Epidemics started to be noted in the UK from the 1890s onwards. Contracting the infection later in life increased the chance of paralysis (1/70), hence the massive epidemics of the 1950s just before immunization was begun in 1956.

This quote is from a medical textbook written in 1927 when doctors would have routinely seen and diagnosed polio:

The first phase is characterised by fever and by a peculiar and characteristic condition of the child, who is flushed and apt to be irritable and apprehensive. Those who are familiar with epidemic outbreaks of poliomyelitis, state that this aspect of the picture marks out the disease from the other infectious fevers of childhood. In severe cases the child may be restless, his movements are jerky, and irregular tremors are seen from time to time.

(Cecil 1927, cited in Conybeare 1946:841)

Sometimes there was also a change in personality. At this point the differential would have been very wide and the diagnosis could have been any number of viral or bacterial infections. The second phase would then begin a few hours later, with aches and pains, especially in the back or neck, unsteadiness of movement and weakness.

At this stage 70% of cases recovered, so-called ‘abortive cases’. For the rest, 1–3 days from the onset of the illness, the third stage, that of paralysis, would emerge suddenly, over hours, varying from weakness in a single muscle to widespread paralysis of a whole limb or side of the body, including the trunk muscles. Some patients then got ascending paralysis, terminating in the involvement of the respiratory muscles and (before ventilation was widely used) death within a period of hours.

The affected muscles remained tender for several weeks during which time it was advised that the affected limbs should be supported in the neutral position. At this time there was weakness and reduced tendon jerks but no sensory loss. When the tenderness resolved the patient was then said to be convalescent and physiotherapy started. Some muscles recovered over the following weeks and for up to 2–3 years afterwards. Some remained permanently paralysed and wasting and fibrosis of these could lead to deformity.

Complications in the long term (10–50 years after infection) include post-polio syndrome as seen in Sam Gale. Post-polio syndrome is onset of new deterioration in function, with fatigue,
weakness, joint and muscle pain, reduced respiratory function, and dysphagia. Treatment is supportive with walking aids, physiotherapy, etc.

There are two sorts of vaccine. Inactivated polio vaccine given intramuscularly (Salk vaccine) introduced in 1956 and live oral polio vaccine (Sabin vaccine) introduced in 1963. Following immunization the notification of polio in the UK fell from 8000 annual notifications in the 1950s at the height of the epidemic to fewer than 1000 by 1962.

The live attenuated vaccine has been used until recently (and is still used for the Global Eradication Plan), because it is cheap, effective, and easy to administer (orally). It can also spread between infants and therefore protect unimmunized children. Very occasionally though, the live attenuated vaccine viruses can cause paralysis (vaccine-associated paralytic polio). Therefore in the UK the vaccine schedule switched to the inactivated intramuscular vaccine in 2004.

The Global Eradication Plan was started in 1988 and polio is now only present in a few countries in Africa and Asia, particularly those affected currently by conflict.

Further reading

Case 11.4

Chickenpox

Case example

It is cold outside, but warm in paediatric A&E. The unit is quiet and peaceful. It is Christmas Eve morning; you are the only doctor present in the department. There is a festive atmosphere in the reception area and all the support-staff have expressed their hopes that it will be a quiet day. They have asked after your Christmas plans, and straightened up the Christmas cards and decorations next to their screens.

It has been steady work-wise. Patients have come in with tangible things such as lacerations, pulled elbows, or ankles needing X-rays.

You call Louise Manon (8), who has been asked to wait in a separate part of the waiting area until she could be seen. Her mother stands up first, smartly dressed with an expensive handbag, and then Louise gets to her feet. She looks miserable and fed up and you see at a glance she has a spotty rash on her face and hands, likely to be chickenpox.

You show them through to a cubicle and sit them down, and then sit down yourself facing them. ‘We think Louise has chickenpox,’ says her mother crisply. ‘Her younger brother had it 2 weeks ago; it was going round at nursery so we knew what it was. He was fine and had a few new spots each day for a few days and then the last ones crusted over last week and we hoped we were all fine for Christmas and then on Saturday Louise got her first spot, like a sort of blister. At first we hoped it was something else, but now she’s got hundreds. It looks so different to her brother, we are not even sure it is chickenpox.’

While Mrs Manon has been talking, you have been listening attentively. What she says about the timing makes sense; the illness is infective 2 days before the spots appear until 3–5 days after the spots have crusted over, and the incubation period is 10–21 days. If Louise started her spots on Saturday then this is the fourth day and she will not benefit from an antiviral. An antiviral such as aciclovir or valaciclovir has to be given in the first 24 hours of infection to make a difference, and in any case is only used in certain at-risk groups: elderly people, people with immunosuppression, neonates, and in pregnancy.

You have also been gazing at Louise while her mother has been speaking. She looks deeply fed up and scratches irritably at her head or ribs every few moments, at least when she dares. She earns a sharp aside from her mother each time it is noticed. In between she looks around the room or kicks her chair leg. She is not lethargic. You catch her eye. ‘Can I have a look at you? Can you stand up for me?’

Her mother pushes Louise forward and lifts up her t-shirt for her. You have a close and unhurried look at the spots. They really are all over her, mostly on her trunk but plenty on her arms and face and even her scalp. Some of them are crusted over; one or two are fresh like blisters, like a drop of water on the skin. But most look spotty, like pink spots.

‘Thank you Louise.’ You pull down her top. ‘Oh dear, it does all look sore. It definitely is chickenpox,’ you say to her mum. ‘Does she have any other illnesses, like eczema, or take any medicines?’ This is to make sure Louise is not in an at-risk group.
Mrs Manon shakes her head. ‘And she’s drinking all right? Eating a little?’ Mrs Manon nods.

‘Well we just have to wait for her to get better now,’ you say.

‘But look at her,’ Mrs Manon says. ‘Can’t you do something? It’s really bad and it’s Christmas tomorrow. Is she meant to just stay like this; itching and in pain? There must be something, some treatment.’

‘No, I’m sorry,’ you say. ‘She really does have to get better by herself. There isn’t any treatment. We can help with symptoms though. She can have paracetamol if she is sore. Have you tried calamine with aqueous cream for the spots?’

‘I can’t believe you’re just going to leave her like this!’ Louise sitting next to her stirs uneasily and glances up at her mother’s face.

You turn down your mouth sympathetically. It is pretty miserable being sick for Christmas, and for the mum, having made all these preparations and bought all those presents for a happy day.

Mrs Manon stands up, ushering Louise before her and opens the door of the cubicle without another word, and leaves. You stand too, and your last view, as the door swings shut is of Louise irritable, spotty, scratching again behind her mother’s back, this time at her neck.

So you don’t get to explain about infectivity and complications, and when she might need to bring Louise in for a review, and why aciclovir wouldn’t work, or give them a leaflet or anything.

**Microbiology**

Chickenpox (also known as varicella) is caused by the varicella zoster virus, of the Herpesvirus family. Following resolution of chickenpox the virus lies dormant in the dorsal ganglia but can remerge many years later as shingles herpes zoster (see Case 10.5, Shingles).

Chickenpox, as the doctor in Louise Manon’s case tried to explain, is very infectious. Louise could have caught it from her brother either by droplet spread from her brother’s nasopharynx, or by direct contact with virus from her brother’s spots, once these developed. The fond hope of Louise’s mother, that Louise wouldn’t catch chickenpox, was rather forlorn, as it is well known that in households with a case of chickenpox over 90% of non-immune contacts will catch it.

Chickenpox starts with a temperature and malaise for 1–2 days before the rash develops. The spots evolve in a centripetal fashion (head and trunk first and then arms and legs) and in successive crops, lasting 3–5 days. The spots develop with well described phases, starting with a papule, which then progresses to a vesicle, then to a pustule before finally crusting over. It is typical to see examples of all these stages present at the same time and in the same patient, just as the doctor observes with Louise.

Although the majority of children have a mild illness that resolves without problems, there are complications that can develop. The incidence of these is much higher both in adults and in pregnancy as well as in those with a reduced immune system as mentioned in the case. Complications can include pneumonia, encephalitis, and disseminated varicella. In these at-risk groups a course of oral or IV aciclovir is recommended.

Chickenpox in pregnant women is a particularly important consideration. The risk of fulminating varicella pneumonia is much higher in pregnancy, usually presenting with cough and wheeze 3–4 days after the onset of the rash. The other very important consideration is the risk of congenital varicella syndrome. This can cause intrauterine growth retardation, microcephaly, limb hypoplasia, cataracts, chorioretinitis, and increased mortality (2% mortality rate). The risk of congenital varicella syndrome is greatest when the pregnancy is less than 20 weeks. It has not been seen in pregnancies over 20 weeks.
Chickenpox later in the pregnancy is not so harmful, as long as the woman has at least a week to generate immunoglobulin to pass on to the fetus. However, if the baby is born less than a week after she has had chickenpox, or she has chickenpox while the baby is very young (less than a week old) then the fetus does not receive maternal immunoglobulin or have a mature immune system of its own and so again has an increased mortality rate.

Therefore, when a pregnant woman has had contact with chickenpox and says she has never had it, it is best to have a discussion with the microbiology team. They will advise you to check the pregnant mother for serum varicella zoster antibody. In fact the blood sample taken on antenatal booking is stored partly for this reason. Over 90% of the adult population will have had chickenpox even though some of these cases would have been subclinical and unnoticed by the patient, so this is worth checking for first and the great majority of women can be reassured at this point that there is no risk to themselves or the baby.

If serum varicella zoster antibody is negative then you will be advised by the microbiology team to administer varicella zoster immunoglobulin (VZIG) intramuscularly, which they will arrange to be delivered to you. This is not a popular treatment, requiring four vials to be injected into the buttock, which is not a little painful. This treatment is to try and avoid or at least attenuate the infection and can be used up to 10 days after exposure. Over 50% of patients still go on to develop chickenpox but data on fetal outcomes suggests the fetus is still protected.

For Louise (who is not eligible for aciclovir or VZIG) analgesia for pain, and sedating antihistamines for the itch may be useful. Advising patients to try not to scratch is important as the commonest complication, occurring in over 20% of patients, is secondary bacterial infection and minor scarring. Calamine lotion is sometimes recommended, although it is a traditional treatment for chickenpox. Even older remedies include treating with ‘carbolized oil applied gently with a feather’ to loosen scabs, again with the intention of avoiding scarring and secondary infection.

Varicella vaccine is available and is used universally in some countries. It is used only in at-risk groups in the UK. It is a live attenuated vaccine made of the Oka/Merck virus strain and is given IM as a single dose in children, at the same time as the MMR (12 months). It gives an 85% protection for at least 3 years; those who do get infected despite the vaccination tend to have very mild cases. There are concerns that the varicella vaccine may increase the incidence of herpes zoster, partly because vaccine immunity tends to wane over time and partly because less chickenpox is circulating and so there are less natural boosters to immunity. For these reasons this vaccine is at present not routinely recommended in the UK.

Further reading

Chickenpox in Pregnancy. Greentop Guideline no. 13. rcog.org.uk
Case 11.5

**Slapped cheek disease**

**Case example**

‘Well doctor, I thought I better get her checked over by you. I mean she’s been under the weather for the last week or two but she’s woken up today with a red face. Well, but I mean it wasn’t that sunny yesterday was it doctor? I don’t think it’s sunburn. And I know she hasn’t fallen or nothing.’

This is Mrs Janes and her 4-year-old daughter, Clare.

‘She cannot seriously be phoning me up because of pink cheeks,’ you think to yourself. Mrs Janes has two older children and you have met her several times with very reasonable issues such as high temperatures or rashes.

When Clare and Mrs Janes arrive, Clare comes straight in and pulls up the children’s chair and sits right in front of you.

She does have a red face. Her cheeks are red all over: an even, confluent, flushed tone up to her cheekbones but with sparing around the mouth. You reach for her forearms and turn them over to see the inner arm, which has a kind of outlined rash different from the confluent rash of her face. This rash appearance is known as a ‘lacy rash’ found on the forearms and lower legs and is also typical of slapped cheek disease. Previously when you have seen this rash one cheek has been more affected than the other and it has tended to be a red patch high up on the cheek.

‘Yeah, I thought, is it slapped cheek? The others have had it. Cause it’s not sunburn is it?! I mean it wasn’t sunny yesterday.’

‘No, I think you are right. She’s eating and drinking ok?’ You raise your eyebrows at Clare as you speak and show her your auroscope, then you lean forward gently to look at her ears and throat, which are fine. Her temperature is 37.4 and her chest is clear. Clare is very grown up and serious and cooperates fully with your examination.

‘Drinking. Not eating much. To be honest she was worse last week, grizzling and running around slapping people.’ She eyes Clare for a moment who wriggles uncomfortably in her chair. ‘I thought she was on the mend yesterday.’

You catch Clare’s eye again, ‘Thank you Clare. You were very good.’ You smile at her and she looks away shyly. ‘Ok, well I think that’s what it is. She will probably be off colour for 4–5 more days,’ you say to Mrs Janes, ‘And will then gradually improve.’

‘What about nursery? Can she go?’

You feel uncomfortable when Mrs Janes mentions the nursery and the implications of infectivity, because as it happens you are pregnant and you have a feeling that parvovirus infections are meant to be avoided in early pregnancy. It’s too late now however. You print off a leaflet for Mrs Janes to remind yourself of incubation times and briefly scan through it. ‘She’s fine to go to nursery,’ you say handing the leaflet to her. ‘Apparently they are more infectious in the week leading up to the rash. So once she feels ok she’s good to go back.’

You say goodbye and a particular goodbye to Clare who was so helpful during your examination.
Microbiology

Slapped cheek disease or erythema infectiosum is caused by human parvovirus B19. This virus was identified in 1974 and is of the Parvovirus family. It is a non-enveloped icosahedral linear ss DNA virus of a minute size, only 18–26 nm. Its small size makes it distinctive from other viruses, in that it can only replicate in rapidly dividing cells, such as erythroid progenitor cells, bone marrow cells, and fetal cells.

It is transmitted by droplets and has an incubation of 4–14 days (see Table A5.1 in Appendix 5). During this time the virus is rapidly reproducing and there is a high level of virus in the blood stream, sometimes known as the ‘viraemic phase’. In a normal child this will manifest itself as a non-specific febrile illness for about 5–7 days, as it has done with Clare. At this stage children are very infectious, but once the rash appears the child is no longer infectious.

The interesting aspect of parvovirus is what happens if it infects someone with a haemolytic disorder, such as sickle cell or thalassaemia. In these patients the viraemic stage of the illness can be severe, causing a drop in Hb of over 2.0 g/dL and sudden marked anaemia. At this stage parvovirus can sometimes be demonstrated in the patient’s blood using electron microscopy or viral DNA may be detected by PCR. IgM will not yet have been developed.

If a non-immune pregnant woman is exposed to the infection, it can be transmitted to the rapidly dividing fetal cells and cause anaemia and cardiac failure in the fetus, leading to hydrops fetalis and sometimes fetal death.

What about the doctor looking after Clare then? Has she had a significant exposure to parvovirus? Exposure is regarded as being a household contact such as Mrs Janes’ or Clare’s siblings, or over 15 minutes in a room, or face-to-face contact before the rash develops (the viraemic phase). Examining Clare’s throat could be regarded as face-to-face contact, but the fact that she has now developed the rash is reassuring for the doctor as it means she is much less infectious. In addition over 50% of adults are seropositive to parvovirus B19 and are therefore immune.

If exposure had occurred, the chance of it being transmitted to the fetus is about 25% (usually after a 6-week incubation). The peak risk is the mid-trimester. Parvovirus infection causes fetal death in about 10% of those infected but those fetuses that do survive are healthy. There is now a proven effective treatment for fetal parvovirus infection: intrauterine transfusion, which significantly reduces fetal loss. Therefore, in cases of significant parvovirus exposure in a pregnant woman, the details should be discussed with the microbiology team with a view to paired serology (on the antenatal booking blood sample plus a new sample) and referral to obstetric if positive, for 2-weekly fetal ultrasound monitoring and intrauterine transfusion if indicated.

Further reading


Case example

You are in A&E in your second month as a casualty officer. The triage nurse asks you to see a baby, Robbie Salton, next. ‘His mum’s a GP and I think she’s a bit panicky. She says the baby isn’t breathing properly. She’s come straight here from home. The baby looks ok,’ she adds, handing you the casualty card with the baby’s obs on it. You read, ‘RR 40, HR 120, temp 37.5, PaO₂ on air 99%.’ ‘The paediatric A&E isn’t open yet but when it does we can always hand him over.’

You nod and call the baby from the waiting room. A short lady with a 3-year-old boy beside her and a 6-month baby in her arms stands up and threads her way towards you. She doesn’t look too stressed.

You take her into a cubicle and she sits down with the baby and you perch on the trolley. The little boy quietly stands next to his brother; he is eating a slice of brown bread with nothing on it.

‘That looks like nice bread,’ you say. ‘Not from round here?’

Robbie’s mum smiles. ‘No, it’s from the baker. We missed breakfast and came straight here as soon as I could get us all dressed, so I just shoved the loaf in a bag.’

‘Tell me what happened,’ you ask.

