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Clinical and Diagnostic Virology

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Plates

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Preface

This book is intended for trainee doctors, healthcare scientists, infection control nurses and other healthcare workers working in infection-related specialties (virology, microbiology, infectious diseases and public health).

It will also be useful for medical students and other healthcare professionals (doctors, nurses, general practitioners etc.) working in non-infection specialties who deal with patients with suspected virus infections.

It has easily accessible information with tables, figures and algorithms to aid easy reference for the busy clinician. It is divided into two main sections. The first is an alphabetically arranged series of chapters on the most important viruses that cause symptomatic disease in humans in the developed world; we have kept a standard chapter format throughout this section to enable the reader to access important information quickly. The second is a set of clinical syndromes (e.g. hepatitis and skin rashes), where the different viruses and their clinical symptoms are presented. Other sections provide information on diagnostic techniques, antiviral drugs, viral vaccines, occupational health issues, infection control and travel-related infections. We are aware that most virologists in the UK deal with non-viral pathogens, such as Chlamydia, toxoplasma, atypical pneumonia organisms and Creutzfeldt–Jakob disease (CJD) and variant CJD (vCJD), so a section on these pathogens is also included.

The aim of the book is for it to be a quick-reference guide to differential diagnosis, giving details of which specimens and tests are best for laboratory diagnosis, which treatments to use and what the control of infection implications are. We provide a list of websites that are useful for getting up-to-the-minute accurate information on viruses and viral syndromes and their management.

We hope you enjoy this book and find it a useful source of information, whether you are a student, work in the laboratory or are a clinician who needs to brush up on virology. We hope it will help you in managing your patients better, or to learn more about viruses and their impact on human health.

Acknowledgements

Section 1 – Individual viruses

Introduction to virology

History of viruses

The existence of viruses was first suspected in the nineteenth century when it was shown that filtered extract of infective material passed through filters small enough to stop all known bacteria could still be infectious, and hence the 'virus' (Latin for poisonous liquid) concept was first introduced. However, viral diseases such as smallpox and poliomyelitis had been known to affect mankind since many centuries before this.

Subsequent to the discovery of viruses, the next major step in elucidating their role in human disease was the invention of the electron microscope, followed by cell culture and now molecular diagnostic techniques to detect the presence of viruses in infected material. Many new viruses have been discovered in the past two to three decades, but it was the discovery of human immunodeficiency virus (HIV) (the virus responsible for acquired immunodeficiency syndrome (AIDS)) in 1983 and the explosion of the AIDS epidemic that brought clinical virology to the forefront as a significant specialty. Millions of dollars have been spent by pharmaceutical companies in discovering drugs to treat AIDS; a by-product has been that our understanding of virus replication and pathogenesis has improved substantially and this has resulted in new antiviral drugs becoming available to treat other viral infections.

The availability of rapid and sensitive molecular diagnostic techniques and effective antiviral drug therapy means that patients can now be treated in real time. Almost all physicians and healthcare workers have to deal with the consequences of viral infections, and the aim of this book is to demystify virology and to provide sufficient information to enable the reader to deal with day-to-day virus-related problems.

To do that we must first understand some basic principles of virology.

Viral taxonomy

Viruses have either an RNA or DNA genome (never both) and are classified *in families* on the basis of their genome (RNA or DNA) and whether it is single or double stranded (SS or DS). Single-stranded RNA viruses are further split on the basis of whether they carry a negative (−RNA) or a positive (+RNA) strand as this affects their replication strategy (see below). As a rule of thumb *all DNA viruses except those belonging to Parvoviridae are double stranded and all RNA viruses except those belonging to Reoviridae are single stranded* (see Table 1).

Table 1. *Classification of human viruses.*

Family	Example viruses	DNA/RNA	DS/SS	Enveloped	Chapter
Poxviridae	smallpox, cowpox, monkey pox, orf, molluscum contagiosum viruses	DNA	DS	Yes	21
Herpesviridae	herpes simplex viruses types 1 and 2 (HSV), varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein–Barr virus (EBV), human herpes viruses 6, 7 and 8 (HHV 6, 7 and 8)	DNA	DS	Yes	3, 4, 10, 12
Adenoviridae	adenoviruses	DNA	DS	No	1
Papovaviridae	papilloma and polyoma viruses	DNA	DS	No	19
Hepadnaviridae	hepatitis B virus	DNA	DS	No	7
Parvoviridae	human parvovirus B19	DNA	SS	No	20
Reoviridae	rotaviruses	RNA	DS	No	25
Picornaviridae	enteroviruses, rhinoviruses, hepatitis A virus	+RNA	SS	No	5, 6, 24
Caliciviridae	hepatitis E virus, noroviruses	+RNA	SS	No	9, 17
Coronaviridae	coronaviruses	+RNA	SS	Yes	27
Flaviviridae	hepatitis C virus, yellow fever virus	+RNA	SS	Yes	8
Togaviridae	rubella virus	+RNA	SS	Yes	26
Paramyxoviridae	parainfluenza viruses, respiratory syncytial virus (RSV), measles virus, mumps virus	–RNA	SS	Yes	15, 16, 18, 23
Orthomyxoviridae	influenza A and B viruses	–RNA	SS	Yes	14
Rhabdoviridae	rabies virus	–RNA	SS	Yes	22
Filoviruses	Ebola virus	–RNA	SS	Yes	2
Bunyaviridae	hantavirus, Crimean–Congo haemorrhagic fever virus etc.	–RNA	SS	Yes	2
Arenaviridae	Lassa fever virus	–RNA	SS	Yes	2
Retroviridae	human immunodeficiency virus (HIV), human T-cell lymphotrophic virus (HTLV)	+RNA	SS	Yes	11, 13

Other features taken into consideration are their size and shape, and the presence or absence of a lipid envelope, which some viruses acquire as they bud out of cells. RNA viruses generally tend to be enveloped and have outer proteins (required for attachment to the cell surface) projecting out of this lipid envelope, e.g. haemagglutinin (HA) of influenza A virus.

The viral genome is packaged within a nucleoprotein (*capsid*) which consists of a repetition of structurally similar amino acid sub-units. The viral genome and the capsid are together referred to as nucleocapsid. The viral nucleoprotein or capsid gives the virus its shape (helical or icosahedral). Table 1 shows the classification (with examples) of human viruses.

Virus replication

Viruses are obligate intracellular pathogens and require cellular enzymes to help them replicate. Unlike bacteria, which replicate by binary fission, viruses have to 'disassemble' their structure before they can replicate. The steps of viral replication can be broadly divided into: attachment, cell entry, virus disassembly or uncoating, transcription and translation of viral genome, and viral assembly and release.

Attachment
The first step in the replication cycle is the attachment of the virus particle to the cell surface. To do this specific viruses use specific cellular receptors on the cell surface and therefore are very specific in the cell type that they can infect – this gives them the 'cell tropism' and is important in disease pathogenesis (i.e. why some viruses affect certain organs only). Influenza viruses use the haemagglutinin (HA) protein to attach to the sialic acid-containing oligosaccharides on the cell surface. Viruses may use more than one cell receptor, for example HIV uses the CD4 receptor to attach to the CD4 T-helper cells, but it also uses a chemokine receptor CCR5 as a co-receptor. It is now believed that most viruses use more than one receptor on the cell surface in a sequential binding process.

Cell entry
Viruses may enter the cell directly by endocytosis or, for enveloped viruses, by fusion of their lipid envelope with the cell membrane.

Virus disassembly or uncoating
Before the virus can replicate, the viral genome has to be exposed by removal of the associated viral proteins. This is usually mediated by the endocytosed viral particle merging with cellular lysosomes; the resulting drop in pH dissociates the viral genome from its binding protein.

Transcription and translation of viral genome
How a virus replicates is dictated by the structure of its viral genome.
- Viruses containing SS +RNA use their +RNA as mRNA and utilize the cell's ribosomes and enzymes to translate the information contained in this +RNA to produce

viral proteins. One of the first proteins to be produced is a RNA-dependent RNA polymerase, which then transcribes viral RNA into further RNA genomes. These viruses, because they can subvert the cellular system for their own replication, do not need to carry the information for the initial replication enzymes within their genome.

- Viruses containing SS −RNA need to convert it first to a +RNA strand, which is then used as an mRNA template for translation or direct transcription to the genomic −RNA. They therefore need to carry a viral-specific RNA-dependent RNA polymerase.
- DS RNA viruses have to first convert the −RNA strand of the DS RNA into a complementary +RNA to be used as mRNA. The +RNA strand of the DS RNA acts as a template for viral genome replication. These viruses also need to carry the RNA-dependent RNA polymerase to initiate the first steps of viral replication.
- Retroviruses are unique SS +RNA viruses. Instead of using the SS +RNA as an mRNA template, the RNA is first transcribed into complementary DNA by an RNA-dependent DNA polymerase in a process called reverse transcription (hence the name, retro = reverse). The normal transcription is always from DNA to RNA. Further transcription then occurs as for other SS DNA viruses, see below.
- DNA virus mRNA is transcribed from the DS DNA viruses in a similar fashion to cellular DNA replication. These viruses can therefore completely depend upon the cellular process to replicate. The genome of these viruses (e.g. cytomegalovirus (CMV), Epstein–Barr virus (EBV)) needs to carry information to code for the virus specific proteins only. Regulatory proteins and those required for viral DNA synthesis are coded early on and the later proteins are generally structural proteins.
- Single stranded DNA viruses are first converted into double stranded, and then mRNA is transcribed as for the DS DNA viruses.

Viral assembly and release

Before the virus particle can be released its proteins and genome have to be assembled within the cell as a 'viral package'. This process may require the cell to alter viral proteins by glycosylation etc. Viral release may occur either through cell death or through viral budding from the cell membrane. Enveloped viruses use the latter mechanism and acquire their lipid envelope at this stage. Viral enzymes such as the neuraminidase (NA) of influenza viruses (which acts on the sialic-acid bond on the cell surface to release the infectious virus particle) may be required for the viruses released via budding.

Viral pathogenesis

Viral pathogenesis can be described as the process by which the virus interacts with its host to produce disease. As this is a process which involves virus–host interaction, both viral and host factors have a bearing on the pathogenesis of viral disease.

Viral factors

Tropism

The disease manifestation depends upon the organs infected, which in turn depends upon viral tropism. The ability of viruses to infect only certain cell types due to the presence of specific viral receptors on the cell surface has already been discussed. Other factors that affect this tropism are the route of viral entry (e.g. viruses that infect through the respiratory or genital route tend to be limited to infections of those systems). Furthermore certain cells may regulate the expression of viral genes and some viruses can code for tissue-specific enhancers to stimulate transcription of viral genes in certain cells.

Spread

The mechanism of viral spread is significant in pathogenesis. Up to a million potentially infectious particles can be produced as a result of sneezing. The smaller the particle size the more likely it is to escape the mechanical trapping barriers within the respiratory system. Only those viruses that can resist the acidity of the stomach can cause gastro-intestinal infections. Enteric viruses that spread by a faecal–oral route need to be acid resistant to escape destruction by gastric juices, which may have a pH as low as 2.

Many viruses cause only a localized infection as they are unable to spread. Viruses that spread further afield from the infecting site may use virus-encoded proteins to direct their transport within the cell in a way that enhances their spread via blood or along nerves (polio and rabies viruses). Other viruses, such as CMV, EBV and HIV, are carried by infected blood cells to distant parts.

Measles virus, varicella-zoster (chickenpox) virus and rubella virus all spread via the respiratory route but cause systemic infections. These viruses have a transient 'primary viraemia' just after infection to lodge in the reticuloendothelial system (lymph nodes and spleen). The virus replicates there for a period of time (*incubation period*) without causing disease symptoms. This is followed by a second longer phase of viraemia (secondary viraemia) when the infection is spread to the target organs to manifest the disease symptoms.

Viral persistence

Many viruses cause persistent infection, which can be latent, as in herpes virus infection, or chronic, as in hepatitis B virus infection. In latency the virus lies dormant. The mechanisms of latency are not understood very well but the virus reactivates from time to time to cause localized infection, as in the case of herpes simplex virus, or may spread along the nerves, as in varicella-zoster virus (shingles). In chronic infection the virus replicates and continues to cause damage. Viruses are able to persist to cause chronic infection: (1) by escaping the immune system by constantly mutating e.g. HIV; (2) by downregulating the host immune system e.g. CMV, which codes for proteins that reduce the expression of major histocompatibility complex (MHC) class 1 receptors on the cell surface; (3) by integrating in the viral genome and replicating with the cells e.g. HIV, hepatitis B virus (HBV).