‘Robbie was fine yesterday. Then I was feeding him this morning and I noticed he wasn’t feeding properly and when I looked he was breathing really fast. I felt his forehead and he didn’t have a temperature. When I checked his capillary refill on his toes and fingers I felt it was delayed. I don’t have any other equipment at home with me like a stethoscope or an auroscope so I was stuck about what to do next. I couldn’t explain the breathing so I came up here. He’s been awake and alert all the time.’

You nod and feel discomfited because this description is a cross between a history and a case presentation, but you try and stick to your usual routines.

‘Has he fed since?’

‘I haven’t tried him.’

You ask mum if you can look at the baby and undress him on the trolley. Undressing him yourself gives you the opportunity of interacting with him and checking his tone and you do a sort of 8-week check on him. He is alert, ears fine, throat fine, fontanelle fine, moving all four limbs. From a chest point of view there is no respiratory distress; his chest is clear, heart sounds normal. He has no rash and his tummy is soft. You test the capillary refill for yourself on his chest and peripheries and it is <1 second in both areas. ‘Any other symptoms? Any cough, cold, vomiting?’ Robbie’s mum shakes her head.

You decide to get a CXR to address the issue that mum has raised about his breathing, and to discuss the case with a colleague in the meantime. The CXR will take a bit of time, which will allow you to see how the baby is over the next hour or two.
One hour later the CXR comes back as clear and you are wondering what to do next. At 3 months or less a baby with a temperature would need a septic screen, but at 6 months the picture is less clear. At this point an A&E nurse comes to get you.

‘That mother has gone frantic again. I think it’s just a nappy rash.’

You walk back to the cubicle. Robbie’s mother is in tears and her older son is looking at her anxiously. ‘He’s got a rash. The nurse just said it’s nappy rash, but it isn’t, it wasn’t there this morning.’

You look at the baby and the nappy area and there is a bright red rash in all the crease marks that wasn’t there when you examined the baby earlier. He feels different too. You fetch a thermometer and check his temperature again. It is 39°C. ‘It’s not a petechial or a meningitis rash,’ you say. ‘But look; his temperature is up. I think it’s to do with that. I’ll get you some paracetamol and then refer you to paediatrics. The CXR is normal by the way.’ The baby is crying and his mother looks really upset and anxious. ‘Is he hungry?’ you ask. ‘Could you try feeding him and see how he takes it?’

Robbie’s mum nods, glad of something sensible to do. When you see she is about to lift up her top to breastfeed, you decide this is a moment for privacy and back out of the cubicle swishing the curtain across behind you.

The paediatric team takes ages to come and when you get round to finding out what has happened you find the baby has been discharged. However, 2 months later a letter finds its way to your pigeonhole. There is an attached note from the A&E consultant saying, ‘I think this is you. Well done.’

The letter is addressed to the consultant and is from Dr Salton and describes the presentation of her son accurately, going on to say:

I was then discharged by paediatrics without further tests with a diagnosis of coryzal symptoms. Over the course of the next week Robbie had intermittent temperatures of up to 39°C and down to 34°C but throughout he fed well and was alert. On the seventh day he developed a morbilliform rash on his trunk and face and the temperature then resolved at that point. The rash indicated, I think, that the diagnosis must have been roseola infantum.

I wanted to write to inform the doctor who saw me of the diagnosis and also to say thank you for that doctor’s kindness and calm approach, which was very helpful.

Microbiology

Roseola infantum, sometimes known as exanthema subitum, is the single most common cause of hospital visits in infants with raised temperature. It is often brushed over or treated very briefly in textbooks; however, clinically it is important, because the differential for very high temperature in an infant has to include meningitis. The presentation of this illness, though, can be difficult to interpret. Very high temperatures are seen, of over 39°C, but in an infant that continues to feed well and is otherwise reasonably alert, with perhaps just a runny nose.

The rash does not occur in all infants, but in those that do get the rash it can confirm the diagnosis. As the rash heralds the resolution of the illness, the diagnosis is unfortunately only made once it has lost all its value.

Roseola infantum is caused by human herpesvirus 6 and 7 (HHV6 and 7) and is of the Herpesvirus family. HHV6 was first isolated in 1986. It is an enveloped, icosahedral, linear ds DNA virus, 10 nm across. Serological testing has found seroconversion for HHV6 in almost 100% of the population.
by the age of 2; therefore, the great majority of infections must be subclinical. Incubation is 5–10 days and transmission is by droplet spread to the oropharynx. Infants continue shedding virus for several months after the infection has resolved, which must partly account for that high seroconversion rate. Treatment is symptomatic and the infection resolves spontaneously. There is no immunization.

**Further reading**

Case 11.7

Hand, foot, and mouth

Case example

The brief notes made about Holly (19 months) by the receptionist say: ‘unwell, 3 days, no temp, drinking not eating. ?sore mouth.’

As you read this you hear a rustling at the door and you get up to open the door to find a mum struggling with the door, an empty pram and a toddler who is wandering around. The mum smiles and nods hello and reaches for Holly’s hand, but Holly (after looking at you for a moment) wanders into your office, walking past you to admire your weighing machine.

She has bright red cheeks, dry looking. She is alert and exploratory but also a bit grumpy. Holly’s mum parks the pram and sits down and you sit down and Holly agreeably sits down too, on a little children’s chair you have placed next to her mother’s.

You check their names and recap the history, also asking if Holly has any other symptoms such as runny nose or cough or vomiting and diarrhoea, which she hasn’t.

‘I’m just wondering if it’s hand, foot, and mouth,’ you say. ‘Or other things it could be are teething or simply mouth ulcers—aphthous ulcers . . . Can I have a look at her?’

Holly’s mum pulls her onto her lap saying convincingly, ‘Look Holly, the doctor’s going to have a look at you!’

‘She’s got red cheeks hasn’t she?’ you say reaching for your thermometer.

‘She’s always a bit like that,’ her mum says. ‘She has a bit of eczema.’

Holly is suspicious but very good and you check her temperature (36.4°C) and ears (fine). However, it’s difficult to explain to a 19-month-old that she should sit still to have a lollypop stick poked in her mouth to check her throat, especially if her mouth is sore. She cries in outrage and upset as you carefully look at her lips and tongue and finally throat. Her tonsils are fine but she has a white ulcer on her soft palate about 3 mm across, and two smaller ones on her tongue and another 4-mm one on her lower lip. She possibly has more but she is struggling and it is difficult to see.

More to settle her down and build trust again than because you are seriously interested, you elect to listen to her chest. The stethoscope distracts her and she allows you to listen to her chest. Next you reach for her hands and find a deep pustular spot on her left palm and another on her right, to the side of a finger. She watches interested while you tug off her boots and socks and find another spot on her left foot. ‘Does she have any nappy rash?’

‘A bit,’ says her mother. ‘She was staying with the grandparents and I just put it down to a less thorough wet-wipe technique.’

She brings Holly over to the couch while you spread paper on it and undresses Holly’s lower half as if she’s changing her nappy. Holly doesn’t resist because she’s used to nappy changes. There are three or four blisterly spots each 3 mm across around her upper legs.

Holly’s mum says, ‘I was just thinking. Holly was at a children’s party last week and then the mum of the birthday boy rang up and said he’d just been diagnosed with hand, foot, and mouth.’
‘That’s interesting. So that might fit. Just let me check the incubation dates.’ You print off a leaflet for Holly’s mum whilst she gets Holly dressed. Incubation time is 3–7 days.

‘What about nursery?’ she says. ‘When can she go back?’

‘Do you work?’ you ask. She nods.

‘Mmm it is tricky,’ you say sympathetically. ‘You must have had today off? She can go back to nursery because it’s regarded as a mild illness. She’ll be infectious for several weeks after the rash has gone. It’s spread faecal-orally you see, through the poo, so be careful of hand hygiene. But it wouldn’t be practical to keep her off all that time.’

‘So she can go back tomorrow?’

‘Oh. Well. She needs to be eating normally before she goes back, like back to her normal self. Otherwise you know what it’s like for children at nursery; if they’re not well they just pick up the next thing going round.’

Holly is now dressed and is pottering about the room. She takes the leaflet from you and then solemnly hands it back. You give it to her mother.

‘Ok. Hope she feels better soon,’ you say opening the door again. Holly wanders out the door again. Holly wanders out the door and her mum has just time for a quick goodbye before she chases after her.

**Microbiology**

Hand, foot, and mouth disease is caused by group A coxsackie virus (Fig. 11.7.1). This is an RNA virus of the Enterovirus family, 28 nm across. It is one of a group of viruses known as non-polio enteroviruses which also include group B coxsackie virus, echovirus and enterovirus 68.

The non-polio enteroviruses cause non-specific symptoms, including pyrexia, sore throat, and headaches, as well as the more severe manifestations of pericarditis and viral meningitis (Case 4.2, Viral meningitis). Non-polio enteroviruses are felt to be very common, generally mild, and spread by close contact, either faecal–orally, or droplet-spread from coughing or direct contact from lesions.

Hand, foot, and mouth is the one easily recognizable syndrome, with deep pustular lesions on the palms and soles and ulcers in the mouth, as described with Holly.
Laboratory diagnosis is rarely undertaken for hand, foot, and mouth or non-polio enteroviruses, but can be obtained by PCR of the stool, or by viral isolation from cell culture of swabs from the mouth lesions. Treatment is supportive with analgesia and fluids and the infection resolves spontaneously after a few days.

**Further reading**

Chapter 12

Pregnancy, postnatal, and congenital

Case 12.1 Infections in pregnancy 235
Case 12.2 Post-miscarriage infection 239
Case example

You are an obstetrics doctor and are just between patients in your antenatal clinic when one of the midwives, Sandra, knocks on the door. ‘Can I disturb you a moment?’ she asks. ‘I was just checking some of the blood test results for one of the patients that you are due to see this afternoon and there’s one that I think you need to know about now before you see her. I can get the results up on the computer for you to have a look if you want. The patient’s been calling about the results as well. She’s very anxious. I’m not really sure what they mean.’ Sandra gets the patient’s results up on the screen and you see the following:

Sarah Fitzpatrick: Antenatal booking blood
Rubella IgG antibody: DETECTED
HIV 1 and 2 antibodies/antigen: NOT detected
Hepatitis B surface antigen: NOT detected
Syphilis antibody: NOT detected
CMV IgG: DETECTED
CMV IgG avidity: LOW
CMV IgM: DETECTED
Toxoplasma IgG: NOT detected
Toxoplasma IgM: NOT detected
Comment: Additional CMV serology tests were performed on this 13 week booking blood. Please see blood sample taken at 20 weeks for further results and interpretation.

You scroll to the result of the later blood sample and see the following:

CMV IgG: DETECTED
CMV IgG avidity: HIGH
CMV IgM: equivocal
Toxoplasma IgG: NOT detected
Toxoplasma IgM: NOT detected
Comment: Please see booking blood specimen to compare. These results are compatible with recent primary CMV infection acquired shortly before the time of the booking blood specimen. No serological evidence of toxoplasma infection.

You grimace to yourself while you read these results. You recall the patient and why you had asked for the CMV tests. A week ago the ultrasonographer had called you in to look at
PregnanCy, Postnatal, and CongenItal

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the 20-week scan because of possible increased bowel echogenicity. You had introduced yourself to the patient and then had a look yourself with the scanner and confirmed the increased bowel echogenicity. You then had a look at the rest of the scan hoping it would be normal, but unfortunately you also spotted signs of intrauterine growth retardation although the rest of the scan was normal, in particular no fetal anomalies. Following the scan you organized an initial viral screen.

It is going to be a difficult consultation. You will need to discuss the implications of CMV infection during pregnancy, the chances of the fetus catching it and subsequent outcomes, and what the possible options are for the parents.

Microbiology

Important congenital infections used to be denoted by the acronym TORCH, which stands for Toxoplasmosis, Other (syphilis, VZV, Parvovirus B19), Rubella, CMV and HSV, but this is now a little out of date, as is denoted by the rather weak ‘other’ and the fact that it misses out hepatitis B, HIV, measles, and listeriosis (see Table 12.1.1).

What is more important is to know what is routinely screened for in pregnancy: HIV, hepatitis B, syphilis, and rubella, as has been done with Sarah Fitzpatrick. Furthermore, advice on avoiding toxoplasmosis infection (avoiding eating raw meat and cleaning out cat litter) and listeriosis (avoiding raw milk, pâté, blue cheeses, and soft cheeses) is routinely given to pregnant mothers in the UK.

The echogenic bowel picked up on Sarah Fitzpatrick is a non-specific finding found in 0.2–1.8% of pregnancies, and the great majority are due to intra-amniotic bleeding. This is a common occurrence in pregnancy, with no clinical significance. It is explained by the fact that the baby swallows the blood, but its bowel can’t digest it at this early stage (20 weeks) and so it shows up brightly in the bowel on the ultrasound. Usually a glitter of red cells is also seen in the amniotic fluid, also known as the ‘snow globe sign’. As Sarah Fitzpatrick did not have the snow globe sign the doctor then asked about exposure to viral illness and family history of cystic fibrosis, and arranged the further tests. This has included the additional infectious screen as seen in the case: CMV and toxoplasmosis and depending on the clinical factors can also include parvovirus B19, VZV, and HSV. A viral explanation for echogenic bowel is seen in about 3–4% of these cases. Additional tests would involve further viral screening on the amniotic fluid, and also tests for chromosome disorders and cystic fibrosis. Further testing after picking up the finding of echogenic bowel is a controversial topic, with some sources saying all patients should be tested for everything, and other sources that mostly the finding is non-specific and non-significant and amniocentesis in everyone would cause harm.

CMV, the diagnosis in this case, is a large (200 nm) ds DNA virus of the Herpesvirus family (Fig. 12.1.1). As with other members of this family, it is known for its ability to stay latent and reactivate, as well as its unique attribute that infection does not protect from re-infection. Its presentation is very variable and depends in part upon the age of the patient. CMV mainly causes subclinical infection and is spread by droplet from the nasal pharynx in children. There is a second surge of CMV infection during adolescence, caused by salivary spread from kissing, when it can sometimes cause a glandular-fever-like illness. Infection is very common and 50–80% of adults are seropositive. It can cause severe problems in the immunocompromised, when it can reactivate, and is an issue particularly in patients with AIDS, when it can cause retinitis, polyradiculopathy, and oesophageal erosions, or transplant recipients when it can cause pneumonia, hepatitis, and leukopenia. It is usually treated with the antiviral ganciclovir.
<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Maternal infection</th>
<th>Investigations</th>
<th>Treatment/prophylaxis</th>
<th>Examples of neonatal consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Toxoplasmosis</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td><em>Toxoplasma gondii</em>&lt;sup&gt;b&lt;/sup&gt; protozoan parasite from cat faeces and uncooked meat</td>
<td>Subclinical infection, or non-specific headache, fever and lymphadenopathy</td>
<td>Serology and amniocentesis and PCR</td>
<td>Spiramycin throughout pregnancy, Jaundice, uveitis, hydrocephaly, and chorioretinitis</td>
</tr>
<tr>
<td><strong>Listeriosis</strong></td>
<td><em>Listeria monocytogenes</em> bacteria from contaminated food</td>
<td>Non-specific fever, headache, sore throat and back pain</td>
<td>Blood culture, CSF culture, urine culture</td>
<td>Ampicillin, Stillbirth, neonatal septicaemia, neonatal meningitis</td>
</tr>
<tr>
<td><strong>Syphilis</strong></td>
<td><em>Treponema pallidum</em></td>
<td>Genital ulcers, primary, secondary or late syphilis</td>
<td>VDRL serology, or swab of lesion for PCR</td>
<td>Penicillin, Stillbirth, IUGR, hydrops fetalis, ocular syphilis, saddle nose deformity</td>
</tr>
<tr>
<td><strong>Slapped cheek disease</strong></td>
<td>Parvovirus B19</td>
<td>Subclinical infection or minor febrile illness, or joint pain</td>
<td>Clinically diagnosed or serology and fetal ultrasounds</td>
<td>Intrauterine transfusion, Stillbirth, anaemia, hydrops fetalis</td>
</tr>
<tr>
<td><strong>Chickenpox</strong></td>
<td>Varicella zoster virus</td>
<td>Fever and vesicular rash</td>
<td>Clinically diagnosed, serology or PCR of swabs</td>
<td>Varicella zoster immunoglobulin, Skin scarring, chorioretinitis, microcephaly</td>
</tr>
<tr>
<td><strong>Rubella</strong></td>
<td>Rubella virus</td>
<td>Swollen cervical lymph nodes, fever, fleeting rash of face and neck</td>
<td>Serology and PCR</td>
<td>Immunization before pregnancy, Congenital rubella syndrome; mental impairment, cataracts, deafness</td>
</tr>
<tr>
<td><strong>CMV</strong></td>
<td>Cytomegalovirus</td>
<td>Subclinical infection of non-specific glandular-fever-like symptoms</td>
<td>Paired serology, amniocentesis PCR</td>
<td>IV ganciclovir for the neonate, Neurological damage at birth, chorioretinitis, neurodevelopmental delay, sensorineuronal hearing loss</td>
</tr>
<tr>
<td><strong>Genital herpes</strong></td>
<td>Herpes simplex virus</td>
<td>Subclinical infection or vesicular rash orally or on genitals</td>
<td>Swab of vesicle for PCR, serology</td>
<td>Oral aciclovir, consider caesarean birth, Stillbirth, congenital herpes simplex, neonatal encephalitis</td>
</tr>
<tr>
<td><strong>Measles</strong></td>
<td>Measles virus</td>
<td>Fever, rash, coryza and conjunctivitis</td>
<td>Serology and PCR</td>
<td>Immunization before pregnancy, Human normal Ig, Stillbirth, premature labour</td>
</tr>
<tr>
<td><strong>HIV</strong></td>
<td>HIV</td>
<td>Subclinical infection or seroconversion illness or AIDS</td>
<td>HIV serology and viral load</td>
<td>Antiretroviral drugs during pregnancy and breast feeding and neonatally, Neonatal HIV infection</td>
</tr>
<tr>
<td><strong>Hepatitis B</strong></td>
<td>Hepatitis B virus</td>
<td>Subclinical infection or jaundice</td>
<td>Hepatitis B serology and viral load</td>
<td>Immunization before pregnancy, consider caesarean birth, early immunization or treatment with immunoglobulin of neonate, Congenital hepatitis B infection</td>
</tr>
</tbody>
</table>
Maternal infection causes intrauterine infection in about 40% of fetuses. Approximately 10% of infected babies are then affected with jaundice, hepatosplenomegaly, microcephaly, and deafness at birth. Ganciclovir can be used to treat neonates with symptoms at birth. Overall, because there is a good chance that the baby will be unharmed, termination is not usually advised. A further 10–15% of this group will develop problems later in life, with hearing defects and intellectual disability.

As CMV is so ubiquitous and previous infection does not protect against re-infection (also there is no vaccine) so CMV screening antenatally is not advised, nor is neonatal screening.

Further reading

Isolated echogenic bowel; information for health professionals, NHS Fetal Anomaly Screening Programme, version 2 July 2012.


Sepsis in Pregnancy, Bacterial. Greentop Guideline 64a. rcof.org.uk
Case example

You brush your hand over the thick bundle of A&E notes in the minors box and pull out the front one, trying not to think about the build-up of patients. The build-up is occurring because two out of the three A&E doctors are in the Resuscitation Room each seeing an acutely unwell patient. You are the third doctor.

You look at the notes in your hand. The patient’s details have been typed into the system by the receptionist at the front desk and her clinical details carefully written out by the triage nurse. It is 22-year-old Kirtida Nuninder, who had a miscarriage with surgical management 4 days ago and is complaining of bleeding and pain.

You feel immediately on alert about this patient for several reasons. Partly because you know that pregnant and postpartum women can bleed a lot, and partly because you know they can get very septic from surgical interventions postpartum (and die). This is a group of patients who are otherwise perfectly healthy young people in the prime of life and therefore any morbidity or mortality is catastrophic.

So having alerted yourself your eyes flick down to the triage nurse’s observations, blood pressure 126/70, temperature 37.2, heart rate 82, and feel satisfied that this patient appears stable. There is also a urine dip, which is negative except for blood.

You call the patient’s name from the crowded waiting room and a slim looking girl stands up and picks her way through the chairs, moving smoothly and easily towards you. She catches your eye for a moment to check where she is heading.

You invite her to sit down in the two door cubicle room and then lock the door and sit down opposite. You introduce yourself and check her name. She nods.

‘I had, like, the operation on Wednesday and went home and was fine. And the next night I got this tummy pain like a period pain and it’s been there since then. Last night I called the emergency phone advice number and they said I should go to my GP but I thought it would be better to come here. That’s what it said on the leaflet to do if you had any pain or bleeding.’

While she explains you simply listen, absorbing her story and also the way she looks, especially her colour, which seems fine, and her energy, again fine: not lethargic or slow.

‘Have you had any bleeding?’

‘A bit. Not the first night but after that.’

‘A lot of bleeding? Any clots or flooding?’

‘Clots? You mean like big lumps? I had one of them. What’s flooding?’

‘It’s when you bleed so much it runs down your leg even if you’ve got a pad and things.’

‘No. No flooding.’

‘Any smelly discharge.’

‘No. It’s just brown stuff. Not red.’
You ask about the operation and establish it was an ERPC (evacuation of retained products of conception) and that she was also given an antibiotic dose just after the procedure, although she does not know which one.

‘And you didn’t have any tummy pain the first day?’

‘No it was fine. No problems.’

You check that she has passed stool and is not constipated, also that she is passing urine ok with no pain or increased frequency (to exclude a UTI). Her appetite is slightly reduced. You ask to have a look at her tummy and she gets onto the couch and lies down flat on her back. She lifts up her top and slides her skirt down so you can see her whole tummy.

‘Thank you. Just put your arms by your side like this.’ You demonstrate. ‘Where is it painful again?’

She points to her lower abdomen in the centre. This is consistent with uterus pain or bladder pain. She is quite slim so you press with just one hand using your flat fingers and have a good ‘view’ (you can feel clearly). You start pressing gently on the mid-zone of the left side and away from where she says the pain is and then circle round clockwise. Her tummy is nice and soft, she is definitely tender in the suprapubic area and nowhere else. She winces here and grabs your hand to stop you pressing.

You go back to this area. ‘I know it’s sore. Can you bear it for a minute so that I can feel what’s there?’ you ask.

She composes herself and nods and relaxes her tummy. You palpate deeper and can feel the uterus as an enlarged shape (it’s not normally palpable) reaching halfway up to the umbilicus. You can feel around its sides, its smooth curved shape, wider at the top and slightly boggy, not hard or firm, and definitely tender; she doesn’t like you palpating it.

You stop for a moment and think. You can treat this as a post-ERPC uterine infection. But it would be really good to have swabs to check for infection and sensitivities as well as to have seen the cervix and the level of bleeding for yourself. You pause a moment longer thinking of the additional time it will take (30 minutes?) and the equipment you will need (light source, sterile speculum, normal swabs, Chlamydia swabs, lubricating jelly, gloves, microbiology forms, and a chaperone) and where to find it all.

The doctor’s area for the forms, the storeroom on the other side of the department for the speculums etc. (You don’t like that stuffy room; you can never find anything and often stand there helplessly looking right at the thing you need without being able to see it.) The light, the one on the wall, doesn’t work; you click it on and off experimentally but you know where there is a portable one. Gloves are here in the room, but not in your size.

You explain what you want to do, and 15 minutes later you are back with everything. The curtains are drawn and you have a helpful nurse with you as a chaperone (within the curtained area and at the tail end of the patient). You also have a reasonable view of the cervix. This looks fine; there is brown discharge and no obvious smell. You take the swabs and then thank the nurse and let the patient get dressed privately behind the curtains. The nurse leaves as you sit back at the desk to label the forms and the swabs.

You prescribe cefalexin and metronidazole for 7 days and ask the patient to come back if the bleeding gets worse or if she is not feeling better after 48 hours. You explain that you feel she will get better nicely with the antibiotics. But if she is worse and feels she is not improving then the next thing to do would be a pelvic ultrasound to check that nothing has been left behind in the uterus.

‘When will the swabs be back? Can I ring up and find out what the results are?’
‘Your GP can. There is a results hotline. The swabs will take about 3 days. So maybe get your GP to ring up mid next week? Can we make that a definite plan that you’ll speak to your GP next week?’ Kirtida agrees.

After you have unlocked the waiting room door of the cubicle and said goodbye, you spend 5 minutes writing up your notes and then clear up the room and put the disposables, the paper on the couch, the swab packets, and the speculum into the clinical bin.

As you walk out to the minors box you wonder if perhaps you ought to have arranged a pelvic ultrasound after all. You brush your hand over the bundle of notes feeling the whisper of paper over your fingertips and pull out the front one.

Two days later you come across the results:

<table>
<thead>
<tr>
<th>Chlamydia and GC screen NAAT: negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocervical swab:</td>
</tr>
<tr>
<td>++ Group B beta-haemolytic Streptococcus (Sensitive to penicillin, erythromycin)</td>
</tr>
<tr>
<td>+ Alpha-haemolytic Streptococcus</td>
</tr>
<tr>
<td>N. gonorrhoeae NOT isolated</td>
</tr>
<tr>
<td>Yeasts NOT isolated</td>
</tr>
<tr>
<td>Trichomonas none seen</td>
</tr>
<tr>
<td>BV negative</td>
</tr>
</tbody>
</table>

Comment with the endocervical report: These bacteria are of uncertain significance, and may represent colonizing bacteria only. Group B Strep may also be associated with infections of mother and baby in the postnatal period. Clinical correlation advised. Persisting features of infection may indicate the need for surgical intervention as well as broad-spectrum antibiotics. Please contact Microbiology if you wish to discuss further.

You arrange to telephone Kirtida to see how she is and arrange further follow up if necessary.

**Microbiology**

This case of mixed growth, from an endocervical swab, allows an introduction to the many different types of streptococci that crop up in Microbiology reports.

The streptococci are a broad varied group of bacteria that have the common characteristic of being Gram-positive cocci in chains. In the late nineteenth century, the exciting but confusing early days of medical microbiology, it was realized that among streptococci were some sorts that seemed to cause serious or fatal infections, yet others that seemed to live harmlessly as normal flora. The challenge was to distinguish these.

The first clue was when agar was discovered to be good for growing colonies (each colony typically 0.5 mm across) of bacteria. When horse or sheep blood was then mixed with the agar (making the blood agar that is still used today) the streptococci were shown to behave differently. Some strains caused clear haemolysis of the agar—complete lysis of the red cells around the colony, so that, as the old textbooks say, you can read newsprint through it. This was called beta-haemolysis (Fig. 12.2.1). Other strains caused only partial haemolysis, leading to green or brown discoloration of the agar. This was called alpha-haemolysis. The alpha-haemolytic streps were sometimes also called viridans streptococci, from the Latin for green.
The beta-haemolytic streps were noticed to be more associated with severe disease: cellulitis, septicaemia, scarlet fever, puerperal sepsis, and rheumatic fever. Because of these important diseases, it was important to try to understand them better—were they all one species, or were there different types causing different infections?

This question was addressed by an American microbiologist, Rebecca Lancefield, who between the 1910s and 1930s carried out numerous experiments, injecting different beta-haemolytic streps into rabbits, measuring the antibodies produced, and using these antibodies to identify different sub-types of beta-haemolytic streps. She assigned these different groups of streps to letters of the alphabet, and thus we have Lancefield Group A (beta-haemolytic) strep, Lancefield Group B strep, and so on. The names are usually shortened—microbiologists speak of Group A strep, Group B strep, and so on. Most of the alphabet is now used, though not all Lancefield groups are typical human pathogens (Group R streps are common pathogens of pigs, for example).

Since Rebecca Lancefield started with the most serious strains, it is no surprise that Group A strep is associated with the most severe streptococcal infections. Since the 1950s, detailed biochemical and molecular testing of all these strains have been done. It was then realized that the Lancefield scheme, while useful, was a simplification. Strains could be assigned to formal species. These species often matched a Lancefield group—but not always. Thus Group A strep is equivalent to the species \textit{Streptococcus pyogenes} (2 µm in diameter) (Fig. 12.2.2) from the Greek \textit{pyogenes}, which means to makes pus (see Case 9.2, Tonsillitis), Group B strep (often carried vaginally as part of the normal flora, but also possibly a cause of premature birth and neonatal infection) is equivalent to \textit{Streptococcus agalactiae} (Greek \textit{a-galactiae} means lack of milk as the organism also causes mastitis in cattle, with failure of milk production). In contrast the Group D streps include several species, such as \textit{Streptococcus equinus} and \textit{Streptococcus bovis}, as well as the enterococci (formerly known as \textit{Streptococcus faecalis}) (see Case 13.2, Complex intra-abdominal infection). Group F streps include three species—\textit{S. constellatus}, \textit{intermedius}, and \textit{anginosus}.
With regard to this particular result, Group A strep or \textit{S. pyogenes}, which can cause particularly severe postpartum infection, has, thankfully, not been picked up. Group B strep or \textit{S. agalactiae} may be Kirtida’s normal vaginal flora but in this instance may also cause problems as she has had a surgical procedure. The empirical antibiotic combination of cefalexin and metronidazole is commonly prescribed for obstetric and gynaecological infections—the logic behind it that these infections may be caused by a range of gut and skin organisms (or a mixture of them) including staphs, streps, coliforms, and anaerobes—the cefalexin will cover staphs and streps (including Group B strep) and most coliforms, and the metronidazole will cover any gut anaerobes that are present.

The other point of note with this result is that Group B strep (GBS) is the major pathogen of neonates, as well as being a frequent cause of obstetric infections in pregnant women. If someone who is pregnant is found to be a carrier of this organism, the question arises whether intervention is necessary, either to prevent early labour or to prevent the baby later becoming infected. It has been discovered that trying to eradicate the organism in the mother does not work—antibiotics suppress the organism for a while, but it comes back. However, if a pregnant woman is found to be a GBS carrier, giving intravenous antibiotics during labour has been shown to reduce the risk of early-onset neonatal sepsis with GBS. The controversial issue is, whether to screen all pregnant women for GBS carriage. In the USA, universal screening is advocated, with antibiotic prophylaxis during labour for carriers. In the UK, universal screening is not recommended, and a risk-based approach is taken: antibiotics should be given during labour to women who have been found by chance to be carriers, or to women who have had a previous baby infected with GBS. The justification for the UK approach of not screening is that the current rate of GBS infection is very low, the benefits of prophylaxis are not clear, and there is concern about the long-term effects of giving antibiotics to many thousands of women who may not need them.

\textbf{Further reading}

Group B Streptococcal Disease Early Onset. Greentop Guideline no 36. rcog.org.uk
Chapter 13

Hospital

Case 13.1  Sepsis (UTI)  
Case 13.2  Complex intra-abdominal infection  
Case 13.3  Middle East respiratory syndrome
Case 13.1

**Sepsis (UTI)**

**Case example**

You have been asked to do a home visit on an Erica Campbell (84). You bring up her notes to work out who she is and where she is. In fact she is Dame Erica Campbell. The receptionist’s message reads, ‘Unwell 1 day.’

First you look at her medicines to see what illnesses she is treated for. She is on clopidogrel, simvastatin, and allopurinol. From this you surmise she has had a CVA (a stroke), and has gout. Next you move to her summary page and this confirms the CVA and gout. Here you notice CLL (chronic lymphoid leukaemia). And her last blood results show her WCC at 118—massively high. When you click on the WCC result the computer collates all her previous readings for you and arranges it into a graph which shows a steadily rising WCC of around 40 over several years, increasing suddenly in the last 3 months to the aforementioned 118.

She lives nearby. You pack into your bag various equipment you feel you may need and wave at the receptionist on the way out to tell her where you are going. Dame Campbell’s door is answered by her daughter. ‘I’ll just tell her you’re here,’ she says nervously. ‘No, actually it’s fine. Just come up. It’s fine.’

On the way upstairs you notice an oil painting of the Middle East and then several portraits. Dame Campbell is in a small bedroom, off the landing. She is lying flat in bed and wearing night things. ‘She says she needs the toilet,’ her daughter says.

When Dame Campbell sees you she tries to get up. Initially you don’t help her so you can see how she manages. She sits up, dangles her legs off the bed but then slowly leans back and finds herself lying down again. She reaches her hands out for help and this time you reach forward and pull her upright, but the same thing happens again. Again she slowly leans back and again looks surprised to find herself lying flat again. After she has see-sawed slowly on the edge of the bed three more times you say, ‘Look, I need you to lie down comfortably so I can talk to you.’ She looks at you blankly and continues trying. Her daughter stands next to her indecisively. ‘This is no good,’ you say at last, perhaps more strongly than is needed. ‘I need Dame Campbell to stay in bed; she can do a urine sample here. Can you get some kind of container?’ to her daughter. The daughter hurries downstairs. At this point Dame Campbell lurches to her feet. Colour drains from her face as she totters there.

‘I want you to sit down. Sit down,’ you say to her clearly. If she falls over she could end up with a fractured hip. She sits with a plop.

Her daughter returns and you politely stand outside in the hallway until her daughter comes out with a container and you transfer the sample of urine into a sterile urine bottle.

Dame Campbell is lying down again in bed apparently asleep. ‘Hello,’ you say, at last introducing yourself. She opens her eyes and nods agreeably and then closes her eyes again. ‘Can you tell me what’s happened?’ you ask her daughter.

‘Yes,’ she takes over. ‘She was fine yesterday, we went out for lunch. Then yesterday evening she suddenly became unwell. She was complaining of a headache and she felt cold. She went straight
to bed and has been the same all night, and sweating. She’s not really drunk anything and today she’s no better. I’m frightened for her to get up, she doesn’t look stable . . . I’m only staying with her for a conference, you know,’ she adds. ‘It’s just luck that I was here last night. Usually she’s here on her own. She’s pretty independent. Of course you know she had a stroke?’

‘And her memory?’ you ask.

‘Her memory is fine. In fact she is giving a speech in 5 days time at a Foreign Office function.’

‘Does she work for the Foreign Office?’ you ask curiously. ‘She used to. She’s a retired diplomat,’ answers the daughter.