Viruses and cancers

Many viruses can induce malignancies and this is discussed further in Chapter 44.

Viral virulence factors

Viral virulence is defined as the amount of virus required to produce disease or death in 50% of a cohort of experimentally infected animals. This virulence is dependent on virus and host factors. The host factors are discussed below. Viral virulence determinants are often viral surface proteins. Viruses can also induce apoptosis (genetically programmed cell death) or block apoptosis, depending upon the best strategy for its continued replication and spread.

Host response

Disease manifestations may be the direct result of infection or may be immune mediated as a result of the host immune response to the infection. Hepatocellular damage in HBV infection is a result of destruction of infected hepatocytes by the cytotoxic T-cells. In influenza, most of the symptoms are mediated by interferon produced in response to the infection. Human immunodeficiency virus induces immunodeficiency by destroying the helper T-cells (CD4 cells) of the cell-mediated immune system.

Environmental factors

Some of the viral routes of spread (e.g. respiratory and faecal–oral route) require the viruses to remain stable in a defined environment for a period of time before they can initiate infection. Enteric viruses need to be able to withstand the acidic pH of the stomach before they can reach the intestine to establish infection. For the enveloped viruses, the viral proteins responsible for attachment to the cells are on the outside of the lipid envelope. As this lipid envelope is easily stripped by detergents or 70% alcohol, such viruses can be easily destroyed in the environment. Non-enveloped viruses, such as enteroviruses and noroviruses, are much harder to destroy.

Conclusion

Study of viruses is providing insight into many cellular mechanisms. Understanding of the steps in the viral replication cycle has enabled many designer antiviral drugs (such as the influenza A virus neuraminidase inhibitor, oseltamivir) to be manufactured. It is hoped that this brief introduction to basic virology will enable the reader to understand some of the underlying mechanisms that are relevant to the subsequent chapters in this book, and help the reader to make the most of the information contained within.

1 Adenoviruses

The viruses

Adenoviruses are double-stranded DNA viruses and belong to the family Adenoviridae.

Epidemiology

Route of spread

There are 51 different serotypes of adenoviruses (each designated by a number) and several disease syndromes associated with different serotypes. Respiratory adenoviruses are spread by the respiratory route. Enteric adenoviruses (adenovirus 40 and 41) are spread via the faecal–oral route, and adenoviruses causing conjunctivitis are very infectious and spread by direct contamination of the eye.

Prevalence

Adenoviruses are very prevalent in the UK. Respiratory adenovirus infections occur every year in the community, causing outbreaks in persons of all ages, often in children in schools and other institutions throughout the year. Enteric adenoviruses are a cause of sporadic diarrhoea and vomiting, mainly in young children, throughout the year. Although they cause small outbreaks, usually in community settings, they are not associated significantly with large outbreaks of diarrhoea and vomiting in hospitals and cruise ships. Adenoviruses associated with conjunctivitis occur sporadically, often associated with clusters of cases.

Incubation period

2–5 days.

Infectious period

Patients are infectious while they are symptomatic.

At-risk groups

Immunocompromised persons, who often have prolonged carriage of the virus, especially in enteric infections.

Clinical

Symptoms

- Respiratory adenoviruses cause a range of respiratory symptoms from mild coryza to pneumonia. Clinical symptoms include fever, cough and sore throat due to

Table 1.1. *Laboratory diagnosis of adenoviruses.*

Clinical indication	Specimens	Test	Interpretation of positive result
Respiratory symptoms	Nose and throat swab in virus transport medium.	Virus culture	Indicates adenovirus infection. Particular serotypes can be diagnosed by neutralization assays.
	Bronchoalveolar lavage fluid.	PCR	Indicates adenovirus infection. Type-specific primers can be used to distinguish between different types of adenoviruses.
	Nasopharyngeal aspirates.	Immunofluorescence test on nasopharyngeal aspirates (takes less than 2 hours)	Indicates adenovirus infection.
		EIA	Indicates adenovirus infection.
Conjunctivitis	Conjunctival swab in virus transport medium.	Virus culture	Indicates adenovirus infection. Particular serotypes can be diagnosed by neutralization assays.
		PCR	Indicates adenovirus infection. Type-specific primers can be used to distinguish between different types of adenoviruses.
Diarrhoea and vomiting	Faeces.	PCR	Indicates adenovirus infection. Type-specific primers can be used to distinguish between different types of adenoviruses.
		Rapid test devices	Indicates adenovirus infection.
		Electron microscopy	Indicates adenovirus infection.

PCR, polymerase chain reaction; EIA, enzyme-linked immunosorbent assay.

pharyngitis and tonsillitis. Some infections are asymptomatic. It is difficult to differentiate adenovirus infection from other respiratory virus infections symptomatically, although adenoviruses, unlike influenza viruses, do not usually produce myalgia. Some adenoviruses can also cause a maculopapular rash. Rarely death occurs due to disseminated adenovirus infection.

- Enteric adenoviruses cause diarrhoea, vomiting and fever, particularly in children less than 2 years of age. The diarrhoea lasts for an average of 8 days (range 3–11 days), longer than diarrhoea caused by rotaviruses.
- Ocular adenoviruses cause conjunctivitis with red, sore infected conjunctiva. It is a very infectious condition and scrupulous infection-control procedures are necessary to prevent spread, particularly by the direct-contact route. Large outbreaks have been reported. One famous outbreak called 'shipyard eye' occurred in a shipyard in the north of England, when metal workers were treated for metal slivers in their eyes. Contaminated eye instruments were blamed for transmitting the virus.

Immunocompromised patients

Organ transplant recipients, especially children, infected with respiratory adenoviruses can have measles-like symptoms. Bone marrow transplant recipients can experience severe or fatal infection. Enteric adenoviruses can cause prolonged symptoms and viral excretion in transplant recipients, especially children. Many paediatric centres therefore follow their high-risk bone marrow transplant recipients with regular laboratory screens for adenovirus infection.

Laboratory diagnosis

Several laboratory methods and clinical specimens can be used to diagnose adenovirus infection. See Table 1.1.

Management

Treatment

There is no antiviral treatment for immunocompetent persons. Bone marrow transplant recipients can experience severe and fatal infections, and can be treated with cidofivir (see Chapter 50).

Prophylaxis

There is no prophylaxis available.

Infection control

All adenovirus infections are infectious and patients should be isolated whenever possible, especially when in the same ward as immunocompromised patients.

2   Arboviruses and haemorrhagic fever viruses

Haemorrhagic fever viruses

Haemorrhagic fever viruses are viruses that cause outbreaks of severe or fatal infections with haemorrhagic symptoms, principally in the tropics. These infections are occasionally imported into the UK and other countries outside the tropics, usually causing disease in individual persons, but occasionally resulting in clusters of cases of those infections with person-to-person spread. Since there are several different viruses with different geographical distributions, animal vectors and symptoms, these details have been collated in Table 2.1 to aid differential diagnosis. Knowledge of the outbreaks occurring in different parts of the world and the recent travel history of returning travellers is very important for initial clinical diagnosis. Malaria should always be considered in the differential diagnosis. If haemorrhagic fever is suspected patients should be initially cared for in the highest security isolation rooms available, and immediately transferred to a specialist facility designed to care for cases with haemorrhagic fever once malaria is excluded. No special infection control precautions are required for hantavirus and dengue virus infections.

Although dengue fever is the most common of these viral infections to be imported into the UK, the haemorrhagic form of the disease is relatively rare.

Specimens for diagnosis

EDTA blood for virus culture, or polymerase chain reaction (PCR) and clotted blood for specific IgM antibody. In the UK all diagnostic tests are carried out, according to the Advisory Group on Dangerous Pathogens (ACDP) guidelines, in a category 4, high-security facility.

Lassa fever

Lassa fever virus is an arenavirus. *Incubation period* is 1–3 weeks. Initial symptoms include fever, retro-sternal pain, sore throat, back pain, vomiting, diarrhoea, conjunctivitis, facial swelling, proteinuria and mucosal bleeding. Clinical diagnosis is often difficult because symptoms of Lassa fever are so varied and non-specific. Eighty per cent of people have mild or asymptomatic infection; 20% have severe multisystem disease; 15–20% of hospitalized patients die, but the overall death rate is about 1%. In West Africa 100 000–300 000 infections occur per year with 5000 deaths. There are a number of ways the virus can be transmitted to humans. Virus can be *transmitted* by

Table 2.1. *Haemorrhagic fever viruses.*

Disease	Endemic countries	Animal host	Treatment	Person-to-person spread?
Lassa fever	West Africa; Guinea, Liberia, Sierra Leone, Nigeria. The geographic spread may extend to other countries in the region.	The multi-mammate rat, *Mastomys*, which are numerous in the savannas and forests of West, Central and East Africa.	Ribavirin (antiviral agent) given early in infection. Good supportive care.	Yes When a person comes into contact with virus in blood tissue, secretions and excretions from an infected patient.
Marburg disease	Marburg disease is indigenous to Africa. The exact geographical spread of infection is unknown, but includes Uganda, Kenya and Zimbabwe.	This remains a mystery, but human infection has been acquired after contact with African green monkeys or their tissues.	No antiviral treatment available. Good supportive care.	Yes When a person comes into contact with virus in blood, tissue, secretions and excretions from an infected person.
Ebola	The disease is maintained in animal host(s) in Africa. Confirmed cases have been reported in the Democratic Republic of the Congo, Gabon, Sudan, the Ivory Coast and Uganda.	The exact geographical spread of the disease in animals is not known, but the first case in an outbreak becomes infected through contact with an infected animal.	No antiviral treatment is available. Good supportive care.	Yes By contact with blood or secretions of an infected person.
Crimean–Congo haemorrhagic fever	The disease is endemic in many countries in Africa, Europe and Asia.	The virus is transmitted by argasid, hyalomma or ixodid ticks.	No antiviral treatment. Good supportive care.	Yes

Table 2.1. (*cont.*)

Disease	Endemic countries	Animal host	Treatment	Person-to-person spread?
		The virus may infect a wide range of wild and domestic animals. Ostriches are also susceptible.		
Dengue haemorrhagic fever	Dengue fever and dengue haemorrhagic fever are primarily diseases of tropical and sub-tropical parts of the world, with a distribution similar to that of malaria.	Dengue is transmitted to humans by *Aedes aegypti* mosquitoes, which only bite in the daytime.	No antiviral treatment. Good supportive care.	No
Haemorrhagic fever with renal syndrome	Worldwide in various species of rodents.	Infection occurs through direct contact with faeces, saliva or urine of infected rodents, or by inhalation of aerosolized rodent excretion.	No antiviral treatment. Good supportive care and renal support.	No

direct contact via multi-mammate rat urine and droppings, especially through cuts and sores. Contaminated inhaled air in rat-infested households is also another source. The virus is transmitted by blood contact, but is *not transmitted* through casual contact with infected humans.

Marburg disease

Marburg disease virus is a filovirus. *Incubation period* is 5–10 days. Marburg haemorrhagic fever is a severe disease, which affects both humans and non-human primates. Recorded cases are rare and have been identified in only a few locations. *Patients present with* sudden onset of fever, chills, headache and myalgia. After 5 days a maculopapular rash appears, which is most prominent on the trunk. Nausea, vomiting, chest pain, sore throat, abdominal pain and diarrhoea usually follow. Symptoms become increasingly severe and may include jaundice, severe weight loss, delirium, shock, massive haemorrhage and multi-organ failure. The fatality rate is about 25%.

Ebola

Ebola virus is a filovirus. *Incubation period* is 2–21 days. Ebola haemorrhagic fever is a severe disease of humans and non-human primates, which usually appears in sporadic outbreaks, usually spread within a healthcare setting. The *onset of symptoms* is abrupt, characterized by fever, headache, muscle and joint aches, sore throat, followed by diarrhoea and vomiting. A maculopapular rash, internal and external bleeding may also occur. The *infection often spreads* within families involved in caring for infected persons. Monkeys, gorillas and chimpanzees have been the source of outbreaks.