‘So she’s not herself at the moment,’ you conclude. ’No. Not herself at all,’ agrees the daughter sombrely.

You take her temperature which is a very high 39.8°C. Her oxygen saturations are 91%, HR 91, respiratory rate 20, and BP low for her, a lying down reading at 118/58. Her urine dip shows WCC+ and RCC+. Her chest is clear and her abdomen is tender suprapubically.

This is a UTI, but not a normal UTI. She has become very sick, very quickly. Her observations are abnormal and she is not acting right. In short, she is delirious. You pause a little while staring at the observations, which you have noted down, digesting all the information. You now need to explain your findings and what it means and what you mean to do about it to Dame Campbell and her daughter, even though the patient will not quite get it all in this state.

You look up and catch the daughter’s eye. You look rather serious so that she knows something serious is about to be said. You say, ‘I think she needs to go to hospital.’ You pause to allow this to be absorbed, and then continue, ‘I think she’s got a urine infection. But she’s much sicker than people usually get with an infection like this. I think it’s because of the chronic leukaemia. I think she’s not fighting off this infection properly. I don’t think this is a situation where I should just give antibiot-

ics and leave you to it. I’m worried Dame Campbell will fall and I’m concerned about dehydration.’

Her daughter nods in a worried way. Dame Campbell wakes up for a moment. ‘Oh no, not hospital!’ she says, smiling genially as if she is at a meeting rather than lying on her back in bed.

‘Mum, I think you do need to go to hospital,’ her daughter says. ‘What if you fall?’

You continue speaking again. ‘People who can’t fight infection properly can get very ill, very ill indeed.’

‘I understand what you are saying,’ her daughter says.

‘I think she will probably get better nicely with antibiotics, but we’ve just got to see how it goes.’ She nods again.

Because you want antibiotics for Dame Campbell quickly (the septic guidelines aim for a door-to-needle time of less than 1 hour), you call 999. You hear, ‘Fire, police, or ambulance please?’ and answer, ‘Ambulance please!’ and then explain the nature of the emergency.

The daughter vanishes to phone her brother and let him know what is happening. Within 15 minutes two paramedics arrive. You hand over in detail and say goodbye to Dame Campbell and her daughter. You go back to the practice to fax over a letter to the hospital and continue your clinic.

Her discharge letter which you receive 1 week later reads:

This 84-year-old lady was admitted with a 2-day history of pyrexia, lethargy, and nocturia. She has known CLL and gout, with PMH of CVA. CRP 97, WCC 81.6. She also developed delirium likely secondary to UTI. CXR was NAD. Blood cultures showed E. coli. MSU also showed a
Microbiology

It has become recognized that patients are routinely dying of septicaemia because health care workers are either not identifying it accurately or are slow to treat. Hence the drive of the Clinical Excellence Commission SEPSIS KILLS, which is promoting the concept of a ‘door-to-needle’ time of less than an hour, in the same way that has been done for MI and CVA. Box 13.1.1 shows an excerpt from the sepsis guidelines to apply to the case.

Dame Campbell has four risk factors/signs/symptoms of infection and therefore counts as severe sepsis until proven otherwise. Calling the ambulance has moved her on to the senior review in A&E and the discharge letter indicates that the correct samples were obtained (except that coagulation was omitted) and that IV antibiotics were given (exactly how quickly is not documented).

Commonly septicaemia is caused by a focus of infection such as a UTI, as here (these account for 30% of cases of septicaemia), or an abscess or an invasive procedure such as surgery or cystoscopy. Often patients with septicaemia are also immunocompromised, for example those on steroids, or asplenic, or with HIV, or as here with CLL.

Common microbes implicated in septicaemia include *Staphylococcus aureus*, *E. coli* and *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Streptococcus agalactiae*. Others often seen are *Enterococcus* spp., *Pseudomonas*, *Klebsiella*, *Enterobacter*, and *Candida* spp.

Complications are common. For example, progression to septic shock, disseminated intravascular coagulation (DIC), renal failure, and multi-organ failure. Mortality is high: up to 30%.

Because of the nature and diversity of sepsis and its causes, control measures need to be similarly flexible and adaptable. Some cases can be prevented, for example those associated with an invasive device such as an intravenous line or urinary catheter. Care on insertion, on handling, and monitoring of those devices greatly reduce the risk of infection.

When faced with a potentially septic patient, early antibiotic treatment is essential. The choice of antibiotics will be guided by local hospital guidelines, and also on the likely focus of infection (if known), and the immune state of the patient. The policies in turn are likely to be based on local antibiotic resistance rates in different organisms. In treating sepsis there is a need to start with a broad spectrum agent or agents to ensure broad coverage of most likely pathogens, as is done here, but there is also a conflicting desire not to use too many broad-spectrum antibiotics for fear of driving up increased antibiotic resistance in the hospital or community. A compromise approach included in the UK guidelines is to, ‘Start smart, then focus’. This means treatment should be started with something broad spectrum, but once the focus or organism is established, to switch to a narrower-spectrum antibiotic.

When the focus of infection is unknown, the aim is to cover the most likely pathogens. *Staphylococcus aureus*, streptococci, and *E. coli* or other *Enterobacteriaceae* are associated with the most likely sources of sepsis—pneumonia or UTI. A typical choice is to give a combination of co-amoxiclav and gentamicin.
Box 13.1.1 Does your patient have risk factors, signs or symptoms of infection?

Immunocompromised. Indwelling medical device. Recent surgery/invasive procedure. History of fever or rigors. Re-presentation within 48 hours. Fall. Abdominal pain or peritonism. Cough or shortness of breath. Altered consciousness, confusion, neck stiffness or headache. Wound or cellulitis. Dysuria or frequency or odour.

AND

Does your patient have two or more yellow criteria?

Respirations less than 10 or over 25 per minute. Oxygen saturations less than 95%. Systolic BP of less than 100 mmHg. Heart rate less than 50 or over 120 a minute. Altered consciousness or new onset of confusion. Temperature less than 35.5 or over 38.5.

IF YES

Does your patient have any red criteria?

Systolic BP less than 90. Lactate over 4 mmol/L. Base excess less than 5.0. Age over 65. Immunocompromised.

IF YES

Patient has SEVERE SEPSIS or SEPTIC SHOCK until proven otherwise.

♦ Obtain immediate senior clinician review
♦ Expedite transfer to resuscitation area or equivalent
♦ Commence resuscitation as per SEPSIS SIX

SEPSIS SIX

1. Oxygen to keep oxygen saturations above 95%
2. Blood cultures, also FBC, U&E, LFT, coagulations, glucose, other cultures
3. Lactate measurement
4. IV fluids bolus 20 mL/kg normal saline stat. If no response repeat unless there are signs of pulmonary oedema
5. IV antibiotics prescribe and commence within 60 minutes from triage/time of diagnosis. Do not wait for results of investigations
6. Monitoring: respiratory rate, oxygen saturations, BP, heart rate, temperature, consciousness, fluid balance, urinary output


Further reading


Case 13.2

Complex intra-abdominal infection

Case example

It is Wednesday afternoon, and you are the microbiology consultant making your daily visit to the intensive care unit (ICU)—what the intensive care unit registrars have begun to call the Bug Round. You discuss the patients with the doctors on duty, reviewing their (multiple) microbiology results and correlating these with the clinical story, and trying to give sensible advice about investigating and managing the patient’s infections.

You come to Bed 6. The relatives by the bed look up apprehensively, and then they recognize you. The patient, Mr Ivor Evans, has been in ICU for nearly 3 weeks, and you have already met the family several times.

‘So what’s been happening with Mr Evans?’ you ask the ICU registrar. ‘Do you know the story?’ comes the reply, and you answer that you do (and quickly check the notes to make sure you remember the details). Mr Evans is a 78-year-old Welshman, a retired builder, who has a long history of diabetes and peripheral vascular disease. He presented 6 weeks previously with rectal bleeding and altered bowel habit. A colonoscopy showed an upper rectal tumour, which necessitated an anterior resection. He seemed to make a good recovery, and was discharged home at 8 days. He had the clips removed at 10 days, but 3 days later noticed some greenish ooze from the wound. He was given oral flucloxacillin by his GP, not unreasonably, but a few days later (about 3 weeks ago) the wound started to dehisce and discharge more, and he became very unwell. He was readmitted septic, and went to theatre for a laparotomy. The surgeons found some free fluid, but no actual perforation of the colon, so the abdomen was washed out and re-closed, leaving some drains in place. The swab sent by the GP grew *Escherichia coli*, explaining why the flucloxacillin had no effect.

After his operation he was transferred to ICU, and has remained there since, ventilated and needing inotropic support. He has been on antibiotics since admission; these were escalated at various points during his stay, as he developed septic episodes. He was first on co-amoxiclav and metronidazole, then gentamicin was added, then this was changed to piperacillin–tazobactam plus gentamicin. Then when he deteriorated further, with a rising CRP (peaked at 253) and needing haemofiltration, he was switched to meropenem. The abdominal fluid sampled during his original laparotomy was reported as:

| Mixed coliforms including Proteus +++ |
| Bacteroides sp. + |
| Comment; this represents mixed faecal flora. |

A later sample of drain fluid was ‘no growth’, and now a more recent drain fluid taken 2 days ago, is reported as:

| Enterococcus faecium +++ amoxicillin (R), vancomycin (S) |
It is this particular result the ICU registrar wishes to discuss. ‘Do we need to change the antibiotics?’ he asks.

‘Well, it’s not that straightforward,’ you reply. ‘We need to understand the context of the result. Is Mr Evans any better in the last few days? Is he actually septic? How was the sample collected—from the drain itself, or from the collection bag? Why exactly was the sample sent?’

The ICU registrar seems a bit intimidated by the wave of questions, but gradually you both work through the issues. It was a drain fluid sample that was sent when he deteriorated 2 days ago, as part of a general septic screen. His blood cultures are still negative, respiratory samples have grown upper respiratory tract flora only, and a catheter specimen of urine has grown the same *Enterococcus faecium* as in the recent drain fluid. He has actually improved slightly since starting meropenem and haemofiltration—he needs less inotropes, and his CRP has come down to 174.

The *Enterococcus* is likely to be resistant to the meropenem (though it has not been tested). The abdominal drain is still working, with free drainage of fluid, and he is improving, so it is reasonable to hold back on changing treatment. However, if Mr Evans deteriorates at any stage over the next few days, then it would be sensible to add in antibiotics to cover the *Enterococcus*—you suggest vancomycin. If he does deteriorate, it is important not to rely just on the change of antibiotics; he should have a further septic screen, and his abdomen should be imaged in case there are further collections that need surgical drainage.

The ICU registrar agrees to the plan you suggest, and you pass on to the next patient. However, the following day, when you visit the ICU again, you discover that Mr Evans was febrile and hypotensive again during the night, and has been started on vancomycin. He has just had an abdominal ultrasound, and this shows a pelvic collection. A second drain is being inserted under ultrasound guidance, and you await the results from further microbiology samples, hoping that the multiple antibiotics he has been exposed to will not select even more resistant organisms.

**Microbiology**

*Enterococcus* is a genus of bacteria that resembles streptococci, and were formerly included in that group as ‘faecal streps’, or ‘strep faecalis’, since their normal habitat is in the gut. For a long time they were regarded as not particularly pathogenic, but in the last 25 years they have received much more attention. They mainly cause disease in debilitated, elderly, or hospitalized patients, as with Mr Evans; they seldom cause disease in healthy adults or children.

The genus contains many species, including at least 18 isolated from humans, but most human infections are due to two species—*Enterococcus faecalis* and the *Enterococcus faecium* seen in Mr Evans. Enterococci exist as Gram-positive cocci in chains (which may be short, or they may just be in pairs). They grow well on most laboratory media and grow in air or anaerobically. They are relatively tolerant of heat, surviving up to 55–60°C, and also tolerant of disinfectants. As they are adapted to live in the gut, they are tolerant of bile (unlike most other streps), and so bile-containing media such as MacConkey agar may be used to help select and differentiate these organisms. One approach to distinguishing them from the other streps is a particular biochemical test in which they hydrolyse aesculin (an extract of horse chestnuts). This test may be combined with bile tolerance as the bile aesculin test. Agar containing bile, aesculin, and ferric acid is inoculated with the suspect organism, and incubated for 4 hours. The appearance of a dark brown colour indicates the organism both tolerates bile and can hydrolyse aesculin—strongly suggesting it is *Enterococcus*.

Many laboratories will only take the identification to this level, but as antibiotic resistance becomes a problem with Enterococci, further identification to species level is often necessary.
This is done with kits containing a combination of biochemical tests, such as the commercial API system, or molecular tests (based on DNA sequencing), or more recently advanced mass-spectroscopy technology such as MALDI-TOF: matrix-assisted laser desorption/ionisation-time of flight (Box 13.2.1).

Enterococci are intrinsically resistant to many antibiotics, including penicillin and cephalosporins (which again distinguishes them from the other streptococci), as well as quinolones such as ciprofloxacin. *E. faecium* is also resistant to amoxicillin, but usually remains sensitive to vancomycin or teicoplanin. More worrying, strains that are resistant to glycopeptides also occur, and can become established in hospitals. These strains (usually referred to as VREs, or vancomycin-resistant enterococci—because they are generally resistant to vancomycin) have somehow acquired a complex of genes that act in combination to produce abnormal cell wall precursors which have a lower affinity for vancomycin. These genes are carried on a transposon that may be within a plasmid.

### Box 13.2.1 MALDI-TOF and bacterial species identification

The most complex part of diagnostic microbiology is species identification. For a long time laboratories relied on a combination of colony appearance on agar, Gram stain, simple rapid biochemical tests such as catalase and oxidase, and more sophisticated biochemical assays in test tubes, and serological tests. Then companies developed batteries of biochemical tests in a single plastic strip containing multiple small wells, each well with a different chemical reagent. The different reactions produce colour changes, and the colour changes can be recorded as a numerical code, like a telephone number. The numbers can then be matched with a database to see which bacterial species they most resemble.

These methods are still somewhat laborious, and also take a day to get a result (the organism is usually left to grow overnight in the wells). It was long assumed that genetic techniques would be the next breakthrough in routine bacterial diagnostics, as sequencing has become gradually cheaper and quicker. In fact bacterial speciation is now being revolutionized by a completely different technology, a specialized technique of mass spectroscopy known as MALDI-TOF: matrix-assisted laser desorption/ionisation-time of flight.

Mass spectroscopy is an old technique, and involves heating the specimen to break it up into ionized particles that are then accelerated in an electromagnetic field, and detected in various ways. The detector can measure their speed, their deflection in a magnetic field, or some other indicator of the mass/charge of the particles.

When this was tried initially with bacteria it was not particularly good at distinguishing different species. When heated the bacteria fragmented into a soup of small molecules giving confusing patterns of results.

The newer, more subtle technique of MALDI-TOF, however, is to embed the bacteria in a chemical matrix that stabilizes the bacterial molecules when heated. Now when the bacteria break up, the molecules (mostly proteins) are more or less intact, rather than blasted into tiny fragments.

In addition, the development of better, more sophisticated computing techniques has meant that each complex pattern of fragments (different for each species of bacteria) can be identified and then compared with a database of known bacterial patterns.

The MALDI-TOF equipment is expensive, but is a one-off investment and very cheap to run, quick (batches of dozens of tests can take a few minutes) and takes up little space (it can sit on a laboratory bench). MALDI-TOF is set to become the standard bacterial identification method used in modern labs from now on.
Enterococci, as normal gut inhabitants, cause two principal types of infections. They can enter the urinary tract, usually by an ascending route, and cause a UTI. Or if the gut is damaged in some way, as with Mr Evans, then enterococci can cause peritonitis or local intra-abdominal collections and abscesses.

Enterococci can colonize the respiratory tract of these patients, particularly if they are being ventilated, causing ventilator-associated pneumonia, and Mr Evans is at risk of this. They may also colonize and infect surgical wounds, pressure ulcers, or intravenous lines. Any of these infections may then seed elsewhere via the bloodstream, leading to bacteremia, endocarditis or bone infections (usually spinal).

Most enterococcal infections are caused by the patient’s own bacterial flora, but these bacteria can spread between patients in hospital, aided by overcrowding, poor handwashing and poor hygiene, and also by the organism’s intrinsic resistance to heat and disinfectants. This is a particular problem when hospitals become colonized with multiple antibiotic-resistant strains, making treatment even more challenging.

Carriage of enterococci, and especially VRE, is promoted by the use of antibiotics, especially cephalosporins. There is no vaccine (enterococci are part of normal flora after all) but infections can be reduced by attention to antibiotic prescribing in hospitals combined with improved hospital hygiene, so that multiple-resistant strains are not selected and allowed to spread.

**Further reading**

Case 13.3

Middle East respiratory syndrome

Case example

It is three in the morning and you are the medical registrar on call. Your bleep goes off. You call back and it is the infectious diseases consultant to speak to you.

‘Have you been face-fit tested for an FFP3 mask?’ she asks out of the blue.

‘Er.’ You cast your mind back to when you had your face-fit test for the filtering face piece 3 mask (FFP3). Once a well-fitting mask had been found you had had to put on a sort of hood and then a strong smelling substance was squirted into the hood, to see if you could detect it when the mask was on (you couldn’t, which meant it was a good fit). ‘Yes, I’ve been face fitted,’ you agree.

‘We have a possible MERS case arriving into our negative pressure room at the infectious diseases department. I’m coming up to the hospital too, but we’ll need to assess him.’

You’re not so sleepy now. MERS (Middle East respiratory syndrome) is a highly contagious respiratory pathogen a bit like SARS (severe acute respiratory syndrome), but from the Middle East. With a mortality rate of 50% and aerosol spread it is something that you will definitely need personal protective equipment (PPE) for. You have had training in how to put it on and take it off and as you walk towards the infectious diseases department you run through the routines in your head.

The patient is a 22-year-old man with diabetes. He arrived by plane today from Saudi Arabia, where he had been visiting family. He had been feeling pretty unwell with a temperature, cough, and difficulty breathing, so his hotel had arranged for him to see an out of hours GP. The GP had found a temperature of 38°C and crackles on one side, consistent with a pneumonia, had considered MERS early and phoned the consultant directly, as per the local guidelines.

Now that the idea of MERS has been raised, it has to be treated as MERS until proven otherwise. This means transferring the patient from the GP practice in an ambulance handled by an experienced and fully protected paramedic crew, and closing the GP practice for the rest of the night in order to deep clean the premises. The GP will also need to self-quarantine until the results are known.

Up in the infectious diseases department there is an unexpected calm. The nurses there are experienced in isolation procedures. They have the designated room ready and waiting, and an array of PPE at the nurses’ station, including the FFP3 masks and the instruction manual. You have half an hour before the patient arrives, so you refresh your memory on the gowning up and degowning procedures and start to get dressed. The consultant arrives to help and talk you through the procedure as you both gown up.

You put on the surgical gown and two pairs of gloves. Then you put on the mask. This has to fit snugly over your face. When you suck in air as you have been taught, to double test the fit, you feel it grip against your cheeks, a tight seal. No air is coming in except through the filter. You put on the eye protection. Now all your mucous membranes are covered (eyes, mouth, nose) so that virus can’t land on them and cause a direct infection. It can land on other parts of your body though and you feel a sense of vulnerability. Once dressed you feel hot and claustrophobic, your movements are restricted.
The patient arrives and in the brief glimpse of him before he is shut into the negative pressure room, you see a miserable, tired, and breathless young man. To minimize staff contact with the patient you act as both doctor and nurse. You take a history and establish his symptoms as well as his risk factors, take his temperature and blood pressure, get IV access and take bloods, blood glucose, cultures and throat swabs in a viral medium to be transported double bagged to the laboratory marked HIGH RISK. He has difficulty communicating with you and the consultant through your plastic visors although his English is fine. You find it difficult to speak clearly to him through the mask. You try to be as calm and friendly as you can through all the protective clothing. You gain IV access with a view to treating what seems a likely community-acquired pneumonia.

When you come to leave the room you are keen to get all the gear off as quickly as possible. But it has to be done in the right order to reduce the chance of contaminating yourself from the outside surface of the gown, gloves, eye guard and mask. You take the gloves off first, then the gown, then the eye protection and lastly the mask, before washing your hands. You go outside to hand over your instructions for the management of the patient to the infectious diseases nurses after discussion with the consultant.

The results will be processed in the morning, so the patient must remain in quarantine until that time. You must both go back to bed now, or to attending to the rest of the hospital if you get any further calls. Sleep does not come quickly as you mull incoherently over the equipment you have just used: mask off first or gloves off first . . . gown off first.

Microbiology

Coronaviruses, also the cause of the common cold (see Case 9.1, Cold/rhinitis), were catapulted into our imagination following the SARS outbreak of 2003. Once it was identified that doctors were dealing with a new and severe respiratory infection, the WHO issued a global alert. The CDC and other health protection agencies around the world then had a number of urgent tasks:

- developing a case definition
- managing the care of patients
- protecting health care workers
- determining in the laboratory what was causing SARS
- once the microbe was identified to create diagnostic tests
- isolation and quarantine advice to prevent spread

as well as communicate to the public and health and other agencies. Amazingly within 12 days of announcing a global alert, scientists had identified the causative microbe: a novel coronavirus, probably originating from a bat.

Worldwide there were 8096 reported cases of SARS and 774 deaths. Containment of the infection was helped by the fact that infectivity was low, mainly droplet although some aerosol \((R_0\) value 3), and that incubation was long (10 days) which meant quarantine was effective. In addition, subclinical or mild cases were uncommon. This allowed most cases to be identified and then contact traced. Compare this to influenza, which is spread by aerosol \((R_0\) value 2), has a short incubation (4 days) and where subclinical cases are very common.

MERS appeared in 2013. This is also caused by a coronavirus, 150 nm in diameter (MERS-CoV) (Figure 13.3.1) and also probably originated from a bat source, although the intermediate animal appears to be camels. Most human cases have had direct contact with an animal but there
have been cases caught directly from other people following close contact. There have been cases in France (imported), Italy (imported), Jordan, Korea (imported), Kuwait, Oman, Qatar, Saudi Arabia, Tunisia, UK (imported), and the United Arab Emirates. At present there is, of course, no treatment apart from supportive measures.

**Further reading**


Interim Guidelines for Collecting, Handling and Testing Clinical Specimens from Patients under Investigation for MERS-CoV. www.cdc.gov/coronavirus/mers/guidelines

Remembering SARS: A Deadly Puzzle and the Efforts to Solve It. http://www.cdc.gov/about/history/sars/feature.htm
Chapter 14

International

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Case 14.1

**Fever: foreign travel**

**Case example**

You are the on-call microbiology consultant taking phone calls. You are in the middle of a telephone conversation advising one of the wards, when you feel the vibration of your mobile phone in your pocket alerting you to a text message. As you finish your conversation you quickly read the text. It’s from Maria, one of the infectious diseases registrars in your hospital. ‘Sorry, couldn’t get through to you on the phone. Call me urgently please. Possible Ebola VHF at GP.’ You read it again and think that it was only a matter of time before something like this would crop up.

You bleep Maria and while waiting for her to reply you get the hospital’s guidelines for managing patients with possible viral haemorrhagic fever (VHF) up on the monitor. Maria calls straight back. ‘I’m sorry to bother you, but I’ve been called by a GP about somebody who came to his surgery this morning. She’s a 42-year-old lady, Memory Conteh, who just came back from Sierra Leone 7 days ago. The GP says she’s had a fever for 2 days. She sounds quite well but I think we can’t take any chances given the current situation, so we are planning to bring her in. I just wanted to touch base about the diagnostic specimens and the infection control arrangements.’

‘OK,’ you say. ‘Can I just check a few things with you?’ You go through the VHF algorithm together to make sure you are both happy that you’re following the right course of actions.

The important questions are: has she had a fever of more than 37.5°C within the last 24 hours or alternatively a history of fever, and have the symptoms started within 21 days of returning from an endemic area (21 days being the incubation time of Ebola). Mrs Conteh has not knowingly been in contact with anybody with Ebola infection, didn’t visit any hospitals or attend any funerals, didn’t have contact with bats, primates, or antelopes in an Ebola endemic area and didn’t visit any caves or mines where bats may reside. Your minds are both focused on Ebola but you also establish that she hasn’t travelled to any other areas where other viral haemorrhagic fevers can occur. According to the GP she doesn’t have any signs of haemorrhaging or bruising. In fact she has no symptoms other than the history of fever. In normal circumstances she would only fit into the category of a low possibility of VHF but the circumstances at present are different. She has been in West Africa in the midst of an outbreak of Ebola virus infection and anybody who has been there and has a fever has to be recognized as being in the high-risk category until proven otherwise. Both you and Maria agree that the chances of Ebola are slim, but it can only be proved by coming up with a differential and testing her.

‘Yes, I agree she’ll have to come in. What’s the GP done with her?’ you ask.

‘The GP was on to it very quickly. The patient phoned before she came to the surgery and she went straight to a room by herself and she’s waiting there now. I’ll ask the GP to arrange the ambulance.’ You remind Maria to make sure that the ambulance service is warned of the possible diagnosis so that the correct infection control precautions are used. ‘Can you also ask the GP to alert the local Health Protection Team as well,’ you say to Maria. ‘They will be able to advise the GP about anything that needs to be done at his surgery if this turns out to be a genuine case.'
Speak to the A&E department too so that they can get the designated room ready and seal off the exit and entry to the corridor where the room is. I’ll go and speak to the Infection Control Team now. They probably ought to go down to A&E to check everything is ready and all the necessary personal protective equipment is there. I’ll also speak to our lab staff so that we can get ready to deal with the specimens. Give me a call when she arrives.’ To yourself you think, ‘It’s a good job we did that practice run last week,’ and walk quickly to the Infection Control Nurses’ office.

Over the next 2–3 hours, things move quickly. The patient arrives and is taken straight away into a single room. Access to the corridor leading to the room is shut off except to designated individuals. Maria makes the initial assessment of the patient along with the consultant in infectious diseases. Both wear the appropriate personal protective equipment (PPE)—gloves, fluid repellent gown and hat, eye protection, FFP3 face mask and rubber boots. You meet them as they are coming out of the room. You’ve come down with the chief biomedical scientist to collect the specimens and also to check that everything in regard to infection prevention and control is going smoothly. You watch closely as they carefully remove the PPE in the correct sequence to avoid contaminating themselves in the process.

‘I think it’s very unlikely,’ says the consultant in infectious diseases. ‘She’s not got a fever and all her observations are normal. No other symptoms. She says she thought she might have malaria as she didn’t take any prophylaxis. She’s had it before and self-treated. She would have done the same this time, but didn’t have any treatment at home. She said her son had a bit of a cold last week, so another possibility is that she has just got a cold. She wasn’t worried about Ebola—but she is now after seeing us dressed like this.’

‘I know,’ you reply, ‘But you can’t take any chances. Did she say why she had been over in Freetown?’

‘She was over visiting her husband who still lives over there. I wonder if we will have some more people with the same story. I gather there are quite a few people from Sierra Leone who live locally.’

You have a look around and are happy that everything seems to be in order. The correct waste bins are in position and the signage is all correct. The other door that leads to the corridor has been locked. You and the biomedical scientist take the specimens in a metal box back to the laboratory to be handled in a safe manner. The VHF algorithm allows some necessary testing to manage the patient, in particular to make sure that other life-threatening conditions are not overlooked, such as malaria.

An hour later the initial blood test results are back (FBC, U&E, and CRP, clotting and malaria screen). They are all normal and the malaria screen is negative. The next stage is to test for Ebola and this is done at the Rare and Imported Pathogens Laboratory run by Public Health England at Porton Down. Before sending the specimens they need to agree to do the test and you call Maria and check that she’s happy to speak to the Imported Fever Service, as this is better done by the doctor who has actually seen the patient. Maria calls back a bit later. It’s now 3.30 in the afternoon. ‘They say they’ll do the test, but not tonight. Although they agree she’s in the high possibility category, they say clinically it seems unlikely. But they said that if we send the samples by courier overnight, they’ll run them tomorrow morning with a result by the end of the day.’ You look at the algorithm again wondering whether to ring the Royal Free (the designated high isolation unit) but it advises that she should remain here as the two available beds are for confirmed VHF.

The following day you get a call from Porton Down. They have used PCR to test for a variety of viruses and bacteria that might cause fever in a returned traveller from Sierra Leone,
including the microbes causing typhus, Rift Valley fever, Congo–Crimea haemorrhagic fever, Chikungunya fever, Lassa fever, dengue fever, Ebola, and Marburg. She is negative for all of them. You telephone Maria. ‘She’s been afebrile the whole time she’s been here,’ she says. ‘I guess she just had a cold. Well, it was good practice for the real thing . . . . I better go and discharge her straightaway.’

**Microbiology**

Mrs Conteh illustrates a systematic approach to imported fever. The key elements to this are taking the history of the presenting complaint and then a detailed travel history. Subsidiary to that, the patient’s travel vaccine history (cholera, typhoid, hepatitis A and yellow fever), treatment history (particularly malarial prophylaxis), and also any risk-taking behaviour, such as high-risk sexual partners, contaminated food, swimming in fresh water in schistosomiasis endemic areas, and insect/animal bites.

Included in every guideline, the first and most common diagnosis to consider is malaria and, as is done here, the malaria tests are always done first.

The presenting complaint can be simply fever, as with Mrs Conteh, in which case the differential is wide, as is illustrated by the microbes Porton Down tested on her samples. It can include (depending on the country visited) viral haemorrhagic fever (VHF), such as Ebola and Lassa fever (discussed here), insect-borne VHF such as dengue fever and yellow fever, also typhus and typhoid, as well as more familiar infections such as influenza, HIV, and hepatitis.

The doctors in this case have carefully followed the VHF algorithm and asked Mrs Conteh about her exact travel history, contacts, and high-risk activities just as outlined above, and have also done the initial tests including FBC, thick and thin films for malaria, U&E, LFT, CRP, and urine, stool, and blood cultures.

If the presenting complaint is more specific then this helps to direct the differential. For example, diarrhoea and vomiting would direct questions and investigations towards traveller’s diarrhoea (see Case 1.3, Traveller’s diarrhoea), respiratory symptoms to other respiratory illnesses (and MERS if travelling from the Middle East, see Case 13.3, Middle East respiratory syndrome), and CNS symptoms to rabies, polio, and viral meningitis (see Case 4.2, Viral meningitis).

The other major concern in cases of imported fever is transmission; therefore, isolation measures and PPE have to be considered. This case illustrates isolation issues with regard to droplet transmission. The MERS case in contrast illustrates the measures to be taken for aerosol transmission and the traveller’s diarrhoea case for faecal–oral transmission.

The case of Memory Conteh particularly illustrates the importance of communicating, both with the primary and secondary care teams and to the specialist centres such as the Royal Free hospital and the Rare and Imported Pathogens Laboratory. The Imported Fever Service (see Further reading) is another important resource for doctors, to enable them to discuss cases with a specialist (having first discussed with their microbiology team).

VHF is caused by various RNA viruses, including Ebola, a very elongated virus (970 nm long) (Fig. 14.1.1) and Marburg (Filovirus family), Lassa fever ( Arenavirus family), yellow fever and dengue fever (both of the Flavivirus family). Incubation for Ebola is up to 21 days but varies for the other VHF s. VHF typically starts with fever, headaches, myalgia, and conjunctivitis followed by a rash and diarrhoea and vomiting after 5 days, associated with symptoms of bleeding, bruising, and petechiae and bleeding from injection sites, the nose, intestines, or genitals. Bleeding can then lead to shock and death within a few days. Treatment is supportive with careful attention to isolation and PPE. Mortality varies between 40% and 50% with Ebola and 0.5% and 3% with dengue fever.
Fig. 14.1.1 A transmission electron micrograph of an Ebola virus demonstrating the filiform shape.

Reproduced from Centers for Disease Control and Prevention, Public Health Image Library (PHIL), Image ID#1833, Dr Frederick Murphy, 1976, available from http://phil.cdc.gov/phil/details_linked.asp?pid=1833

Further reading

Case 14.2

Malaria

Case example

You get a call late in the afternoon, about a young man with confirmed *Plasmodium falciparum* malaria and a parasite count of 18%. Your infectious diseases consultant is next to you in the doctors’ mess and overhears the parasite count. ‘If I had a parasite count of 18% I’d be near death, I think!’ he says.

The patient, Nelson Chikwangwe, however, is reasonably well. He is a 21-year-old man from Uganda who has had malaria before, perhaps several times, and has acquired a certain amount of immunity. He has recently entered the UK to study, but began to feel unwell 5 days ago with symptoms of a temperature, malaise, and myalgia. Because he recognized the symptoms and knows what malaria feels like, he has attended hospital.

Nelson is well aware of the impact that malaria has on everyone’s lives in Uganda. He normally sleeps under a mosquito net and rarely gets bitten in the evenings, but he doesn’t take prophylactic medication as this is simply not sustainable over a lifetime. He works in an office and is unaware of any contact with viral haemorrhagic fever.

In A&E he has been found to have a temperature of 38.5°C, jaundice, and is a little dehydrated but able to maintain a normal blood pressure and pulse. On examination he has a tender hepatomegaly.

Nelson’s bloods are markedly abnormal:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>119</td>
</tr>
<tr>
<td>MCV</td>
<td>72</td>
</tr>
<tr>
<td>Plt</td>
<td>&lt;1</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1</td>
</tr>
<tr>
<td>U&amp;E</td>
<td>Normal</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>130</td>
</tr>
<tr>
<td>ALT</td>
<td>128</td>
</tr>
<tr>
<td>ALP</td>
<td>130</td>
</tr>
<tr>
<td>Urine dip</td>
<td>Blood+, protein+</td>
</tr>
<tr>
<td>Malaria film</td>
<td><em>P. falciparum</em> 18%</td>
</tr>
</tbody>
</table>

Parasitaemia of >2% in a return traveller who is non-native to an endemic malaria area is regarded as ‘severe’.

Nelson himself doesn’t know what the fuss is about. Can’t we give him a tablet and send him home again as they do at home? Instead he is admitted for IV artesunate (unlicensed but given on a named patient basis) and oral doxycycline. By the next day he is symptomatically improved and his parasite count is less than 1%.