Crimean–Congo haemorrhagic fever

Crimean–Congo haemorrhagic fever virus is a bunyavirus. The *onset of symptoms* is abrupt, characterized by fever, headache, muscle and joint aches, sore throat, followed by diarrhoea and vomiting. A maculopapular rash, internal and external bleeding, headache, backache, sore eyes and photophobia, nausea, vomiting, diarrhoea and sore throat also occur. A petechial rash may develop with large areas of a purple rash, melaena, haematuria, epistaxis and bleeding from gums. Humans acquire the virus *from direct contact* with blood or other infected tissue from livestock or from an infected tick bite. The majority of cases have been in agricultural and slaughterhouse workers and vets.

Dengue haemorrhagic fever

Dengue fever and dengue haemorrhagic fever are caused by dengue virus. *Incubation period* is 5 days. Patients have a *sudden onset* of fever, headache, muscle and joint pains, and red petechial rash, which usually appears first on the lower limbs and chest, but can cover the whole body. Milder cases develop much milder symptoms, similar to influenza. Patients with dengue haemorrhagic fever, which is rare, have fever, haemorrhages from gums, bowel and mucosa, and thrombocytopaenia.

Dengue haemorrhagic fever is more likely to occur in persons who have a second infection with a different serotype of virus. Dengue shock syndrome has a high mortality. The fatality rate of Dengue haemorrhagic fever is 5% (but can be reduced to 1% with good supportive care). Infection is *spread* by mosquito bites of *Aedes aegypti* mosquito. Dengue fever is endemic in many countries with outbreaks every year. Large outbreaks occur every 5–6 years. See also dengue fever below.

Haemorrhagic fever with renal syndrome

Haemorrhagic fever with renal syndrome is caused by hantaviruses, family bunyaviridae. Infections occur in the Far East, China, Korea, eastern Russia and the Balkans. Different rodents transmit the infections to humans in different parts of the world. *Acute illness is characterized* by fever, hypotension, shock and impaired renal function. (Respiratory distress due to pulmonary oedema occurs in hantavirus pulmonary syndrome). Infection occurs most frequently in adults aged between 15 and 40 years of age; children are rarely symptomatically infected. Puumala virus causes infections in Scandinavia, particularly in rural areas. Humans are *infected by* inhaling aerosolized rodent urine.

Arboviruses

Arboviruses are infections (usually acquired in the tropics) that are *transmitted* to humans by insects. Some of these (e.g. dengue fever) can produce haemorrhagic symptoms. There are several different viruses with different geographical distributions, animal vectors and symptoms. Details of some of the more important ones are shown below.

Specimens for diagnosis

EDTA blood for virus culture or PCR and clotted blood for specific IgM antibody. In the UK all diagnostic tests are carried out, according to the Advisory Group on Dangerous Pathogens (ACDP) guidelines, in a category 4, high-security facility.

Dengue fever

Dengue fever is the most common arbovirus infection in the UK, with infection being acquired abroad in tropical and sub-tropical regions of the world where malaria is also prevalent. These include Southeast Asia, South America, Central and South America, the Caribbean and the Northern Territory of Australia. Dengue fever virus is a flavivirus, which is transmitted to humans by *Aedes aegypti* mosquitoes. There are four different serotypes of dengue fever virus, which are not cross-protective, so inhabitants of areas of the world where these viruses are endemic may experience infection with more than one serotype in their lifetime. The *incubation period* is 2–5 days. *Symptoms* usually begin with the sudden onset of fever, headache, muscle and joint pains, and a bright-red petechial rash, which usually presents first on the chest and lower limbs, but may become widespread over the body. The bone and

muscle pain can be so severe that the disease is known as 'break-bone fever'. Milder forms of the disease may be confused with other diseases such as influenza or malaria. The mortality rate is low (unless the haemorrhagic form develops). Symptoms usually last for 5–7 days. Severe cases can develop into dengue haemorrhagic fever, which is described earlier in this chapter. There is no antiviral treatment; good supportive care is required. Infection cannot be transmitted from one human to another unless via a mosquito vector. It can be transmitted via blood donation.

Chikungunya

Chikungunya virus is an alphavirus, which is transmitted to humans by *Aedes aegypti* mosquitoes. The *incubation period* is 2–10 days. Symptoms usually start with a sudden onset of malaise, fever and joint pains. Myalgia and joint pains can be very severe. A maculopapular rash may appear with the onset of symptoms or several days later. Large outbreaks occur in Asia and sub-Saharan Africa, but there have been outbreaks in islands in the Indian Ocean and, more recently, in Italy. The fatality rate is low. In Africa, the virus also infects monkeys.

Yellow fever

Yellow fever is a disease of the tropics caused by a flavivirus. It is transmitted to humans by mosquitoes who also infect monkeys. It has an *incubation period* of 2–5 days. The virus affects the liver, causing jaundice and fever (hence the name). Mortality rates can be up to 30%. There is an *effective vaccine* available; travellers to countries where the disease is endemic are strongly advised to be vaccinated.

Eastern equine encephalitis

Eastern equine encephalitis is an alphavirus, which is transmitted to humans by mosquitoes. Severe, and sometimes lethal, infection occurs in humans, horses and pheasants. After an *incubation period* of 3–10 days, the most severe cases have a *dramatic onset* of neurological symptoms, leading to coma and death in 30% of cases. Other symptoms include fever, myalgia, headache, photophobia and vomiting. Outbreaks occur, usually in the summer, from Ontario and Quebec to Wisconsin, Texas and the Caribbean. It also causes outbreaks in South America as far south as Argentina.

Western equine encephalitis

Western equine encephalitis is caused by an alphavirus, which is *transmitted by* several mosquito species. Outbreaks occur in western USA, Canada, Mexico, Guyana, Brazil, Argentina and Venezuela. The *incubation period* is 2–10 days and *symptoms* usually begin with a sudden onset of headache, dizziness, fever, chills, myalgia and malaise. The continuing headache, dizziness and drowsiness often prompts medical intervention. The overall mortality rate is 4%. The infection also occurs in birds and horses.

West Nile fever

West Nile fever is caused by a flavivirus, which is *transmitted* to humans by mosquitoes. The infection has an *incubation period* of 1–6 days. West Nile fever has a wide geographical distribution; outbreaks occur in Africa, the Middle East, Asia and Europe. The virus emerged in New York in 1999, and outbreaks now occur throughout North America each year. The mosquitoes become infected by biting infected birds; horses can be infected as incidental hosts too, as can humans. Most infected people have no symptoms or mild illness with fever, headache and myalgia lasting 3–6 days. A maculopapular rash appears in about 50% of symptomatic patients. In a few people, especially the elderly, West Nile fever causes severe symptoms; it can cause permanent neurological damage. Severe headache, high fever and a stiff neck can herald the onset of encephalitis and coma. The death rate in hospitalized patients is 3–15%, but overall it is less than 1%. There is no specific treatment.

Useful websites

For more detailed and up-to-date information visit:
www.who.int/ith/en
www.hpa.org.uk
www.cdc.gov/travel
www.traveldoctor.co.uk
www.advisorybodies.doh.gov.uk/acdp

3 Cytomegalovirus (CMV)

The virus

Cytomegalovirus is a double-stranded DNA virus and member of the Herpesviridae family of viruses.

Epidemiology

Route of spread
Cytomegalovirus is transmitted via saliva and sexual contact, or from infected donated blood and organs.

Prevalence
Cytomegalovirus infection occurs worldwide and the prevalence of infection varies considerably. In the UK a rule of thumb is that the percentage of the community with CMV infection is equivalent to the age (e.g. approximately 20% of 20-year-olds will have had CMV infection). Prevalence tends to be higher in lower socio-economic groups, people born outside Western Europe, inner city areas and in communities living in overcrowded conditions.

Incubation period
3–6 weeks.

Infectious period
This varies for different groups of people. In immunocompetent people, the virus is present for a few weeks in saliva, blood and some other body fluids after primary infection. In immunocompromised people, the infectious period may be prolonged after primary infection. Also, when they experience reactivation of CMV, the infection may last for weeks or months.

Cytomegalovirus is a herpes virus, which becomes latent in humans once active infection has been resolved. The virus can reactivate to produce another infection later in life – this is much rarer in persons who are not immunocompromised.

At-risk groups
Cytomegalovirus can infect anyone who has saliva or sexual contact with an actively infected person, or who receives blood or organs from a CMV positive person.

Clinical

Symptoms

Cytomegalovirus infection is usually mild or asymptomatic in immunocompetent persons. However, infection in pregnancy can lead to congenital infection, and immunocompromised patients (HIV positive, transplant recipients) often experience severe or fatal infection.

Immunocompromised patients

Cytomegalovirus symptoms vary in different groups of immunocompromised patients.

- In patients with HIV/AIDS, CMV disease is associated with retinitis, colitis, encephalitis and falling white blood cell counts. This occurs more frequently when the CD4 count falls below 200 in AIDS. Primary infection is relatively uncommon and most infections are caused by a reactivation of latent CMV infection.
- In patients who have received solid organ transplants, the highest risk of severe or fatal CMV disease occurs with primary infection, when CMV infection is acquired with the donated organ. Eighty per cent of CMV antibody-negative recipients who receive organs from CMV antibody-positive donors will acquire CMV infection. The severity of disease associated with this infection will vary according to the amount of immunosuppression given. In general, patients receiving kidney, liver and heart transplants will have less severe disease than those receiving bowel, heart–lung and lung transplants.

  Reactivation of CMV is usually associated with less severe disease, but can be fatal in severely immunocompromised patients.
- In patients who have received bone marrow transplants, severe infection can arise as a result of reactivated infection in the recipient or donor-acquired disease.

Immunocompetent patients

Most infections are asymptomatic, but in those who develop symptoms, these most commonly present as fever, malaise, sweats, jaundice and raised liver function test values.

Infection in pregnancy

Cytomegalovirus infection at any stage of pregnancy can give rise to congenital infection even in women who have no symptoms. Forty per cent of women with primary infection will transmit infection to their babies. Of those babies infected, 1% will have severe/fatal infection, 10% will have mild symptoms. Approximately 90% will be asymptomatic at birth, although they may develop signs and symptoms of congenital CMV disease (retinitis, deafness) early in life. Primary infection is associated with a higher risk of congenital infection than reactivation. Symptoms in newborn babies include chorioretinitis, deafness, brain damage, hepatosplenomegaly, petechial rash, and inter-uterine and neonatal death.

Expert virological and obstetric advice should be sought in women with CMV infection in pregnancy.

Table 3.1. *Laboratory diagnosis of CMV.*

Clinical indication	Specimens	Test	Interpretation of positive result
HIV/AIDS	EDTA blood	Qualitative PCR Quantitative PCR	Indicates CMV infection. Can indicate likely severity of disease and disease progression if done sequentially.
Transplant/ immunocompromised	EDTA blood	Qualitative PCR Quantitative PCR	Indicates CMV infection. Can indicate likely severity of disease and disease progression if done sequentially.
	Urine, BAL	Qualitative PCR, virus culture, DEAFF test	Indicates CMV infection.
	Clotted blood	CMV IgM	Low-level positive results must be interpreted with extreme caution and a second confirmatory specimen sought. Strong positive results good indicator of recent infection if laboratory has validated tests. CMV IgM can be detected up to 2 years after primary infection in solid organ transplant recipients.
		CMV IgG	Seroconversion indicates recent infection.
Immunocompetent	Clotted blood	CMV IgM	Low-level positive results must be interpreted with extreme caution and a second confirmatory specimen sought. Strong positive results good indicator of recent infection if laboratory has validated tests.
		CMV IgG	Seroconversion indicates recent infection.
	Urine/BAL	Qualitative PCR, virus culture, DEAFF test	Indicates CMV infection.
Neonates	Urine	Qualitative PCR, virus culture, DEAFF test	Indicates congenital infection if specimen taken in first 3 weeks of life.

BAL, bronchioalveolar lavage; DEAFF, detection of early antigen fluorescent foci.

Laboratory diagnosis

Several laboratory methods and clinical specimens can be used to diagnose CMV infection. See Table 3.1.

Management

Treatment

Ganciclovir is the drug of choice for treating CMV infection. It is only licensed for use in severe or life-threatening CMV infection in immunocompromised patients. Dose is iv 5 mg/kg bd for 10–14 days (note: always check latest nationally agreed protocols and drug data sheets before prescribing antiviral drugs).