Further investigations are fine; his hepatitis screen is negative and his haemoglobin and platelet counts are improving. His HIV test is also negative. After 24 hours the IV treatment is switched to oral *Riamet*® and Nelson has follow up arranged with the infectious diseases team to repeat his bloods in one week with a view to discharge if well.
**Microbiology**

Malaria affects millions of people worldwide, but in the UK it is only seen in migrants and returned travellers from endemic areas, as in the case here. It is now absent from Europe (except some parts of eastern Turkey) but it is often forgotten that it existed in marshy areas of south-eastern England until the early twentieth century.

It is caused by four main species of *Plasmodium* parasite. *P. falciparum* (the most serious) is the parasite that Nelson has. There are also *P. vivax*, *P. ovale*, and *P. malariae*. *P. ovale* is mainly found in Africa, though some cases also occur in Asia; the others occur in all tropical and subtropical areas, though *P. vivax* is rare in Africa.

The name ‘malaria’ means ‘bad air’, and it was assumed for many years that the fevers suffered by people living in marshy areas were due to toxic vapours released by rotting vegetation. In the late 1800s the *Plasmodium* parasite was discovered to be the cause, and the Anopheles group of mosquitoes discovered to be the vector.

The life cycle is as follows: a biting mosquito injects sporozoite forms of the protozoan. These single-cell parasites are about 10–15 μm in length and 1 μm in diameter. They are motile forms, and they migrate into the circulation and then enter the liver cells, where they develop into schizonts. The schizonts are large forms that then split into multiple offspring known as merozoites. The liver cells then rupture, releasing these into the circulation; each infected liver cell can produce 10–30 000 merozoites. These bloodstream merozoites invade red cells and grow into ring forms called trophozoites, which mature into schizonts and these eventually rupture the red cells and release a flood of new merozoites. This process of red cell invasion, infection and rupture takes 2–3 days, and accounts for the periodic fever seen in many cases. The liver forms in *P. vivax* and *P. ovale* can become dormant (hypnozoites) and emerge to cause disease months or years later—this is important because some treatments do not eradicate liver forms.

The rupture of red cells and release of parasites and cell breakdown products causes the systemic features of the disease—fever, chills, etc., through activation of the immune system, anaemia, acidosis, and hypoglycaemia, and possibly sequestration of red cells in capillaries in different organs, leading to complications such as pulmonary oedema and cerebral malaria. Some of the merozoites in red cells develop into larger gametocytes (in *falciparum*, these are typically banana shaped)—these gametocytes need to be taken up by a feeding mosquito to keep the cycle of infection going.

Patients usually present with a fever and flu-like illness, as here, occurring up to 3 months of travel in an endemic area. People who have grown up in an endemic area and been repeatedly infected may develop some degree of immunity—this does not protect them from infection, but means that they tolerate the parasites in their bloodstream, hence the very high parasite count in Nelson’s case. A high parasite count increases the risk of complications such as severe anaemia, hypoglycaemia, pulmonary oedema, and cerebral malaria. Nelson’s immunity will gradually decrease if he stays in the UK without exposure to recurrent infections. A common scenario is a patient who is returning to visit their country of origin and has a perception of malaria as something trivial and does not take precautions, ending up infected and seriously ill. Therefore, malarial prophylaxis will be important for Nelson when he returns to Uganda.

Malaria diagnosis is not normally carried out in the microbiology laboratory, but in haematology. This is for practical historical reasons; diagnosis is by seeing the parasite in blood films, and haematologists have this expertise. Thick and thin films have both been requested in this instance as well as the other haematology and biochemistry tests.

The usual approach is to begin with a thick film—blood is spread thickly on a slide, and the slide is stained and examined; the staining lyses the red cells, leaving parasites, and white cells
intact. This method is more sensitive, because there is more blood, and therefore more parasites on the slide, but the parasite morphology is often unclear. Therefore, if parasites are seen, thin films are made by drawing out a small drop of blood over a whole slide, using the edge of another slide. These are stained without lysing the red cells, and allow much better views of the parasites.

In recent years, commercial antigen detection techniques have been introduced, and may eventually replace blood films as a first screen. The simplest to use are membrane-bound rapid EIA tests, similar to common pregnancy tests. They have the added advantage of being able to distinguish *falciparum* malaria from the other less serious forms. As with everything else in microbiology, PCR-based tests are also being developed, but they are not yet in routine diagnostic use.

Malaria should be treated if there is clinical suspicion, even if the tests are negative as no test is 100% sensitive. Negative blood films in a high-risk patient should be repeated every 12 hours. Treatment guidelines change all the time so up-to-date information should always be checked before prescribing. Because chloroquine resistance is so widespread, UK recommendations at present are to treat *falciparum* malaria with either quinine (the original ‘Jesuit powder’, brought to Europe from Peru by Spanish missionaries in the 1600s, and still highly active) in combination with doxycycline, or *Malarone*® (a combination of proguanil and atovaquone) or *Riamet*® (artemether with lumefantrine), Nelson’s discharge medication. Artesunate (used in this case intravenously in combination with doxycycline) is a relatively recent introduction derived from a Chinese medicine *Artemisia annua* (sweet wormwood plant) in use for many centuries. Combinations are preferred because of the possibility of resistance. Non-*falciparum* malaria may still be treated with chloroquine—though resistance is reported in South-east Asia. *Vivax* and *ovale* malaria must also be treated with primaquine, which kills the liver hypnozoites and prevents late relapses.

**Further reading**

Case example

The phone rings in your office, and it is a local GP to whom you have spoken before, Dr Ford. ‘Hello. Is that the consultant microbiologist? Is this a good time to speak?’ you hear.

You say you are free to speak and Dr Ford continues, ‘I’ve just seen this 9-year-old boy, James, who was camping with his Dad last week down in Devon, and when he got home his Mum noticed a tick on his leg, just below the groin. She pulled it off in a bit of a panic, but now 3 days later, there is a rash around the site of the bite. One of her friends mentioned Lyme disease, and she started reading about it on the Internet, and now she is really anxious. What do you think?’

‘What’s the rash like?’

‘It’s just a sort of irregular reddish circle around the bite, about 8 cm across. It’s got a pale ring in the middle just like the pictures of Lyme disease. James is very well otherwise—no fever, but the Mum is very anxious. I’ve asked them to wait outside while I get your advice.’

You pull up a Lyme disease guideline on your computer and meanwhile establish that James and his father were camping in Exmoor, and that there is no abscess at the actual bite site.

‘Well it could, of course, be a simple cellulitis related to the tick bite—especially if the mum pulled the tick off by force and some of the head parts were left behind. But the pale area in the middle does sound like the typical bulls-eye rash, so I think it could well be Lyme disease. The thing is, testing for Lyme at this point is likely to be negative, as it’s so early in the illness; the antibody response takes time. If we did do a test and it was negative we would have to repeat it in a few weeks’ time. The rash sounds so typical that testing is probably not necessary—but sometimes patients are anxious so you end up doing the tests anyway.’

‘What shall we do then?’

‘Definitely treat the child for presumed early Lyme—amoxicillin for three weeks is the recommendation for children (doxycycline is advised for adults) and explain to the mother that the test result won’t change what we do now but if she is keen then take two tests several weeks apart. Also, try to encourage her to avoid the more extreme websites about Lyme disease. This disease is very controversial, especially in the USA. There’s a counterculture view that chronic fatigue is really chronic Lyme infection with private laboratories offering unregulated tests, and claims of an official cover-up. The Public Health England website has good objective information, and the NHS Choices website is pretty good too.’

‘Ok, we’ll do that. I’ll start the antibiotics, and have a think about the testing. Thank you so much. Good-bye. Bye.’

Microbiology

Lyme disease is caused by infection with a spiral bacterium Borrelia burgdorferi (20–30 μm long but only 0.5 μm wide) and is spread by ticks of the Ixodes genus (Fig. 14.3.1). These are often called deer ticks, but in fact they feed on a range of animals, including deer, but also rodents
and birds. It occurs in temperate areas in Europe and America. In America, most cases occur in forested areas of New England (the disease is named after the town of Lyme, Connecticut). In the UK, most cases occur in woods or heathland in the south of England (especially the New Forest and Exmoor), as well as the Lake District, the North York Moors, and Thetford Forest. Fifteen percent of UK cases are acquired abroad.

The spirochete enters the body during feeding, via the tick’s saliva, and within a few days starts to replicate in the surrounding skin. The first and most common manifestation of disease is often a rash spreading out from the site of the bite, known as erythema migrans. The rash may become ring-like or target-like over time. Important differentials at this stage include ringworm, psoriasis, and cellulitis (as mentioned in the case). The patient may be otherwise well, as here, or may have fever and a flu-like illness.

During the rash, the spirochete can spread through the body and cause secondary infection and inflammation. Sites most often affected are the joints, causing arthritis, and the central nervous system, causing cranial nerve palsies or meningitis. More rarely, the heart may be affected, causing conduction problems. Untreated patients can develop long-term complications including chronic encephalomyelitis and radiculitis, and a chronic skin condition known as acrodermatitis chronica atrophicans.

Diagnosis is normally made using serology. While it is possible to grow the organism, or do PCR, on a sample of infected tissue, this is highly specialized and not practical in a routine laboratory. IgG serology for Lyme disease is very sensitive, but not completely specific. Therefore if the screening test is positive, it should be sent to a reference laboratory for further testing for Borrelia proteins. It is important to note that early antibiotics may abort the antibody response as well as cure the infection. Antibiotic treatment is usually straightforward: oral amoxicillin or doxycycline as the microbiologist advises. Neurological or cardiac complications, as well as arthritis are usually treated with intravenous ceftriaxone. Full recovery may take several weeks or months, but the overall prognosis is good.

Patients without a rash also sometimes present following a tick bite requesting testing. This is not generally recommended, but if done the test should be taken 8 weeks or more after the bite has occurred or otherwise it may be falsely negative.
There has been much publicity given to so-called chronic Lyme disease, which covers a range of symptoms including chronic fatigue. Most specialists in this area are of the opinion that seronegative chronic Lyme disease either does not exist or is extremely rare. It is important that people should not be labelled as chronic Lyme without valid evidence of genuine Lyme infection at some stage.

Further reading
Appendix 1

Medically important bacteria

Classifying medically important bacteria in the laboratory

There are thousands of named species of bacteria, of which maybe a few hundred are known to be able to cause human disease; of these, only a few dozen are likely to be encountered on a regular basis by most doctors. Bacterial taxonomy and classification is constantly evolving and increasingly dominated by genetic analysis, which allows scientists to make a detailed phylogenetic tree of bacteria.

The phylogenetic classification is not the only way to classify bacteria, however, and for the purpose of understanding medically important bacteria, and identifying them in the laboratory, a simpler pragmatic approach is more helpful, arranging bacteria according to their shape, how they appear on Gram stain, where and how they live in humans, presence/absence of a cell wall, whether they can grow independently, whether they form spores, and so on (Table A1.1).

Table A1.1 Medically important bacteria

<table>
<thead>
<tr>
<th>Gram stain</th>
<th>Shape and characteristics</th>
<th>Major genera (groups of species)</th>
<th>Example species</th>
<th>Usual habitat and example disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram positive</td>
<td>Cocci in clusters</td>
<td>Staphylococci</td>
<td><em>Aureus</em></td>
<td>Skin, nares—skin &amp; soft tissue infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>Epidermis</em></td>
<td>Skin—infections of IV devices</td>
</tr>
<tr>
<td></td>
<td>Streptococci</td>
<td></td>
<td><em>Pyogenes</em></td>
<td>URT—pharyngitis, septicaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>Agalactiae</em></td>
<td>Gut—neonatal sepsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>Pneumoniae</em></td>
<td>Pneumonia, meningitis</td>
</tr>
<tr>
<td></td>
<td>Cocci in chains</td>
<td></td>
<td><em>S. sanguinis</em></td>
<td>Mouth, dental colonies, endocarditis</td>
</tr>
<tr>
<td></td>
<td>Enterococci</td>
<td></td>
<td><em>E. faecalis</em></td>
<td>Gut—can cause UTIs, or part of mixed flora in intra-abdominal sepsis</td>
</tr>
<tr>
<td>Gram positive</td>
<td>Clostridia (anaerobic)</td>
<td></td>
<td><em>C. perfringens</em></td>
<td>Soil—food poisoning, gas gangrene</td>
</tr>
<tr>
<td></td>
<td>Spore-forming rods</td>
<td></td>
<td><em>C. difficile</em></td>
<td>Gut/soil—antibiotic-associated diarrhoea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>C. tetani</em></td>
<td>Soil—tetanus</td>
</tr>
<tr>
<td></td>
<td>Bacillus (aerobic)</td>
<td></td>
<td><em>C. botulinum</em></td>
<td>Soil—paralytic food poisoning</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>B. anthracis</em></td>
<td>Soil/animal products—anthrax</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>B. cereus</em></td>
<td>Soil—food poisoning</td>
</tr>
</tbody>
</table>

(continued)
## Table A1.1 (continued) Medically important bacteria

<table>
<thead>
<tr>
<th>Gram stain</th>
<th>Shape and characteristics</th>
<th>Major genera (groups of species)</th>
<th>Example species</th>
<th>Usual habitat and example disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-spore forming rods</td>
<td>Listeria</td>
<td><em>L. monocytogenes</em></td>
<td>Soil/food—food poisoning, miscarriage</td>
<td></td>
</tr>
<tr>
<td>Corynebacteria (branching, anaerobic)</td>
<td><em>C. diphtheriae</em></td>
<td>URT—diphtheria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propionibacterium</td>
<td><em>A. israelii</em></td>
<td>Soil—actinomycosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>P. acnes</em></td>
<td>Skin—acne</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram negative</td>
<td>Cocci</td>
<td><em>Neisseria</em></td>
<td><em>N. meningitidis</em></td>
<td>Respiratory mucosa—meningitis and septicaemia</td>
</tr>
<tr>
<td>Moraxella</td>
<td><em>M. lacunata</em></td>
<td>Genital mucosa—gonorrhoea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae (‘Coliforms’)</td>
<td><em>Escherichia coli</em></td>
<td>Gut—UTI, intra-abdominal sepsis, bacteraemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td><em>Enterobacter cloacae</em></td>
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<tr>
<td><em>Proteus vulgaris</em></td>
<td><em>Shigella dysenteriae</em></td>
<td>Dysentery</td>
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<tr>
<td><em>Salmonella typhi</em></td>
<td>Gut—typhoid fever</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><em>Salmonella enteritidis</em></td>
<td>Animal gut—food poisoning</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><em>Yersinia pestis</em></td>
<td>Rats (spread by fleas)—plague</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gardnerella</td>
<td><em>G. vaginalis</em></td>
<td>Genital tract</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas</td>
<td><em>P. aeruginosa</em></td>
<td>Moist/wet environments—acute otitis externa, opportunistic infections such as UTI, hospital pneumonia, wound infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Campylobacter (curved rod)</td>
<td><em>C. jejuni</em></td>
<td>Farm animals (all types)—food poisoning</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>H. pylori</em></td>
<td>Human gut</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilus</td>
<td><em>H. influenzae</em></td>
<td>URT—respiratory tract infection, bacteraemia, meningitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brucella</td>
<td><em>B. abortus</em></td>
<td>Cattle—brucellosis</td>
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<td></td>
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<tr>
<td>Legionella</td>
<td><em>L. pneumophila</em></td>
<td>Freshwater—Legionnaires’ disease</td>
<td></td>
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<tr>
<td>Bordella</td>
<td><em>B. pertussis</em></td>
<td>Respiratory—whooping cough</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteroides</td>
<td><em>B. fragilis</em></td>
<td>Gut—intra-abdominal sepsis (part of mixed flora); abscesses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaerobic rods</td>
<td>Fusobacteria</td>
<td><em>F. necrophorum</em></td>
<td>URT—head and neck abscesses, necrobacillosis</td>
<td></td>
</tr>
<tr>
<td>Gram stain characteristics</td>
<td>Major genera (groups of species)</td>
<td>Example species</td>
<td>Usual habitat and example disease</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
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<tr>
<td>Acid-fast rods (seen on ZN or auramine stain)</td>
<td>Mycobacteria</td>
<td><em>M. tuberculosis</em></td>
<td>Human respiratory tract/lymph nodes—tuberculosis</td>
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<tr>
<td></td>
<td></td>
<td><em>M. kansasii</em></td>
<td>Freshwater—opportunistic skin and lung infections</td>
<td></td>
</tr>
<tr>
<td>Spirochetes</td>
<td></td>
<td><em>Treponema pallidum</em></td>
<td>No environmental reservoir—survives by infecting humans—syphilis, yaws, pinta</td>
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</tr>
<tr>
<td></td>
<td></td>
<td><em>Borreliia burgdorferi</em></td>
<td>Wild mammals and <em>Ixodes</em> ticks—Lyme disease</td>
<td></td>
</tr>
<tr>
<td>Lacking cell wall</td>
<td>Mycoplasma</td>
<td><em>M. genitalium</em></td>
<td>Genital mucosa—STI (urethritis/cervicitis)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. pneumoniae</em></td>
<td>URT—pneumonia</td>
<td></td>
</tr>
<tr>
<td>Bartonella</td>
<td></td>
<td><em>B. henselae</em></td>
<td>Cats—cat scratch disease</td>
<td></td>
</tr>
<tr>
<td>Obligate intracellular bacteria (cannot grow on agar)</td>
<td>Chlamydia</td>
<td><em>C. trachomatis</em></td>
<td>Genital mucosa—STI (urethritis/cervicitis); lymphogranuloma venereum; trachoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>C. psittaci</em></td>
<td>Birds—pneumonia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>C. pneumoniae</em></td>
<td>URT—pneumonia</td>
<td></td>
</tr>
<tr>
<td>Rickettsia</td>
<td></td>
<td><em>R. prowaseckii</em></td>
<td>Spread by human body louse—typhus</td>
<td></td>
</tr>
</tbody>
</table>
Introduction to virus classification

Viruses differ from other infectious organisms in almost every way. They are acellular, do not carry out any of their own metabolic activities, and cannot reproduce independently. They are much smaller than bacteria and cannot be visualized using conventional light microscopy.

In the extracellular state the virus particle is known as a virion. In simple terms a virion is composed of a protein coat (capsid) surrounding nucleic acid (core). Together the capsid and the core are known as the nucleocapsid. The capsid is made up of individual protein subunits known as capsomeres. The capsid acts as a protective coat for the nucleic acid and also a means by which the virus can attach to a host cell when initiating an infection. The different arrangement of the capsomeres means that viruses can take up three basic shapes; helical, polyhedral, or complex. Helical viruses are tubular structures whereas polyhedral viruses, such as those that form icosahedrons, are roughly spherical. Complex viruses are those such as poxvirus, which may show features of both. The nucleic acid within the virus can be either RNA or DNA but never both, and this genome can exist in a variety of forms: single stranded, double stranded, circular, linear, or segmented. RNA may be in a positive or negative sense. Because they are not cellular, viruses do not have their own membranes, but some viruses acquire the host cell's membrane when released from an infected cell. This is termed the envelope. Proteins known as matrix proteins may fill the space between the envelope and the nucleocapsid in these viruses.

Viruses are dependent on the host cell's organelles and enzymes to reproduce new virions. There are five stages in viral replication: attachment, entry, synthesis, assembly, and release. The exact mechanism varies depending on the virion structure and type of nucleic acid.

Every living organism, whether animal, plant, fungus, or bacteria, can be infected with viruses. Thus there are millions of virus types in existence and hundreds, possibly thousands, that can infect human cells. In order to make accurate diagnoses, prevent infections and develop treatments, the type of virus needs to be recognized and the key to this is to have an effective mechanism for classification of viruses. The International Committee of Taxonomy of Viruses (ICTV) was established to oversee this process and regularly publishes reports with up-to-date taxonomy—the most up-to-date taxonomy available online being from July 2013 describing 2827 different species—thus the majority of viruses in nature are yet to be formally classified.

Viruses are classified by their type of nucleic acid, presence or absence of an envelope and their shape and size. There are similarities to the process applied to living organisms but also some major differences. Virus nomenclature is recognized as an exception in the International Code of Bionomenclature in that kingdoms and phyla are not (yet) included. The primary classification is of viruses into species. Species are then grouped into genera and genera classified into families. An example of a fully assigned virus species is as follows; species Mumps virus; genus Rubulavirus; subfamily Paramyxovirinae; family Paramyxoviridae; order Mononegavirales. The alternative Baltimore classification scheme also groups viruses into families based on their genomic properties as well as the methods of replication.

The ICTV classification, although scientifically useful, is not always medically useful. Some viruses, especially those causing common human infections, may be known more familiarly by
other names. In the medical literature it is more common to see human herpesvirus 1 called herpes simplex virus 1 or HSV-1, or human herpesvirus 5 described as cytomegalovirus or human cytomegalovirus. Furthermore, within species there may be many different subtypes, serotypes, or genotypes that are not classified separately in formal taxonomy but may have important medical differences. A good example is the species Enterovirus C. The virus that causes polio is this species and three serogroups are recognized. Immunity against all three serogroups is needed to prevent polio.

Medically it is often more useful to think about viruses in terms of their nucleic acid content (DNA or RNA) and whether they are enveloped or not. The former is helpful when thinking about possible antiviral treatments and the latter has implications for infection prevention and control. For example, RNA viruses, such as hepatitis C, tend to mutate more readily. Enveloped viruses are easily deactivated following exposure to alcohol, whereas non-enveloped viruses, such as norovirus, are not. This is the reason why alcohol-based hand rubs may not be good for decontamination of health care workers’ hands after exposure to viral gastroenteritis.

Segmented viral RNA seen in influenza A (as opposed to non-segmented) can lead more easily to genetic re-assortment. However, whether the nucleic acid is ds or ss or the RNA +ve or –ve, has no impact on pathology or medical considerations.

Table A2.1 and Table A2.2 provide the details of the families of the main viruses known to infect humans, classified according to nucleic acid, presence/absence of an envelope and nucleocapsid structure. The family, subfamily and genus are shown using the ICTV nomenclature. The ICTV species name of example viruses is shown with common medical naming shown in parentheses if different. Examples of infection types are also listed.
Table A2.1 DNA viruses

<table>
<thead>
<tr>
<th>Family</th>
<th>Nucleic acid arrangement</th>
<th>Envelope and nucleocapsid structure</th>
<th>Subfamilies</th>
<th>Genus</th>
<th>Examples of virus species and infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poxviridae</td>
<td>Double stranded linear</td>
<td>Enveloped complex structure</td>
<td>Chordopoxvirinae</td>
<td>Orthopoxvirus</td>
<td>Variola virus (smallpox)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Parapoxvirus</td>
<td>Orf virus (orf)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Molluscipoxvirus</td>
<td>Molluscum contagiosum virus</td>
</tr>
<tr>
<td>Herpesviridae</td>
<td>Double stranded linear</td>
<td>Enveloped icosahedral</td>
<td>Alphaherpesvirinae</td>
<td>Simplexvirus</td>
<td>Human herpesvirus 1, Human herpesvirus 2 (Herpes simplex 1 and 2—cold sores, genital ulcers, encephalitis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Varicellovirus</td>
<td>Human herpesvirus 3 (varicella zoster virus—chickenpox and shingles)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Betaherpesvirinae</td>
<td>Cytomegalovirus</td>
<td>Human herpesvirus 5 (human cytomegalovirus, mononucleosis type illness, congenital infection)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Roseolovirus</td>
<td>Human herpesvirus 6a and 6b (roseola)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gammaherpesvirinae</td>
<td>Lymphocryptovirus</td>
<td>Human herpesvirus 4 (Epstein–Barr virus—glandular fever)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rhadinovirus</td>
<td>Human herpesvirus 8 (Kaposi’s sarcoma)</td>
</tr>
<tr>
<td>Papillomavira</td>
<td>Double stranded circular</td>
<td>Non-enveloped icosahedral</td>
<td>Alphapapillomavirus, betapapillomavirus, gammapapillomavirus, mupapillomavirus</td>
<td>Alphapapillomavirus, betapapillomavirus, gammapapillomavirus, mupapillomavirus</td>
<td>Perhaps several hundred papillomaviruses belonging to 5 genera. Cause of warts and some cancers</td>
</tr>
<tr>
<td>Adenoviridae</td>
<td>Double stranded linear</td>
<td>Non-enveloped icosahedral</td>
<td>Mastadenovirus</td>
<td>Mastadenoviruses A to G (human adenovirus—over 50 types causing respiratory infection, gastroenteritis and conjunctivitis)</td>
<td></td>
</tr>
<tr>
<td>Hepadnaviridae</td>
<td>Partial single and double stranded</td>
<td>Enveloped icosahedral</td>
<td>Orthohepadnavirus</td>
<td>Orthohepadnavirus</td>
<td>Hepatitis B virus (hepatitis)</td>
</tr>
<tr>
<td>Paroviridae</td>
<td>Single stranded linear</td>
<td>Non-enveloped icosahedral</td>
<td>Parovirinae</td>
<td>Erythroparvovirus</td>
<td>Primate erythroparvovirus 1 (Parovirus B19—slapped cheek syndrome or 5th disease or erythema infectiosum)</td>
</tr>
<tr>
<td>Family</td>
<td>Nucleic acid arrangement</td>
<td>Envelope and nucleocapsid structure</td>
<td>Subfamilies</td>
<td>Genus</td>
<td>Examples of virus species and infections</td>
</tr>
<tr>
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<td>-----------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Picornaviridae</strong></td>
<td>Single stranded linear positive sense</td>
<td>Non-enveloped icosahedral</td>
<td></td>
<td>Enterovirus</td>
<td><em>Enterovirus</em> A to J (over 70 enteroviruses that infect humans including polio and coxsackie viruses—cause of poliomyelitis, meningitis, upper respiratory tract infections), <em>rhinovirus</em> A to C—upper respiratory tract infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><em>Hepatovirus</em> <em>Hepatitis A virus</em> (hepatitis A)</td>
</tr>
<tr>
<td><strong>Caliciviridae</strong></td>
<td>Single stranded linear positive sense</td>
<td>Non-enveloped icosahedral</td>
<td></td>
<td>Norovirus</td>
<td><em>Norovirus</em> <em>Norwalk virus</em> (gastroenteritis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><em>Sapovirus</em> <em>Sapporo virus</em> (gastroenteritis)</td>
</tr>
<tr>
<td><strong>Astroviridae</strong></td>
<td>Single stranded linear positive sense</td>
<td>Non-enveloped icosahedral</td>
<td></td>
<td>Mamastrovirus</td>
<td><em>Mamastrovirus</em> 1 (human astroviruses 1 to 8, gastroenteritis)</td>
</tr>
<tr>
<td><strong>Hepeviridae</strong></td>
<td>Single stranded linear positive sense</td>
<td>Non-enveloped icosahedral</td>
<td></td>
<td>Hepevirus</td>
<td><em>Hepatitis E virus</em> (hepatitis E)</td>
</tr>
<tr>
<td><strong>Togaviridae</strong></td>
<td>Single stranded linear positive sense</td>
<td>Enveloped icosahedral</td>
<td></td>
<td>Alphavirus</td>
<td>Numerous arthropod borne viruses including <em>Chikungunya virus</em> and <em>Ross River virus</em> (fever and arthralgia) and <em>Eastern, Western and Venuzuelan equine encephalitis virus</em>—can cause encephalitis in humans</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><em>Rubivirus</em> <em>Rubella virus</em> (rubella)</td>
</tr>
<tr>
<td><strong>Flaviviridae</strong></td>
<td>Single stranded linear positive sense</td>
<td>Enveloped icosahedral</td>
<td></td>
<td>Flavivirus</td>
<td>Numerous arthropod borne viruses such as <em>dengue virus</em>, <em>yellow fever virus</em>, <em>Japanese encephalitis virus</em> and <em>West Nile virus</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><em>Hepacivirus</em> <em>Hepatitis C virus</em></td>
</tr>
<tr>
<td><strong>Coronaviridae</strong></td>
<td>Single stranded linear positive sense</td>
<td>Enveloped helical icosahedral</td>
<td>Coronavirinae</td>
<td>Alphacoronavirus</td>
<td><em>Human coronavirus 229E</em> (upper respiratory tract infection)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Betacoronavirus</td>
<td><em>Human coronavirus OC43</em> (upper respiratory tract infection), <em>severe acute respiratory syndrome-related coronavirus</em> (SARS), <em>Middle East respiratory syndrome coronavirus</em> (MERS)</td>
</tr>
</tbody>
</table>

(continued)
### Table A2.2 (continued) RNA viruses

<table>
<thead>
<tr>
<th>Family</th>
<th>Nucleic acid arrangement</th>
<th>Envelope and nucleocapsid structure</th>
<th>Subfamilies</th>
<th>Genus</th>
<th>Examples of virus species and infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retroviridae</td>
<td>Single stranded linear positive sense, 2 segments</td>
<td>Enveloped icosahedral</td>
<td>Orthoretrovirinae</td>
<td>Lentivirus</td>
<td>Human immunodeficiency virus 1, human immunodeficiency virus 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Deltaretrovirus Primate T-lymphotropic virus (HTLV1 and HTLV2—adult T-cell leukaemia)</td>
</tr>
<tr>
<td>Orthomyxoviridae</td>
<td>Single stranded linear negative sense, segmented</td>
<td>Enveloped helical</td>
<td>Influenzavirus A</td>
<td></td>
<td>Influenza A virus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Influenzavirus B</td>
<td></td>
<td>Influenza B virus</td>
</tr>
<tr>
<td>Paramyxoviridae</td>
<td>Single stranded linear negative sense</td>
<td>Enveloped helical</td>
<td>Paromyxovirinae</td>
<td>Morbillivirus</td>
<td>Measles virus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Respirovirus Human parainfluenza virus 1 and 3 (respiratory tract infections)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rubulavirus Human parainfluenza virus 2, 4 and 5 (respiratory tract infections), mumps virus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pneumovirinae</td>
<td>Metapneumovirus</td>
<td>Human metapneumovirus (respiratory infection)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pneumovirinae</td>
<td>Pneumovirus</td>
<td>Human respiratory syncytial virus (respiratory infection)</td>
</tr>
<tr>
<td>Rhabdoviridae</td>
<td>Single stranded linear negative sense</td>
<td>Enveloped helical</td>
<td>Orthorhabdovirinae</td>
<td>Lyssavirus</td>
<td>Rabies virus, European bat lyssavirus (cause of rabies-like illness in humans)</td>
</tr>
<tr>
<td>Filoviridae</td>
<td>Single stranded linear negative sense</td>
<td>Enveloped helical</td>
<td>Orthofilovirinae</td>
<td>Ebola virus</td>
<td>Bundibugyo, Reston, Sudan, Tai Forest and Zaire ebolavirus (Ebola haemorrhagic fever)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Marburgvirus Marburg marburgvirus (haemorrhagic fever)</td>
</tr>
<tr>
<td>Arenaviridae</td>
<td>Single stranded circular negative sense, segmented</td>
<td>Enveloped helical</td>
<td>Orthoarenavirinae</td>
<td>Arenavirus</td>
<td>Lassa fever virus (haemorrhagic fever)</td>
</tr>
<tr>
<td>Reoviridae</td>
<td>Double stranded linear segmented</td>
<td>Non-enveloped icosahedral</td>
<td>Orthoreovirinae</td>
<td>Rotavirus</td>
<td>Rotavirus A to E (gastrointestinal infection)</td>
</tr>
</tbody>
</table>
Appendix 3

Notification of infectious diseases

Infectious disease notification

The statutory notification of diagnoses of patients with infectious diseases is a crucial measure to help protect the health of others. The main purpose of notification is to ensure that there is a timely response by the appropriate authorities, so that interventions can be put in place to prevent others from being infected. Investigations may reveal the source of infection as well as identifying others that may have either been exposed to that source or have had contact with a patient with an infectious disease. A further benefit of the notification process is that useful epidemiological data may be obtained, and such data are useful for planning wider public health measures such as immunization. The exact processes of notification of infectious diseases will vary from country to country.

In England, notification has been a statutory requirement for Registered Medical Practitioners since the late nineteenth century and was updated most recently as the Health Protection (Notification) Regulations 2010. The regulations state that:

A registered medical practitioner (R) must notify the proper officer of the relevant local authority where R has reasonable grounds for suspecting that a patient (P) whom R is attending
(a) has a notifiable disease;
(b) has an infection which, in the view of R, presents or could present significant harm to human health; or
(c) is contaminated in a manner which, in the view of R, presents or could present significant harm to human health.

Notifiable diseases are listed in schedule 1 of the regulations and are shown in Box A3.1. It is very important to note that notification MUST be made on clinical suspicion and it is NOT necessary to wait for laboratory confirmation. The Proper Officer is appointed by a local authority and is normally a Consultant Public Health Medicine specialist who has been trained in health protection and is often known as a Consultant in Communicable Disease Control (CCDC). These consultants work as part of a Health Protection Team that covers a defined geographical area. Currently there are 26 of these teams in England and they are a constituent part of Public Health England (formerly the Health Protection Agency). Notification can be made by returning a form or by telephone, secure fax or encrypted email. Guidance has been published indicating the urgency applicable to these infections.