Treatment can be monitored by performing quantitative PCR at the start of treatment and after one week of ganciclovir treatment. Falling CMV PCR values indicate that treatment is being effective. If the patient's symptoms are not significantly improved by the end of the course of ganciclovir, and CMV PCR values have not fallen by ≥ 2 logs, ganciclovir-resistant CMV infection should be considered as a possibility and CMV ganciclovir-resistance tests should be done.

Alternative antiviral drugs, including foscarnet and cidofivir, are available for treatment of patients with ganciclovir-resistant severe CMV infection. In babies born with severe congenital infection, iv ganciclovir treatment has been shown to be beneficial. Since ganciclovir is not licensed for this use, the benefits and side effects of treatment should be fully discussed with parents or carers before advocating treatment.

Prophylaxis

Cytomegalovirus disease can be prevented or ameliorated in those patients at high risk of developing severe CMV disease.

- Solid organ transplant patients (especially CMV antibody-negative recipients of organs from CMV-positive donors) should be given 3 months' oral valganciclovir (900 mg/day) (note: always check latest nationally agreed protocols and drug data sheets before prescribing antiviral drugs).
- Cytomegalovirus antibody-positive bone marrow transplant recipients, or those with a CMV-positive donor, should be considered for prophylaxis. However, since valganciclovir can cause leucopaenia, weekly CMV DNA monitoring of EDTA blood and rapid treatment if positive are frequently undertaken.
- HIV-positive patients with low white blood cell counts and/or evidence of recurrent eye or bowel symptoms should be considered for continuous prophylaxis.

Infection control

Cytomegalovirus does not transmit easily between humans in the absence of sexual or intimate contact. It is very rarely transmitted between humans in hospitals. Special precautions are not recommended, normal hand-washing and universal precautions (see Chapter 52) are sufficient to prevent transmission of infection in the hospital setting.

4 Epstein–Barr virus (EBV)

The virus

Epstein–Barr virus is a double-stranded DNA virus and belongs to the family Herpesviridae.

Epidemiology

Route of spread

Epstein–Barr virus is transmitted via saliva and sexual contact, hence the name 'kissing disease'. Infection is common in younger children and sexually active adolescents.

Prevalence

Epstein–Barr virus is an ubiquitous virus, which infects 95% of people in the UK before the age of 25.

Incubation period

2–3 weeks.

Infectious period

Epstein–Barr virus is shed in saliva and genital secretions, and can be present in these for many weeks or months. Reactivation of latent infection can occur frequently in some people, especially if they are immunosuppressed, with prolonged shedding of infectious virus, often asymptomatically.

At-risk groups

Immunosuppressed persons.

Clinical

Symptoms

Classical clinical EBV syndrome is infectious mononucleosis (IM), but is more commonly referred to as 'glandular fever', with symptoms of sore throat, hepatitis, lymphadenopathy, fever and malaise. Hepatosplenomegaly occurs in about 5–10% of cases. Splenomegaly is more common (50–70%). Atypical lymphocytes are present in the peripheral blood, and liver function tests are usually deranged with mildly elevated alanine aminotransferase. Infection can also be asymptomatic.

Table 4.1. *Laboratory diagnosis of EBV.*

Sample	Laboratory test	Result interpretation
Clotted blood (serum)	EBV IgM	Positive result indicates recent EBV infection. Interpret positive results with caution; some will be non-specific. Beware of rheumatoid factor interference.
	EBV virus capsid antigen (VCA) antibody	Indicates EBV infection at some time.
	EBV nuclear antigen (EBNA) antibody	This antibody is produced about 3 months after infection. If positive, it indicates EBV infection more than 3 months ago.
	EBNA antibody negative, VCA antibody positive	Suggests recent EBV infection but beware of false negative EBNA results, especially in patients >60 years old and immune suppressed patients.
	Paul Bunnel/monospot test	Provides a quick diagnosis but can be false positive and false negative. Not useful for persons under the age of 16 years.
EDTA blood	EBV DNA molecular assays	The presence of EBV DNA indicates current infection. Quantitative PCR is a guide to the severity of infection in immune compromised patients and a guide to management.

Complications

Epstein–Barr virus is a self-limiting illness, and complications are rare (see below).

- Chronic fatigue – some patients may suffer with tiredness and fatigue for weeks to months post acute EBV infection; this may or may not be accompanied with lymphadenopathy.
- Rarely, an enlarged spleen may lead to splenic rupture, therefore patients are advised to refrain from contact sports until acute symptoms have subsided.
- Guillain–Barré syndrome is a rare post-infectious complication of EBV infection, and presents as an ascending motor paralysis due to an immune-mediated demyelination of the spinal cord.
- Epstein–Barr virus associated malignancies, such as Burkitt's lymphoma, nasopharyngeal carcinoma and lymphoproliferative disease (LPD)/lymphoma in immune-suppressed patients, are described in Chapter 44.
- X-linked lymphoproliferative syndrome (Duncan's syndrome) is due to a specific X-chromosome-linked recessive genetic defect, which leads to impaired antibody response to EBV alone. It affects the male members of a family who either die of an overwhelming EBV infection, or develop lymphoproliferative malignancies.

Differential diagnosis

Cytomegalovirus, *Toxoplasma gondii,* adenovirus (see Chapter 40 on glandular fever).

Laboratory diagnosis

See Table 4.1.

Management

Treatment

There is no evidence that any antiviral drugs are useful in the treatment of EBV infections. In immunosuppressed patients, reducing the amounts of immunosuppression will reduce the severity of disease and the frequency of EBV reactivation.

Infection control

Epstein–Barr virus does not pose any infection-control risks, although sharing drinking vessels and bottles can transmit infection via saliva.

5 Enteroviruses

The viruses

Enteroviruses are RNA viruses belonging to the family Picornaviridae, to which rhinoviruses (which cause the common cold) also belong. More than 70 serotypes exist. Coxsackie A, Coxsackie B, echoviruses and polioviruses are all different serotypes of enteroviruses. Because of the similarity in viral genome, later serotypes were just called enterovirus followed by a sequential number e.g. enterovirus 71 (EV71), enterovirus 72 (EV72) etc.

Epidemiology

Route of spread
As the name implies these are spread by the enteric route by faecal–oral spread, e.g. by ingesting contaminated food or water.

Prevalence
Enteroviruses are endemic worldwide and a very common infection of childhood. Young children are often infected with more than one enterovirus at a given time. Because of poor standards of hygiene, infection is extremely common in the developing world. Polio, which is caused by an enterovirus, has been eradicated from most of the countries in the world following massive vaccination campaigns under the World Health Organization (WHO) expanded programme of immunizations (EPI). The countries where polio is still considered to be endemic by WHO are India, Pakistan, Nigeria and Afghanistan, and although not endemic it has been reintroduced in a handful of other countries (from where it had been eradicated) in the African and Asian sub-continents.

Outbreaks of infections with different serotypes causing particular clinical manifestations, e.g. conjunctivitis, hand foot and mouth disease, occur from time to time.

Incubation period
Variable, generally 3–7 days, with 7–14 days for polio.

Infectious period
Enteroviruses are shed in the faeces for a long time. Polio virus can be shed in the faeces for many weeks after infection or live oral polio vaccination.

At-risk groups

Polio virus infection is common and can cause illness in all age groups; children generally tend to have asymptomatic infection.

Neonates are at particular risk, as enteroviruses may cause disseminated infection involving multiple systems; such disseminated infections have a high mortality rate, especially in babies with a birth-weight of less than 1500 grams.

Clinical

Enteroviruses replicate in the gut but despite their name they do *not* cause gastro-intestinal (GI) symptoms/illness or gastroenteritis.

Enteroviruses present with a wide spectrum of clinical illness, although the majority of infections, especially in children, are asymptomatic. Infection with one serotype does not offer cross-protection with others; therefore multiple episodes of enterovirus infection can occur in an individual during their lifetime.

- *Non-specific illness*: Fever, malaise, fatigue, non-specific rash
- *Rashes*:
  - Painful ulceration in the mouth is known as *herpangina*. Lesions typically involve the soft palate, uvula and tonsillar fossa.
  - *Hand foot and mouth disease* (a different infection to foot and mouth disease in cattle). If the ulcers occur on hands and soles of feet in addition to those in the mouth then the disease is called hand foot and mouth disease. There may be non-specific systemic symptoms (see above) associated with both.
- *Conjunctivitis*: Severe conjunctivitis, usually bilateral, may be haemorrhagic; out-breaks may occur.
- *Respiratory*: Upper respiratory symptoms may present as common cold, pharyngitis. In small children enteroviruses can cause bronchiolitis and pneumonitis.
- *Central nervous system (CNS)*:
  - *Meningitis and meningoencephalitis*: Headache, photophobia, fever, often preceded by a viral prodrome of upper respiratory symptoms, fever and malaise.
  - *Flaccid paralysis*: Polio viruses 1, 2 and 3 cause infection of motor neurons, which results in the loss of lower motor function and flaccid muscle paralysis. This syndrome is called *poliomyelitis*. The paralysis is usually accompanied by a prodrome of fever and other signs of a non-specific viral illness (see above). Only 1% of infection with polio viruses result in poliomyelitis. The rest are either asymptomatic or cause non-specific illness. Other enteroviruses, such as EV 70, 71 and 72, may also cause flaccid paralysis or 'non-polio poliomyelitis'. The WHO EPI (see above) for polio has been effective in eliminating the dreaded condition from most of the world. Whole continents including Europe have been declared polio free. An active surveillance programme to investigate and identify the cause of flaccid paralysis is in place to ensure that polio does not re-enter the polio free areas.
- *Neonates*: Neonates may acquire infection through the perineal route from the mother at the time of delivery. Use of interventions, such as scalp electrodes to measure fetal blood gases, increase the risk of such infections. Neonatal enterovirus

infection has a relatively high mortality rate due to *disseminated infection* involving multiple systems.

- *Bornholm disease*: Severe chest pain due to infection of chest wall muscle.
- *Myalgic encephalomyelitis (ME) or chronic fatigue syndrome (CFS)*: This is a collection of diverse symptoms rather than a specific syndrome and is a diagnosis by exclusion. The most common complaint is excessive fatigue. It is usually but not always preceded by a viral illness. Enteroviruses (and other viruses such as EBV) have variously been associated as its cause, but there is no conclusive evidence of this association.

Laboratory diagnosis

Serology is of limited use. The mainstay of diagnosis is virus culture and/or PCR for detection of the virus on appropriate specimens depending on clinical presentation (see Table 5.1). Faeces is a useful non-invasive specimen to send in all cases; however, a positive result, especially in children, should be interpreted with caution because asymptomatic enterovirus infection is common in children.

Management

Treatment
There is no specific treatment.

Prophylaxis
There is no prophylaxis, except for polio for which there is a vaccine. Prevention of disease with vaccination has been one of the success stories in almost eradicating polio worldwide. The World Health Organization has declared polio to be endemic only in four countries at present (see 'Prevalence') and there are enhanced vaccination programmes with active case findings going on in these countries, with the ultimate aim to declare the worldwide eradication of polio. While polio is still endemic in some countries there is danger that it may be reintroduced in countries from where it has been eradicated; therefore childhood vaccination still remains the mainstay of prevention globally.

There are two types of polio vaccine, both of which are equally effective and are given as a primary course of three vaccines at age 2, 3 and 4 months followed by two boosters at school entry (3–5 years) and school leaving (13–18 years).

Live attenuated (Sabin) polio vaccine: This contains attenuated polio virus 1, 2 and 3 serotypes. Being an oral vaccine it has ease of delivery. Contraindicated in immunosuppressed patients and those who are in contact with immunosuppressed individuals, as the vaccine virus can be shed in faeces for weeks and may revert to wild type. Vaccine-associated polio is a rare complication in both the vaccinee and their contacts.