An addition to the 2010 regulations is the requirement for laboratories to ALSO notify when a specified causative agent is detected in a clinical specimen from a patient. The list of agents is in schedule 2 of the regulations and is shown in Box A3.2. It contains some additional organisms to those that cause the infections in schedule 1. Thus it is possible that a patient may be notified either once or twice depending on the circumstances. The laboratory notification is also made to Public Health England. Usually this is done automatically by an electronic report directly from the lab to Public Health England, though in urgent cases a result will be telephoned. A laboratory may be fined for failing to comply with the regulations.
### Box A3.1. Infections that should be notified by the Registered Medical Practitioner (Schedule 1 of the Health Protection (Notification) Regulations 2010)

<table>
<thead>
<tr>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute encephalitis</td>
</tr>
<tr>
<td>Acute meningitis</td>
</tr>
<tr>
<td>Acute poliomyelitis</td>
</tr>
<tr>
<td>Acute infectious hepatitis</td>
</tr>
<tr>
<td>Anthrax</td>
</tr>
<tr>
<td>Botulism</td>
</tr>
<tr>
<td>Brucellosis</td>
</tr>
<tr>
<td>Cholera</td>
</tr>
<tr>
<td>Diphtheria</td>
</tr>
<tr>
<td>Enteric fever (typhoid or paratyphoid fever)</td>
</tr>
<tr>
<td>Food poisoning</td>
</tr>
<tr>
<td>Haemolytic uraemic syndrome (HUS)</td>
</tr>
<tr>
<td>Infectious bloody diarrhoea</td>
</tr>
<tr>
<td>Invasive group A streptococcal disease and scarlet fever</td>
</tr>
<tr>
<td>Legionnaires’ disease</td>
</tr>
<tr>
<td>Leprosy</td>
</tr>
<tr>
<td>Malaria</td>
</tr>
<tr>
<td>Measles</td>
</tr>
<tr>
<td>Meningococcal septicaemia</td>
</tr>
<tr>
<td>Mumps</td>
</tr>
<tr>
<td>Plague</td>
</tr>
<tr>
<td>Rabies</td>
</tr>
<tr>
<td>Rubella</td>
</tr>
<tr>
<td>SARS</td>
</tr>
<tr>
<td>Smallpox</td>
</tr>
<tr>
<td>Tetanus</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Typhus</td>
</tr>
<tr>
<td>Viral haemorrhagic fever (VHF)</td>
</tr>
<tr>
<td>Whooping cough</td>
</tr>
<tr>
<td>Yellow fever</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Causative agents that should be notified by Diagnostic Laboratories (Schedule 2 of the Health Protection (Notification) Regulations 2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacillus anthracis</td>
</tr>
<tr>
<td>Bacillus cereus (only if associated with food poisoning)</td>
</tr>
<tr>
<td>Bordetella pertussis</td>
</tr>
<tr>
<td>Borrelia spp</td>
</tr>
<tr>
<td>Brucella spp</td>
</tr>
<tr>
<td>Burkholderia mallei</td>
</tr>
<tr>
<td>Burkholderia pseudomallei</td>
</tr>
<tr>
<td>Campylobacter spp</td>
</tr>
<tr>
<td>Chikungunya virus</td>
</tr>
<tr>
<td>Chlamydophila psittaci</td>
</tr>
<tr>
<td>Clostridium botulinum</td>
</tr>
<tr>
<td>Clostridium perfringens (only if associated with food poisoning)</td>
</tr>
<tr>
<td>Clostridium tetani</td>
</tr>
<tr>
<td>Corynebacterium diphtheriae</td>
</tr>
<tr>
<td>Corynebacterium ulcerans</td>
</tr>
<tr>
<td>Coxiella burnetii</td>
</tr>
<tr>
<td>Crimean-Congo haemorrhagic fever virus</td>
</tr>
<tr>
<td>Cryptosporidium spp</td>
</tr>
<tr>
<td>Dengue virus</td>
</tr>
<tr>
<td>Ebola virus</td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
</tr>
<tr>
<td>Francisella tularensis</td>
</tr>
<tr>
<td>Giardia lamblia</td>
</tr>
<tr>
<td>Guanarito virus</td>
</tr>
<tr>
<td>Haemophilus influenzae (invasive)</td>
</tr>
<tr>
<td>Hanta virus</td>
</tr>
<tr>
<td>Hepatitis A, B, C, delta, and E viruses</td>
</tr>
<tr>
<td>Influenza virus</td>
</tr>
<tr>
<td>Junin virus</td>
</tr>
<tr>
<td>Kyasanur Forest disease virus</td>
</tr>
<tr>
<td>Lassa virus</td>
</tr>
<tr>
<td>Legionella spp</td>
</tr>
<tr>
<td>Leptospira interrogans</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
</tr>
<tr>
<td>Machupo virus</td>
</tr>
<tr>
<td>Marburg virus</td>
</tr>
<tr>
<td>Measles virus</td>
</tr>
<tr>
<td>Mumps virus</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis complex</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
</tr>
<tr>
<td>Omsk haemorrhagic fever virus</td>
</tr>
<tr>
<td>Plasmodium falciparum, vivax, ovale, malariae, knowlesi</td>
</tr>
</tbody>
</table>

(continued)
Box A3.2. Causative agents that should be notified by Diagnostic Laboratories (Schedule 2 of the Health Protection (Notification) Regulations 2010) (continued)

Polio virus (wild or vaccine types)
Rabies virus (classical rabies and rabies-related lyssaviruses)
*Rickettsia spp*
Rift Valley fever virus
Rubella virus
Sabia virus
*Salmonella spp*
SARS coronavirus
*Shigella spp*
*Streptococcus pneumoniae* (invasive)
*Streptococcus pyogenes* (invasive)
Varicella zoster virus
Variola virus
Verocytotoxigenic *Escherichia coli* (including *E.coli* O157)
*Vibrio cholerae*
West Nile virus
Yellow fever virus
*Yersinia pestis*

# Immunization table

## Immunization schedules

The immunization schedule for children and adults in the UK is continually amended as new immunizations are introduced (most recently Rotarix and, under consideration, a group B meningococcal vaccine) so it is important to check the most recent schedules. Immunizations also vary between generations (for example adults over the age of 29 will not have had the MMR) and between countries (see further reading website).

This immunization table (see Table A4.1) is laid out so that schedules for particular vaccines are clearly visible as well as displaying the schedules per age group.

**Table A4.1 Immunization schedules for common vaccines**

<table>
<thead>
<tr>
<th></th>
<th>BCG</th>
<th>DTaP</th>
<th>IPV</th>
<th>Hib</th>
<th>PCV</th>
<th>Rotarix</th>
<th>Men C</th>
<th>MMR</th>
<th>Nasal flu spray</th>
<th>HPV 16,18</th>
<th>flu</th>
<th>Adenovirus</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 m</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
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**NB:** age 4 years equivalent to preschool and 18 years equivalent to school leavers
Further reading

http://ecdc.europa.eu/en/Pages/home.aspx. This website is the European Centre for Disease Prevention and Control and shows the vaccine schedule and history of the vaccine schedule for every European country.
Appendix 5

Incubation and infectivity of important childhood diseases

Childhood disease incubation and infectivity

Table A5.1 is simply to highlight the incubation and infectivity of the most important childhood illnesses and the most frequently asked about. The table could have been extended to include every infection discussed in the text however the incubation and infectivity of each infection has been discussed in the relevant case.

Table A5.1 Incubation and infectivity periods of important childhood diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incubation</th>
<th>Infectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scarlet fever</td>
<td>2-4 days</td>
<td>Until symptoms settled or after 1 day of antibiotic</td>
</tr>
<tr>
<td>Whooping cough</td>
<td>5-21 days</td>
<td>Until 21 days after symptoms started or after 5 days of antibiotics</td>
</tr>
<tr>
<td>Measles</td>
<td>2-18 days</td>
<td>4 days before the rash until 4 days after</td>
</tr>
<tr>
<td>Mumps</td>
<td>14-25 days</td>
<td>6 days before the parotid swelling until 5 days after</td>
</tr>
<tr>
<td>Rubella</td>
<td>14-21 days</td>
<td>7 days before the rash until 4 days after</td>
</tr>
<tr>
<td>Chickenpox</td>
<td>10-21 days</td>
<td>2 days before the spots until 5 days after the last crop, or until the last crop has crusted over</td>
</tr>
<tr>
<td>Slapped cheek disease</td>
<td>4-14 days</td>
<td>5 days before the facial rash, infectivity reduces markedly once the rash has appeared</td>
</tr>
<tr>
<td>Roseola infantum</td>
<td>5-10 days</td>
<td>Infectivity continues for several months after the infection has resolved</td>
</tr>
<tr>
<td>Hand, foot, and mouth disease</td>
<td>3-7 days</td>
<td>Infectivity continues for several weeks after the infection has resolved</td>
</tr>
<tr>
<td>Influenza</td>
<td>2-4 days</td>
<td>1 day before symptoms start to 7 days after (longer in children)</td>
</tr>
<tr>
<td>Viral gastroenteritis</td>
<td>1-2 days</td>
<td>Infectivity continues until 48 hours after the last diarrhoea or vomit</td>
</tr>
</tbody>
</table>

Further reading

Appendix 6

Commonly used antibiotics
### Table A6.1 Commonly Used Antibiotics: mechanisms of action, spectrum of activity, resistance mechanisms, toxicity and clinical uses

<table>
<thead>
<tr>
<th>Target/mode of action</th>
<th>Group</th>
<th>Toxicity and adverse effects</th>
<th>Examples</th>
<th>Spectrum</th>
<th>Resistance issues</th>
<th>Clinical uses and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell wall—peptidoglycan</td>
<td>Penicillins</td>
<td>Rashes, allergy. Occasional GI upset, C. difficile diarrhoea. Generally penicillins are safe and well tolerated</td>
<td>Penicillin</td>
<td>Streps, oral anaerobes, many neisserias</td>
<td>Beta-lactamases, altered peptidoglycan</td>
<td>Pharyngitis, URTI, Streptococcal cellulitis, endocarditis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amoxicillin</td>
<td>As penicillin plus enterococci, some coliforms; Haemophilus</td>
<td></td>
<td>URTI, LRTI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Flucloxacillin</td>
<td>Streps, staphs</td>
<td>Stable to penicillinase. Resistance due to altered peptidoglycan (MRSA)</td>
<td>Staph aureus infections of any type. Empirical treatment of skin infections, wound infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Co-amoxiclav (Amox + clavulanic acid)</td>
<td>Streps, staphs, many coliforms, anaerobes</td>
<td>Not broken down by beta-lactamases</td>
<td>URTI, LRTI, UTI, intra-abdominal sepsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Piperacillin + tazobactam</td>
<td>As co-amoxiclav plus Pseudomonas</td>
<td></td>
<td>Serious hospital infections—chest, abdominal or wound</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td></td>
<td>Rashes, allergy. Occasional GI upset, C. difficile diarrhoea Generally cephalosporins are safe and well tolerated</td>
<td>Cefalexin</td>
<td>Staphs and streps, some coliforms, Haemophilus</td>
<td>Some beta-lactamases can degrade cephalosporins Also, Gram-negatives can develop porin mutations that reduce antibiotic entry into the cell</td>
<td>Minor skin/soft tissue infection. URTI, URTI, LRTI (similar uses to co-amoxiclav)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cefuroxime</td>
<td>Staphs, streps, most coliforms, Haemophilus</td>
<td></td>
<td>Often used in combination with metronidazole to treat/prophylax intra-abdominal surgical infections. Also used for other hospital infections—e.g. pneumonia</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Target/mode of action</th>
<th>Group</th>
<th>Toxicity and adverse effects</th>
<th>Examples</th>
<th>Spectrum</th>
<th>Resistance issues</th>
<th>Clinical uses and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cefotaxime and ceftriaxone</td>
<td>As cefuroxime—broader coliform coverage</td>
<td>Two antibiotics are very similar</td>
<td>Agents of choice for bacterial meningitis</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Ceftazidime</td>
<td>As cefuroxime, plus Pseudomonas</td>
<td>Emerging resistance due to carbapenemases</td>
<td>Serious Gram-negative infections</td>
</tr>
<tr>
<td>Carbapenems</td>
<td></td>
<td>Neurotoxicity at very high dosage</td>
<td>Ertapenem</td>
<td>Streps, staphs, many coliforms, anaerobes</td>
<td></td>
<td>Used to treat serious Gram-negative infections, esp. with resistant organisms</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Meropenem</td>
<td>As ertapenem, plus Pseudomonas</td>
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<tr>
<td>Glycopeptides</td>
<td></td>
<td>Renal and ear toxicity with high levels. Drug levels need monitoring</td>
<td>Vancomycin</td>
<td>All Gram-positives (inc. staphs, streps, enterococci, clostridia)</td>
<td>Some enterococci develop resistance—altered cell wall precursors</td>
<td>Serious staph/strep/enterococcal infections. An option when patient is allergic to penicillins, or organism is resistant Oral vanc also used for C. difficile treatment</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Teicoplanin</td>
<td>Gram-positive bacteria including multi-resistant staphylococci</td>
<td>Reports of S. avers with reduced susceptibility</td>
<td>Similar to vancomycin, but has a longer duration of action allowing a once-daily dose</td>
</tr>
<tr>
<td>Target/mode of action</td>
<td>Group</td>
<td>Toxicity and adverse effects</td>
<td>Examples</td>
<td>Spectrum</td>
<td>Resistance issues</td>
<td>Clinical uses and comments</td>
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<tr>
<td>Ribosomes—protein</td>
<td>Aminoglycosides</td>
<td>Very toxic to kidneys, ears. Careful drug level monitoring needed.</td>
<td>Gentamicin</td>
<td>(Nearly) all Gram-negatives, inc Pseudomonas</td>
<td>Resistance can develop to all the antibiotics that act on ribosomes, by three main mechanisms: Antibiotic modifying enzymes, mutated ribosome target, antibiotic export mechanisms</td>
<td>Serious Gram-negative infections. Only available IV</td>
</tr>
<tr>
<td></td>
<td>Macrolides</td>
<td>Rashes. Phlebitis at injection site. GI upset</td>
<td>Erythromycin</td>
<td>Staphs, streps, some anaerobes; Chlamydia, Mycoplasma</td>
<td></td>
<td>LRTI. An alternative to penicillins in allergic patients</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Clarithromycin</td>
<td></td>
<td></td>
<td>LRTI</td>
</tr>
<tr>
<td></td>
<td>Lincosamides</td>
<td>Rashes. Danger of C. difficile diarrhoea (probably no greater than the risk with other antibiotics)</td>
<td>Clindamycin</td>
<td>Staphs, streps, anaerobes</td>
<td></td>
<td>An alternative for cellulitis and skin/soft tissue infections</td>
</tr>
<tr>
<td></td>
<td>Tetracyclines</td>
<td>Foetal toxicity affects tooth development</td>
<td>Doxycycline</td>
<td>Staphs (inc MRSA), streps, many coliforms, Haemophilus, Chlamydia, Mycoplasma</td>
<td></td>
<td>URTI and LRTI</td>
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<tr>
<td></td>
<td>Chloramphenicol</td>
<td>Rare but serious bone marrow toxicity—aplastic anaemia</td>
<td>Chloramphenicol</td>
<td>Staphs, streps, many coliforms (not Pseudomonas)</td>
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<td>Staph infections—esp MRSA</td>
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<td>Generally only used topically for eye infections</td>
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<thead>
<tr>
<th>Target/mode of action</th>
<th>Group</th>
<th>Toxicity and adverse effects</th>
<th>Examples</th>
<th>Spectrum</th>
<th>Resistance issues</th>
<th>Clinical uses and comments</th>
</tr>
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<tbody>
<tr>
<td>DNA or its precursors</td>
<td>Quinolones</td>
<td>Safe, well tolerated. Risk of <em>C. difficile</em> diarrhoea</td>
<td>Ciprofloxacin</td>
<td>Staphs, streps, coliforms, <em>Pseudomonas</em>, <em>Legionella</em> and other 'atypical' resp. pathogens</td>
<td>Mutations of target (DNA gyrase) relatively common</td>
<td>UTIs, intra-abdominal infections, other Gram-negative infections</td>
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<td>Dihydrofolate reductase inhibitors</td>
<td>Safe and well tolerated Contraindicated in early pregnancy</td>
<td>Trimethoprim</td>
<td>Staphs, streps, many coliforms</td>
<td>UTI now resistant to Trimethoprim</td>
<td>UTIs (seldom used for any other infections)</td>
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<td>Rifamycins</td>
<td>Liver toxicity can develop rarely Drug interactions are common Red colouration of urine, tears is expected</td>
<td>Rifampicin</td>
<td>Staphs, streps, many Gram-negatives inc. <em>Neisseria</em>, <em>Haemophilus</em> (but not coliforms or <em>Pseudomonas</em>) Mycobacteria</td>
<td>Mutations of the target molecule (RNA polymerase) commonly develop during treatment—esp with monotherapy</td>
<td>TB and other mycobacterial infections. Sometimes used in combination treatment for other infections</td>
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<td>Nitroimidazoles</td>
<td>GI upset common. Interaction with alcohol—Antabuse effect</td>
<td>Metronidazole</td>
<td>Anaerobes (and some parasites)</td>
<td>Resistance is very rare</td>
<td>Anaerobic infections—esp as treatment or prophylaxis of intra-abdominal infections. <em>C. difficile</em> treatment</td>
</tr>
<tr>
<td>Bacterial cell membrane</td>
<td>Polymyxins</td>
<td>Renal toxicity</td>
<td>Colistin</td>
<td>Most Gram-negatives including <em>Pseudomonas</em>—but excluding <em>Serratia</em>, <em>Proteus</em></td>
<td>Resistance is rare—mechanism not well understood</td>
<td>Topical in ear infections. Nebulized in chronic lung sepsis—e.g. cystic fibrosis. IV for serious infections with resistant bacteria</td>
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