Killed (Salk) polio vaccine: This is as effective as the live vaccine and also contains poliovirus 1, 2 and 3 serotypes. It is given as an intramuscular injection in combination with other childhood vaccines. This is the vaccine used in most of the developed

Table 5.1. *Clinical illnesses and associated enteroviruses.*

Clinical illness	Associated enteroviruses	Laboratory specimen
Herpangina	Coxsackie A++	Mouth or throat swab
Hand foot and mouth disease (different infection to foot and mouth disease in cattle)	Coxsackie A++ EV70++ Coxsackie B+	Lesion swab, faeces
Conjunctivitis	EV70++ Coxsackie A+	Conjunctival swab
Respiratory	Echo++	NPA, throat swab, faeces
Flaccid paralysis (polio and non-polio myelitis)	Polioviruses 1, 2, 3+++ EV71++ Coxsackie A and B+	Faeces, throat swab if accompanied with non-specific illness
Meningitis and meningoencephalitis	All	CSF, faeces
Myocarditis/pericarditis	Coxsackie B++ Coxsackie A+ Echo+	Muscle biopsy, faeces
Bornholm disease	Coxsackie B++	Faeces, throat swab
Myalgic encephalomyelitis (ME) or chronic fatigue syndrome	? Coxsackie B and A	Not indicated as virus is often not present

NPA, nasopharyngeal aspirate; CSF, cerebrospinal fluid.

countries now. In countries where oral polio vaccine is still being used, killed vaccine is recommended for immunosuppressed patients and their contacts.

Infection control

It is difficult to control the spread in the community, especially where small children congregate. In the hospital, enteric precautions (Chapter 52) with strict hand washing should be instituted to prevent transmission to those patients at risk of severe or fatal infection (e.g. neonates).

6   Hepatitis A virus (HAV)

The virus

Hepatitis A virus is a single-stranded RNA virus, which belongs to the genus *Hepato-virus* in the family Picornaviridae.

Epidemiology

Route of spread

Hepatitis A is spread by the faecal–oral route, through eating and drinking contaminated food and water, and person-to-person spread. Waterborne outbreaks have been described in countries where infection is endemic. Outbreaks have also occurred in intravenous drug users (IVDU) as a result of injecting substances reconstituted in contaminated water, and through oro–anal sex. Rarely it may be transmitted through blood transfusion through a viraemic donor.

Prevalence

In developed countries, because of good hygiene, the majority of adults have not acquired the infection, as compared to the developing countries where >90% of infection occurs in childhood. People travelling to countries with a high prevalence are therefore at risk of acquiring infection during their travel and this is the major risk factor for acquisition of infection in developed countries, most commonly by eating uncooked food e.g. salad washed in contaminated water. Shellfish grown in contaminated water are another source of hepatitis A infection, as they concentrate the virus. In Europe the prevalence of antibody in adults varies from 10–50%. People from lower socio-economic groups are more likely to have had infection.

Incubation period

Average incubation period is 2–6 weeks.

Infectious period

Virus is shed in the faeces of the infected individual from two weeks before jaundice develops to about one week after the jaundice. Maximum amount of virus is shed before the jaundice develops; therefore patients are most infectious in the late incubation period.

At-risk groups

Those travelling to countries where infection is endemic; people from lower socio-economic groups (due to poor hygiene); those occupationally exposed e.g. healthcare workers, sewage workers; men who have sex with men (due to sexual practices); those with chronic liver disease and IVDUs.

Clinical

Acute hepatitis

Infection in children, especially those under 5 years old, is usually asymptomatic. In adults, about 50% have asymptomatic infection.

A prodrome of nausea, myalgia, malaise, fever and joint pains may occur followed by development of jaundice, dark urine and pale stools, and tenderness in the upper-right quadrant of the abdomen. Symptoms may last up to a few weeks but normally clear in a couple of weeks. Investigations reveal abnormal liver function tests, with alanine amino transferase (ALT) in thousands of U/L.

Complications

Infection is almost always self-limiting and chronic infection with hepatitis A does not occur. Rarely deaths do occur, mainly in elderly patients and those with chronic liver disease. Fulminant hepatitis may occur in a very small minority and is an urgent reason for liver transplant without which the mortality rate is high.

Laboratory diagnosis

See Table 6.1.

Other laboratory investigations include liver function tests (LFTs) and liver ultrasound.

Management

Treatment

There is no specific treatment; treatment is supportive. If fulminant hepatitis develops, liver transplantation may be indicated.

Prophylaxis

Pre-exposure

Killed hepatitis A virus vaccine is available. Two doses given one year apart offer protection for up to 10 years. A booster may be required at 10 years but recent evidence suggests that the two doses will give lifelong protection. Pre-exposure prophylaxis is indicated for at-risk groups and those travelling abroad to endemic countries. Depending upon the cost-effectiveness there is a case for instituting childhood vaccination programmes in countries where the virus is endemic.

Table 6.1. *Laboratory diagnosis of hepatitis A.*

Clinical indication	Specimen	Test	Significance	Essential information for the laboratory
Acute hepatitis	Clotted venous blood, 5–10ml	Hepatitis A IgM	Becomes positive 5 days after the onset of symptoms and remains positive for up to 3 months, sometimes for longer. Signifies *acute infection.*	Clinical symptoms, relevant epidemiology, *date of onset of illness.*
Check immune status	As above	Hepatitis A IgG	Becomes positive from a week after onset of illness or receiving hepatitis A vaccination and persists throughout life. When detected alone, e.g. without IgM, signifies immunity to infection due to either past infection or vaccination.	Must state if the test is to check immune status or to rule out acute infection; for latter see above.
Research or epidemiology	Faeces	PCR for hepatitis A virus	Virus present from a couple of weeks before onset of acute hepatitis to a couple of weeks after. *Not used for routine diagnosis.* Research and epidemiological tool.	Same as for IgM.

Post-exposure

Normal human immunoglobulin and/or hepatitis A vaccine should be given to household contacts within 14 days of exposure. There is good evidence that post-exposure vaccination (as the antibody response occurs in 7–10 days) given within a week of exposure is effective in preventing or attenuating infection in exposed individuals and effective (less effective in persons >40 years old) in interrupting outbreaks.

Infection control

Where possible patients should be put in a single room and strict hand washing should be adhered to.

Pre- and post-exposure vaccination should also be used as appropriate.

7   Hepatitis B and D viruses (HBV and HDV)

The virus

Hepatitis B virus (HBV) is a member of the Hepadnaviridae family of viruses, and has a double-stranded circular DNA and a DNA polymerase enzyme. It has two major proteins: hepatitis B surface antigen (HBs Ag), which is an outer protein expressed in excess when the virus replicates in the liver; and hepatitis B core antigen, an inner protein, which is expressed only within hepatocytes in the liver. A third protein, hepatitis B e antigen (HBe Ag), is also shed in the blood when the virus replicates, and its presence is associated with high infectivity.

Hepatitis D virus (HDV) is a defective RNA virus, which cannot replicate in humans in the absence of HBV. Patients can be co-infected with HBV and HDV, or HBV infected patients can be super-infected with HDV.

Epidemiology

Route of spread
The routes of transmission are
- parenteral (blood exposure)
- sexual
- vertical (from mother to baby).

Prevalence
Hepatitis B virus infection occurs worldwide with prevalence of infection varying between <2% to 15%, with 80% of the global population having a 60% lifetime risk of infection.

Incubation period
Infection can develop from 6 weeks to 6 months after exposure to the virus.

Infectious period
Infectivity is related to the presence of HBs Ag in the blood. Patients are infectious as long as HBs Ag or HBV DNA is detected in peripheral blood. The infectivity can be high (up to 90%) or low (1–3%) depending upon the presence of HBe Ag in the blood. Hepatitis B e antigen is a marker of high infectivity, whereas the presence of antibody to HBe Ag (anti-HBe) denotes low or absent infectivity. Recent evidence suggests that

presence or absence of HBV DNA in the blood is a more accurate marker of infectivity. This is because HBV mutants exist, that either do not express HBe antigen (core mutants) or that produce altered HBe antigen (pre-core mutants), and these patients despite being anti-HBe positive have a high level of viral DNA in their blood and are highly infectious. Absence of HBV DNA in the blood signifies absence of infectivity.

At-risk groups

The groups most at risk of HBV infection are shown in Table 7.1 along with the potential route of transmission.

Clinical

Acute hepatitis B

The percentage of patients exhibiting symptoms increases with age, with only 10% of infections in children being symptomatic as compared to about 50% of infections in young adults being symptomatic. Acute infection is accompanied with a rise in ALT of >500 IU/L and jaundice. The hepatitis is immune mediated and liver damage occurs due to cytotoxic T-cells attacking the infected hepatocytes. Fulminant hepatitis and death may occur in <1%.

Ninety-five per cent of adults clear the virus within 6 months after an acute infection. Failure to clear the virus and progress to chronic infection or carriage is associated with inadequate immune response to the virus in the very young, chronically ill or those who are immunocompromised.

The clinical outcome and serological markers of acute hepatitis B infection are shown respectively in Figs. 7.1 and 7.2.

Chronic hepatitis B

Chronic infection is defined as persistence of hepatitis B infection beyond a period of 6 months subsequent to acute infection. Fig. 7.3 shows the hepatitis B serological markers in chronic infection.

Failure to clear the virus may lead (over a period of several years) to progressive liver damage with persistent hepatitis→chronic hepatitis→cirrhosis→hepato-cellular carcinoma. Hepatitis B virus is the single most important risk factor for development of hepato-cellular carcinoma.

Neonatal hepatitis B

Infection is acquired from the mother at the time of birth and commonly leads to chronic infection, especially if the mother is HBe antigen positive.

To prevent neonatal hepatitis B infection, in the UK there is a programme for universal hepatitis B screening of pregnant women to identify and vaccinate babies born to infected mothers.

Countries with a high prevalence of hepatitis B have opted to vaccinate all neonates against hepatitis B.

Table 7.1. *At-risk groups for HBV infection.*

Mode of transmission	At-risk groups	Preventive measures
Parenteral Percutaneous or mucous membrane exposure to blood or blood-contaminated secretions.	Intravenous drug users. Healthcare workers. Blood and blood product recipients. Tattoos/body piercing/ acupuncture. Patients undergoing dental or surgical treatment.	Do not share injecting equipment. Avoid needle-stick injuries. Screening of blood. Clean fresh equipment for each patient. Vaccinate at-risk people. Exclusion of infected healthcare workers from performing exposure-prone procedures.
Sexual Increased risk of transmission if genital ulcers due to other sexually transmitted infections (STIs) are present.	Multiple sexual partners. Men who have sex with men. Sex workers.	Use of barrier method (condoms) during sexual intercourse. Vaccinate at-risk people.
Vertical (from mother to baby) Transmission is in the peri-natal period due to feto–maternal mixing of blood, and mucous membrane exposure to infected maternal secretions at the time of birth.	Babies born to mothers who are chronic carriers of HBV or who have acute HBV infection in pregnancy.	Role of caesarian section not established in decreasing the risk of transmission. Avoid scalp electrodes or use of other sharp instruments on the fetus at delivery. Vaccinate baby at birth and give hepatitis B immunoglobulin for low birth-weight babies $<1500\,g$ and those whose mothers are negative for anti-HBe. Breast feeding is not contra-indicated (unless cracked or bleeding nipples etc.).

Laboratory diagnosis

Hepatitis B infection is diagnosed by testing a clotted blood sample for HBs Ag: 5–10 ml of blood should be sent to the laboratory. Acute or chronic infection can be differentiated by testing for a combination of different serological markers for hepatitis B. See Table 7.2 and Figs. 7.2, 7.3, 7.4 and 7.5.

Figs. 7.4 and 7.5 show clinical interpretation of HBV markers in hepatitis B surface antigen positive and negative patients.
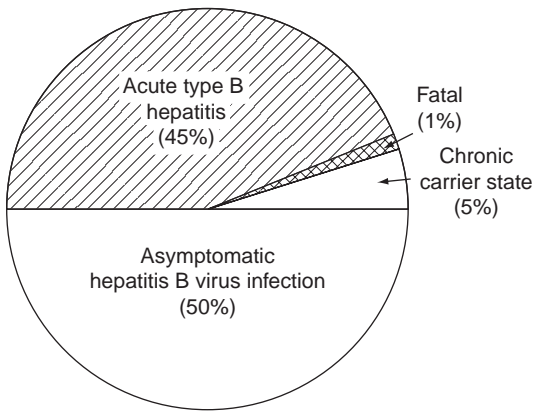
Fig. 7.1. Clinical outcomes of acute hepatitis B infection in adults.
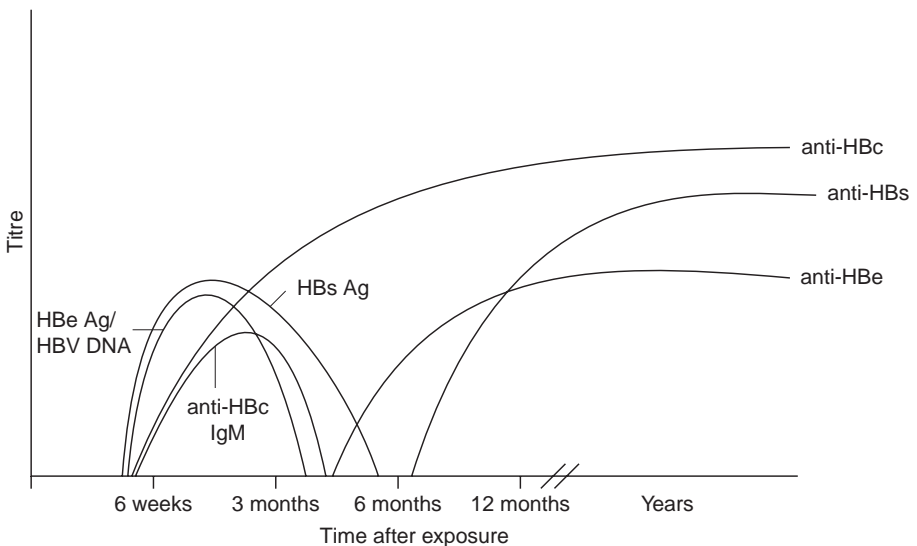
Fig. 7.2. Hepatitis B serological markers of acute infection.

Management

Treatment

Acute hepatitis B

Acute infection is self-limiting and 95% of immunocompetent adults clear the virus within 6 months of onset of acute hepatitis. Fulminant hepatitis may occur in <1% and may require a liver transplant.

Chronic infection

A small number of patients will spontaneously clear the virus, with 10–15% of HBe Ag positive patients per year seroconverting to anti-HBe positive status and then over a period of time clearing the virus altogether.
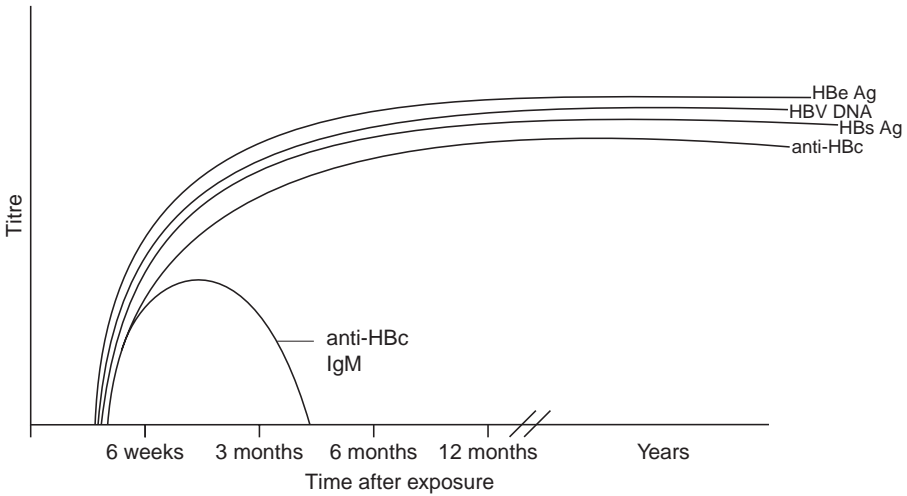
Fig. 7.3. Hepatitis B serological markers of HBe Ag chronic infection.

However, the majority of chronically infected patients will require treatment depending on the type of infection and evidence of ongoing liver damage.

Those who are HBe Ag positive and have evidence of liver disease as indicated by elevated ALT and/or liver biopsy should be treated with interferon alpha. About 25–50% of patients will respond; the response is much higher if pegylated interferon alpha is used.

Newer aminoglycoside analogue drugs, such as lamivudine, adefovir, tenofovir and entecavir (Chapter 50), are more effective either on their own or in combination with interferon, but resistance is a problem especially with lamivudine.

Liver transplantation may be the last resort in case of liver failure.

Prophylaxis

An effective recombinant vaccine made of the outer viral protein, e.g. HBs Ag, is available for both pre- and post-exposure prophylaxis for hepatitis B.

Pre-exposure prophylaxis

Three doses are given, with the first two at an interval of one month and the third 6 months after the first (0, 1 and 6 months); 95% of vaccinees respond after the first course, a booster dose is recommended once after 5 years of primary immunization and provides long-term protection against the disease.

The following groups have a poorer response to the vaccine:
- males
- older age (>40 years)
- obese
- immunocompromised, chronically or on haemodialysis.

Table 7.2. *Hepatitis B serological markers in the blood at different stages of infection.*

Hepatitis B surface antigen (HBs Ag)	Outer protein coat of virus	Detected in blood in both acute and chronic hepatitis B infection. Marker of infection and used as the primary screening test for hepatitis B.
HBV DNA	Viral DNA	Present in hepatocytes and also in the blood of infected patients, presence in blood signifies high infectivity. Level can be quantified and is used to monitor treatment response.
Hepatitis B e antigen (HBe Ag)	Part of inner viral protein	Present in early part of acute infection, may persist if virus not cleared, presence in blood signifies high HBV DNA level and high infectivity. About 10–15% of chronic carriers clear HBe antigen (HBe Ag) spontaneously every year.
Hepatitis B e antibody (anti-HBe)	Antibody to HB e antigen	Anti-HBe appears when the HBe Ag is cleared, its presence normally indicates an inert hepatitis B infection accompanied with low or absent HBV DNA in blood, but up to 20% of patients may have a mutant virus and a high level of DNA even in the presence of anti-HBe.
Hepatitis B core antibody (anti-HBc)	Antibody to the hepatitis B core antigen, the core antigen is present only in the hepatocytes and NOT in the blood	Hepatitis B core antibody (anti-HBc) is detected once the body mounts an immune response to the virus, and accompanies the development of jaundice and acute hepatitis B. HBV core antibody of IgM class (anti-HBc IgM) signifies and is diagnostic of acute HBV infection; it is the only marker that can distinguish between acute and chronic infection. Anti-HBc of IgG class (as measured by anti-HBc total antibody tests) persists for life.
Hepatitis B surface antibody (anti-HBs)	Antibody to hepatitis B s antigen	Hepatitis B s antigen is replaced by the hepatitis B s antibody (anti-HBs) once the virus is cleared. Anti-HBs is the protective antibody and denotes immunity to further infections. This is also the antibody that is produced in response to hepatitis B vaccination.

Many countries with a high prevalence of HBV have opted for universal vaccination programmes to eliminate hepatitis B infection and have been successful. Other countries, such as the UK, have elected a programme of vaccinating those at high risk of infection, for example:

• healthcare workers
• those in close contact with infected patients, including the household and sexual partners of patients with acute and chronic hepatitis B infection

HBs antigen positive

Anti-HBc IgM positive*   Anti-HBc IgM negative

Acute hepatitis B infection   Chronic hepatitis B infection

HBe antigen   anti-HBe
positive   positive

High infectivity   Low infectivity
and high risk   and low risk
of liver disease   of liver disease
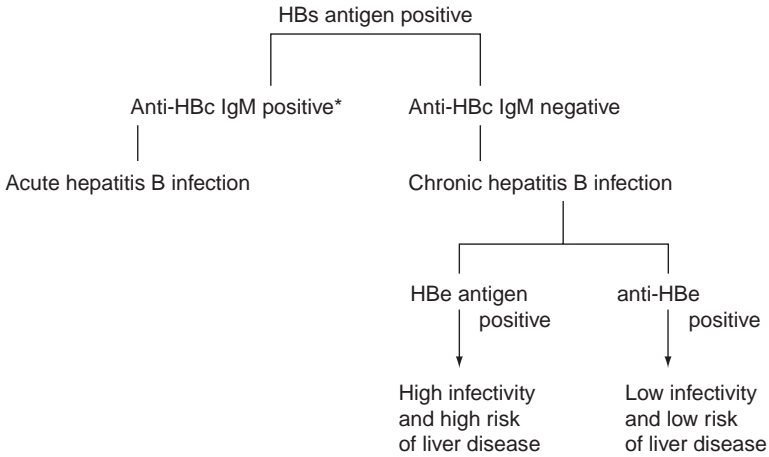
* Strongly positive anti-HBc IgM is consistent with acute hepatitis B infection.
Weakly positive anti-HBc IgM can be found in patients with chronic hepatitis B infection.

Fig. 7.4. Clinical interpretation of HBV markers in hepatitis B surface antigen positive patients.

HBs antigen negative

*anti-HBc (total) positive   *anti-HBc (total) negative

Anti-HBs   Anti-HBs   Anti-HBs   Anti-HBs
positive   negative   positive   negative

Past infection with   Past infection   Evidence of   No evidence of
hepatitis B.   with hepatitis B.   hepatitis B   past infection
Immune to   Likely to be   vaccination.   or vaccination.
hepatitis B.   immune to   Immune to   Susceptible to
                        hepatitis B.   hepatitis B.   hepatitis B.

* There are no specific tests to measure anti-HBc IgG, positive anti-HBc total
antibody in the absence of anti-HBc IgM indicates that antibody is of IgG class.

Fig. 7.5. Clinical interpretation of HBV markers in hepatitis B surface antigen negative patients.

- babies born to mothers who have acute hepatitis B in pregnancy or are chronic carriers; all pregnant women in the UK are offered a screening test for hepatitis B to identify the at-risk babies
- those whose lifestyle puts them at risk of hepatitis B (e.g. IVDUs, sex workers)
- long-term travellers to endemic countries.

Post-exposure prophylaxis

For accidental and sexual exposure

- *Vaccination*: Due to the long incubation period of hepatitis B the vaccine has a high effectiveness for post-exposure prophylaxis; a rapid schedule of three doses at 0, 1 and 2 months with a booster at 12 months is recommended.
- *Immunoglobulin*: Hepatitis B specific immunoglobulin should also be considered for accidental and sexual exposure to hepatitis B. To be effective it should be given within a week of exposure and preferably within 48 hours.

Neonates

Neonates born to mothers who have acute hepatitis B in pregnancy and those with HBe Ag positive chronic HBV infection should be vaccinated and given hepatitis B specific immunoglobulin. Babies born to mothers who are anti-HBe positive do not require immunoglobulin but should receive hepatitis B vaccination.

Control of infection

Hepatitis B virus infection can be spread in hospital and healthcare settings by contamination with blood or blood-contaminated body fluids. Special precautions should be taken when caring for HBV positive patients who are also HBe antigen or HBV DNA positive, especially if they are bleeding. Gloves, gowns and aprons should be worn when in direct contact with HBs Ag positive patients. Eye protection should also be worn if eye splashes with blood or blood-contaminated body fluids are likely.

In addition, healthcare workers (HCWs) who perform exposure-prone procedures should be screened for hepatitis B infection and if positive for HBV DNA should be excluded from doing such procedures. Please refer to Chapter 53.

Hepatitis D (Hepatitis delta)

Hepatitis D or delta is a defective DNA virus and requires the hepatitis B surface antigen (which it uses as its outer protein coat) so it can enter the cells to infect and replicate. As it cannot replicate without the help of HBV, delta infection cannot occur in patients who are not HBV infected. Two types of infection are described:

- *Co-infection*: Where a person who is susceptible to HBV is exposed to someone who is co-infected with HBV and delta virus, this results in acute co-infection with both the viruses at the same time.
- *Super-infection*: When an HBV carrier is exposed to infected blood from co-infected patients then the exposure results in super-infection of the existing HBV infection with delta virus; this may result in development of acute hepatitis (due to delta virus) in an HBV chronic carrier.

Delta infection can clear up after an acute episode or, like HBV, delta virus may persist to cause chronic infection. There is evidence that chronic co-infection or delta virus super-infection of chronic HBV infection has a worse prognosis.

Infection is diagnosed by screening blood for delta virus IgG; although delta virus IgM is not always present in acute infection a positive result is useful in confirming acute delta virus infection.

In the UK, delta virus infection is seen only in those who use recreational intravenous drugs. It is more prevalent in some Mediterranean and southern European countries such as Italy, Spain and some parts of France.

Fortunately, as delta virus requires HBV to infect and replicate, protecting individuals for HBV through vaccination is effective in protecting against delta virus infection as well.

8   Hepatitis C virus (HCV)

The virus

Hepatitis C virus is a single-stranded RNA virus belonging to the family Flaviviridae, to which flaviruses such as dengue and yellow fever viruses also belong. There is one serotype but at least 6 different genotypes (1 to 6). Some of the genotypes are further divided into subtypes. For example there are two subtypes to HCV genotypes 1 and 3 (e.g. 1a, 1b and 3a, 3b).

The genotypes are important because the treatment response depends upon the infecting genotype. Furthermore, genotypes and subtypes are important epidemiological tools as some are geographically limited in their distribution. In the UK most of the infections are due to genotype 1a, 1b, 2 and 3. In Egypt genotype 4 predominates.

Epidemiology

Route of spread

As for hepatitis B, *exposure to infected blood* and secretions contaminated with infected blood is the main route of transmission, through the following:

- *Blood and blood product transfusion*

  A particular tragedy was the transmission of the virus to >90% of haemophiliacs through contaminated factor VIII prior to the introduction of screening of blood for HCV. An outbreak of HCV also occurred in Ireland related to a batch of contaminated immunoglobulin.

- *Intravenous drug use*

  In the UK, intravenous substance use (drug use) accounts for most of the infected cases and up to 50% of all IVDUs have evidence of HCV infection. Sharing of contaminated equipment is the main cause.

- *Iatrogenic (through medical treatment)*

  Reuse of needles, syringes and sharp instruments without proper sterilization for medical treatment in the developing countries has been responsible for the spread of the virus. Egypt has a high rate of HCV infection because of the reported reuse of needles during the national vaccination campaign to eliminate schistosomiasis (bilharzia), a parasitic infection.

- There are case reports of infection being passed on to patients from infected healthcare workers (HCWs) during surgical treatment (performance of exposure-prone procedures).

- Organ and tissue donation from infected donors before HCV screening was introduced has resulted in infection in the recipient.
- Renal dialysis, if proper precautions are not followed. Outbreaks and high HCV prevalence in dialysed patients have been reported, but transmission in UK units is rare.
- *Occupational, e.g. HCWs*
  Infection can be transmitted after a sharps or needle-stick injury from an infected source patient to an HCW. The risk of transmission after exposure to HCV positive blood is approximately 3% and depends upon the level of viraemia, i.e. the HCV viral load in the blood of the source patient.
- *Ear and body piercing, tattooing*
  Due to the use of contaminated equipment.
- *Sexual and vertical (from mother to baby) transmission*
  This may also occur but to a much lesser degree than with hepatitis B. Babies born to HCV RNA positive mothers have a 5% to 15% risk of being infected.

Prevalence

Hepatitis C virus is prevalent worldwide; it is estimated that there are about 200 million carriers in the world. The prevalence in the general population varies from about 20% in Egypt to 1–5% in Mediterranean countries, Africa, South East Asia and the USA. In the UK, the prevalence is low at 0.5–1%. The prevalence of HCV is not uniform throughout the population and varies according to the risk and lifestyle of the population (see above).

Incubation period

Hepatitis C virus does not usually cause acute symptoms, but very occasionally patients experience acute hepatitis. The average incubation period from exposure to development of infection is 2–6 weeks, but may be as long as 3 months.

Infectious period

About 70% of patients who acquire HCV infection go on to become chronically infected and infectious throughout their lifetime.

At-risk groups

These include intravenous drug users, healthcare workers, people who have received blood and blood products (although in the developed countries where blood is now routinely screened for HCV this is no longer a risk), hospitalized patients (because of iatrogenic spread), patients at risk due to their lifestyle (body piercing, tattooing, multiple sexual partners), sexual contacts and babies born to HCV infected mothers.

Clinical

Symptoms

The vast majority of *acute infections* are asymptomatic; symptoms when they do occur are malaise, fatigue, nausea and jaundice. About 20% of patients clear the virus
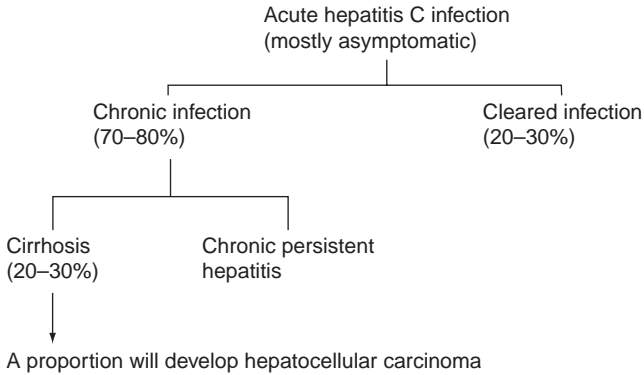
Fig. 8.1. Clinical course of hepatitis C infection.

after an acute infection and the majority (about 70–80%) will go on to develop *chronic HCV infection*. Patients with chronic HCV infection do not have specific symptoms but ongoing malaise and fatigue may occur many years after infection. About 20–30% of those with chronic infection will go on to develop *cirrhosis of the liver* after 20–30 years, a small proportion of whom will develop *hepatocellular carcinoma*. (See Fig. 8.1.)

Older age at infection, male sex and other associated liver damage due to alcohol and co-infection with other hepatitis viruses are factors leading to a *poor prognosis*.

Laboratory diagnosis

As most infections are asymptomatic, diagnosis of acute infection is not normally made and the majority of 'new' infections that are diagnosed are in those who have chronic infection. See Table 8.1.

Management

Patients should be referred to a specialist or a specialist centre for treatment of HCV infection, as the treatment regime and follow-up is complicated and depends upon the infecting HCV genotype, initial viral load and response to treatment.

Patients are treated with a combination of slow-release pegylated interferon and oral ribavirin for 6–12 months. Older age at treatment, male sex, continuing alcohol consumption, high HCV viral load at initiation of treatment and infection with HCV genotype 1 are all poor prognostic factors for treatment response.

The interferon treatment has many systemic side effects, and therefore it is recommended that only those patients who will benefit the most and those who have evidence of persistent or worsening liver disease as shown by liver biopsy should be considered for treatment.

Table 8.1. *Laboratory diagnosis of HCV infection.*

Clinical indication	Specimen	Test	Significance	Essential information for the laboratory
Screening for acute or chronic HCV infection	5–10ml of clotted venous blood	Hepatitis C antibody	Positive result indicates infection, initial screen MUST be confirmed by repeat testing. There is no HCV specific IgM test available to distinguish acute from chronic infection.	Risk factors for infection, history of recent exposure to hepatitis C if any, clinical symptoms if present.
For establishing infection status of patient	As above	Hepatitis C PCR for HCV RNA. Mostly quantitative (viral load) assay	Positive result indicates either acute or chronic infection. Negative result indicates clearance of infection either naturally or post-treatment.	As above, plus any history of treatment.
Assessment of infected patient for treatment	As above	Hepatitis C genotype determination	HCV genotype will guide treatment decisions including duration of treatment.	As above.

```
              Chronic HCV infection
                        |
                        v
        _____
       |                                |
  HCV genotype 1, 4, 5, 6        HCV genotype 2, 3
       |                                |
  +Recommended treatment         Recommended treatment
  duration 48 weeks              duration 24 weeks
  50% with SVR*                  80% with SVR*
```
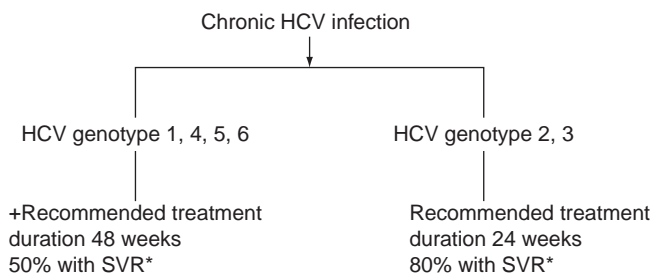
+ Patients infected with HCV genotype 1, 4, 5, 6 should have their viral load measured at week 12 of treatment. Treatment should be discontinued in those who do not show a significant fall in HCV viral load as these patients are not likely to respond.
* SVR – sustained viral response (suppression).

Fig. 8.2. Treatment of chronic HCV infection with oral ribavirin and intramuscular pegylated interferon: treatment duration and response.

Effect of genotype on treatment

About 50% of patients infected with genotype 1 will clear infection as compared to 80% of those infected with genotype 2 and 3. Patients with genotype 1 also need a longer duration of treatment as compared to those infected with genotype 2 and 3 (Fig. 8.2). The good treatment response for genotype 2 and 3 has resulted in the recommendations to treat all such patient without prior liver biopsy.

Prophylaxis

There is no vaccination available for hepatitis C despite active research going on in this area for the past 10–15 years. There is no passive prophylaxis in the form of specific immunoglobulin available either.

Infection control

Infection control is the key to prevention and depends on:
- screening and testing of blood and organ donors to exclude those who are infected, and heat-treating blood products (plasma) to inactivate the virus
- implementing appropriate controls to prevent iatrogenic transmission; these include proper sterilization of instruments before reuse, exclusion of infected healthcare workers from performing exposure-prone procedures and taking appropriate control measures in the renal dialysis units
- education of people at risk (e.g. IVDUs) for risk reduction, including detoxification and needle exchange programmes.

9 Hepatitis E virus (HEV)

The virus

Hepatitis E virus (HEV) is an RNA virus that resembles caliciviruses but as yet remains unclassified. There are at least four genotypes of the virus, genotypes 1 and 2 are limited to humans only, and genotype 3 and 4 have animals as their reservoir and therefore are zoonotic infections.

Epidemiology

Route of spread

Hepatitis E is spread by the faecal–oral route, mostly through drinking water and probably by eating contaminated food. Person-to-person spread may occur but is uncommon. Waterborne outbreaks occur commonly in countries where infection is endemic.

Prevalence

The infection was first reported from the Indian subcontinent and subsequently from other parts of Asia, the Middle East, Central and South America, Africa, Central Europe and Russia. People travelling to countries with high prevalence are therefore at risk of acquiring infection during their travel. Adult populations in endemic areas are generally susceptible and there is a high infection rate in epidemics.

Until recently cases reported from North America and Western Europe were travel related but recently many indigenous cases, including clusters of cases, have been reported indicating that hepatitis E infection is endemic. All the cases reported from the West have been due to genotype 3 of HEV, for which pigs are the main reservoir. The exact route of transmission is not clear and further studies are needed.

Incubation period

This is longer than that of hepatitis A. The average incubation period is 6 weeks.

Infectious period

Virus has been detected in the faeces during the acute phase of disease, but the exact infectivity period is not known.

Table 9.1. *Laboratory diagnosis of hepatitis E infection.*

Clinical indication	Specimen	Test	Significance	Essential information for the laboratory
Acute hepatitis	Clotted venous blood, 5–10 ml	Hepatitis E IgM	Becomes positive within first week of acute hepatitis and remains positive for up to 3 months, sometimes for longer. Signifies *acute infection.*	Clinical symptoms, relevant epidemiology, *date of onset of illness.*
Check immune status	As above	Hepatitis E IgG	Becomes positive from 1 to 2 weeks after onset of illness. When detected alone, e.g. without IgM, signifies immunity to infection due to past infection.	Must state if the test is to check immune status or to rule out acute infection, for latter see above.

At-risk groups

Travellers to countries where infection is endemic are at risk. A high mortality rate (up to 25%) from acute HEV infection has been reported in pregnant women and their babies, especially those who become infected in the third trimester.

Clinical

Acute hepatitis

Unlike hepatitis A, which is a common infection of childhood, HEV usually occurs in young adults (>15 years). Childhood infections when they occur are generally subclinical.

Clinical presentation is indistinguishable from other viral hepatitis, and comprises of nausea, myalgia, malaise, fever and occasionally joint pains accompanied with jaundice, dark urine and pale stools, and tenderness in the right upper quadrant of the abdomen. The infection is self-limiting, but fulminant hepatitis with a high mortality rate occurs in infected pregnant women.

Complications

Infection is self-limiting and chronic infection with hepatitis E virus does not occur. *Fulminant hepatitis* with a mortality rate of up to 25% is reported in pregnant women.

Laboratory diagnosis

See Table 9.1.

Other laboratory investigations include liver function tests (LFTs) and liver ultrasound.

Management

Treatment

There is no specific treatment. Treatment is supportive. If fulminant hepatitis develops, liver transplantation may be indicated.

Prophylaxis

There is no vaccine or passive prophylaxis available; avoidance of infection is the only preventative measure.

Infection control

Strict hand washing should be adhered to, and where possible the patient should be put in a single room.

10 Herpes simplex virus (HSV)

The virus

Herpes simplex virus is a double-stranded DNA virus and a member of the Herpesviridae family of viruses.

Epidemiology

Route of spread
Close personal contact.

Prevalence
Approximately 80% of people in the UK experience HSV type 1 infection at some time in their lives. This figure is approximately 10% for HSV type 2 infections.

Herpes simplex virus infection occurs worldwide and the prevalence of infection varies considerably. Herpes simplex virus is transmitted by sexual contact and skin, genital or eye contact with vesicle fluid from HSV skin lesions. There are two types of HSV (HSV type 1 and HSV type 2).

Incubation period
2–12 days (mean 4 days).

Infectious period
From the onset of symptoms until the lesions are fully crusted or resolved.

At-risk groups
These include immunocompromised persons and neonates.

Clinical

Symptoms
Primary HSV infection occurs when a person first encounters the virus. It first infects an area of skin; then the virus travels down a sensory nerve and establishes a latent infection in the dorsal route ganglia and becomes dormant. Most infected persons do not experience a reactivated infection, where the virus reactivates and causes another clinical episode at the site of the primary infection. However, many do, and some experience frequent recurrences (e.g. cold sores on the lip).

Fig. 10.1. Herpes simplex virus skin blisters on a patient's arm. (See Fig. 1 in colour plate section)

Herpes simplex virus can infect various sites in the body. The most severe infection is HSV encephalitis, which has a 70% mortality rate if untreated. Infection in immuno-compromised patients can be severe or fatal.

- *Skin*: HSV causes fluid-filled skin blisters (vesicles) (Fig. 10.1), which can sometimes be difficult to distinguish from varicella-zoster virus (VZV) infection.
- *Mouth and lips*: Primary infection in children often occurs in the mouth and on the lips. Infection can be missed unless severe gingivostomatitis is present. Reactivated infection is usually seen as a cold sore on the lip.
- *Genitals*: HSV causes vesicles and shallow ulcers on the labia, cervix, penis and perianally. Herpes simplex virus type 2 is more frequently found that HSV type 1.
- *Encephalitis*: The most severe HSV infection, which is often severe or fatal and requires prompt treatment and diagnosis.
- *Meningitis*: Usually associated with HSV type 2.
- *Eye infection*: HSV causes keratoconjunctivitis in the eye. Repeated reactivated infection of the cornea can cause corneal scarring and blindness.
- *Pneumonitis*: This is rarely seen in immunocompetent persons. It is usually a reactivation of latent infection in immunocompromised patients (e.g. after lung transplantation).
- *Neonatal herpes*: Babies who acquire HSV infection from the mother's genital tract at the time of delivery are at risk of severe or fatal neonatal HSV infection. Expert specialist advice on treatment and prophylaxis should be sought as soon as possible.

Table 10.1. *Laboratory diagnosis of HSV infection.*

Clinical indication	Specimens	Test	Interpretation of positive result
Skin lesion	Vesicle fluid	Electron microscopy (EM)	Indicates a herpes virus infection (all herpes viruses look alike in the EM, so cannot distinguish between HSV and VZV).
	Vesicle fluid swab of the base of the lesion in virus transport medium	PCR Virus culture or immunofluorescence test (IFT)	Indicates HSV type 1 or type 2 infection. Indicates HSV type 1 or type 2 infection.
Encephalitis or meningitis	CSF	PCR	Indicates HSV type 1 or type 2 infection.
Eye lesions	Corneal swab Corneal swab in virus transport medium	PCR Virus culture	Indicates HSV type 1 or type 2 infection. Indicates HSV type 1 or type 2 infection.
Pneumonitis	Bronchoalveolar lavage Bronchoalveolar lavage in virus transport medium	PCR Virus culture	Indicates HSV type 1 or type 2 infection. Indicates HSV type 1 or type 2 infection.
Neonatal herpes	Skin swab Skin swab in virus transport medium	PCR Virus culture	Indicates HSV type 1 or type 2 infection. Indicates HSV type 1 or type 2 infection.
Has the patient had HSV infection before?	Clotted blood	HSV type 1 and type 2-specific IgG test	Indicates previous HSV type 1 or type 2 infection.

Table 10.2. *Antiviral treatment for HSV infections.*

Clinical indication	Drug
HSV skin or genital infection in immunocompetent patients	Oral aciclovir or valaciclovir or famciclovir
	Aciclovir cream
HSV skin infection in immunocompromised patients	Oral aciclovir or valaciclovir or famciclovir
Severe HSV skin infection in immunocompromised and immunocompetent patients	Intravenous aciclovir
HSV encephalitis	Intravenous aciclovir
Neonatal herpes simplex infection	Intravenous aciclovir
HSV corneal infection	Aciclovir
	Eye ointment
Prevention of HSV recurrence in immunocompetent patients with frequent recurrences	Oral aciclovir or famciclovir or valaciclovir
Prevention of HSV recurrence in immunocompromised patients at high risk of severe infection	Oral aciclovir or famciclovir or valaciclovir

Differential diagnosis

Vesicular skin lesions caused by HSV can be mistaken as VZV infection. Herpes simplex virus lesions are usually all at the same stage of development in the same cluster. Chickenpox usually causes widespread lesions, especially on the body, with vesicles at various stages of development in one cluster. Shingles vesicles are usually confined to an area of skin (dermatome) on one side of the body served by a sensory nerve (although immunosuppressed patients can have much more extensive lesions).

Laboratory diagnosis

Virus culture takes 1–3 days to get a positive result. Polymerase chain reaction (PCR) can provide a result in a few hours.

Clotted blood/HSV antibody tests are not useful in the diagnosis of acute HSV infection but are helpful for epidemiological studies.

See Table 10.1.

Management

Treatment

See Table 10.2. Oral aciclovir is cheaper than other oral forms of treatment as it is available in generic formulation. Rarely, other antivirals (e.g. foscarnet or adefovir) may be useful, especially in immunocompromised patients with aciclovir-resistant HSV infection. Consult a consultant virologist or microbiologist. (Note: check nationally agreed protocols or drug data sheets before initializing treatment.)

Prophylaxis

Some HSV antibody positive groups of patients (e.g. lung transplant, bone marrow transplant and HIV positive patients) will require aciclovir prophylaxis to prevent severe or potentially fatal HSV reactivation disease. (See note above.)

Infection control

Herpes simplex virus is transmitted by close personal contact and is rarely associated with infection control problems. However, healthcare staff who have HSV skin lesions on their hands should cover them with a waterproof dressing to avoid transmitting infection to patients, and those with severe lesions should seek infection control or occupational health advice before working in direct patient contact, especially with immunocompromised patients.

11 Human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS)

The virus

Human immunodeficiency virus is an RNA virus and belongs to the genus lentivirus (lenti – slow) within the family Retroviridae (retro – backwards), so called because viruses (including HIV) in the family possess a reverse transcriptase (RT) enzyme to convert the viral RNA template into DNA, which integrates in the cellular DNA to cause persistent infection. The other virus in the genus lentivirus is simian immuno-deficiency virus (SIV), which infects monkeys.

There are two known HIV viruses that cause human infection namely *HIV 1* and *HIV 2*. Human immunodeficiency virus 1 is further divided into *three* groups: 'major' group, M; 'outlier' group, O; and 'new' group, N. Group M has several subtypes or clades (subtypes A to K) (see under 'Epidemiology: Prevalence' below).

       HIV 1   HIV 2

  Group M   Group N   Group O

Subtype A–K

For practical purposes these viruses are collectively referred to as HIV as the mode of spread and clinical manifestations are indistinguishable.

Other human viruses in the family Retroviridae are human T-cell leukaemia virus (HTLV) HTLV 1 and HTLV 2 (Chapter 13).

Epidemiology

Route of spread

Human immunodeficiency virus is closely related to SIV, which causes a similar illness to acquired immunodeficiency syndrome (AIDS) in rhesus monkeys, and there is good evidence now that the virus was introduced into humans from monkeys in the first half of the twentieth century through hunting and human consumption. See Table 11.1 for the three main routes of spread of HIV.

Prevalence

Human immunodeficiency virus 1 has a worldwide prevalence that varies from between <1% in the Western communities to 40% in certain countries in Central and sub-Saharan Africa. The World Health Organization (WHO) estimates that overall there are 30–40 million infected people worldwide and 2–3 million deaths per year; *two thirds of the burden of infection is in African countries.* Clade B virus is found

Table 11.1. *Three main routes of spread of HIV.*

Mode of spread	At-risk groups
Sexual: HIV is a sexually transmitted infection (STI). Virus is present in semen and cervical secretions. Unprotected penetration sexual intercourse has a high risk of transmission. Coexistent ulcerative STIs such as herpes increase the risk of transmission.	*Homosexual*: This has been by far the major route of transmission in the Western world. *Heterosexual*: Main source of transmission in Central sub-Saharan Africa, and South East Asia and the Indian subcontinent. In the UK now it accounts for more than a third of infections.
Vertical (mother to child): The most important route in sub-Saharan and Central Africa. About 24% (15–40%) rate of transmission; with intervention (see 'Management' below) risk can be reduced to <3%. Risk is highest if mother has a high HIV viral load.	*In utero*: Transmission may occur in <5% of cases. Chorio amnionitis increases the risk. *Perinatal*: The majority of infections are transmitted at the time of delivery due to exposure of the fetus to contaminated maternal secretions. Premature or prolonged rupture of membranes increase the risk. *Postnatal*: Via breast milk. Breast feeding increases the risk of transmission by up to 28%.
Bloodborne	*Blood and blood products and organ donation*: Blood transfusion with contaminated material has a high risk of transmission. This route has been virtually eliminated from the developed countries by HIV screening of all donors. *Intravenous drug users, tattoos and piercing equipment*: Sharing of contaminated and using unsterile and contaminated equipment. *Needle-stick injuries and health care associated*: HIV infection has been transmitted in the healthcare setting from both healthcare workers to patients and vice versa. Overall risk of transmission after a needle-stick injury is 0.3%, the risk being highest if the injury is with a hollow needle used to withdraw blood from an infected patient.

mostly in the West within the homosexual fraternity. Clades A, C and E are associated with the heterosexual epidemic in Africa and Asia.

Human immunodeficiency virus 2 is confined to small numbers in West Africa, and a lower prevalence of infection within European countries with links to western Africa (e.g. Portugal and Belgium).

Table 11.2. *World Health Organization staging of infection according to clinical presentation and CD4 count.*

	CD4 count (cells/L)		
	>500	200–499	<200
Acute HIV, asymptomatic or PGL	A1	A2	A3
Symptomatic (not A or C)	B1	B2	B3
AIDS defining illness	C1	C2	C3

PGL, persistent generalized lymphadenopathy.

Incubation period
Usually 2–6 weeks, but may be as long as 3 months.

Pathogenesis
Human immunodeficiency virus infects the cells belonging to the cell-mediated immune system, e.g. *helper T lymphocytes (CD4 cells) and monocytes*, by attaching to the CD4 molecule on the cell surface, which acts as the receptor for the virus. Chemokine receptors (CCR5 and CXCR4) are also required as co-receptors for the virus to attach and gain entry to these cells. Once inside the cell, the RNA is transcribed into DNA, which integrates in the cellular DNA.

As CD4 cells are the very cells responsible for T-cell mediated immunity, this leads to the acquired immunodeficiency syndrome (AIDS). See Table 11.2.

Infectious period
Patients are infectious throughout life, infectivity is highest during the acute illness or seroconversion phase and once full-blown AIDS develops, e.g. at times when there is high HIV viral load in the blood.

At-risk groups
These depend on the likely mode of transmission.
- *Sexual*: Those engaging in either homo- or heterosexual unprotected intercourse with frequent and casual sexual partners.
- *Vertical*: Babies born to infected mothers.
- *Blood or blood borne*: intravenous drug users, those undergoing tattoos and body piercing, iatrogenic through unscreened blood or blood products, and from infected healthcare workers (HCWs) to patients or vice versa during exposure-prone procedures.

Clinical
Both HIV 1 and 2 cause clinically indistinguishable illness; however, HIV 2 progresses far more slowly to AIDS.

Acute HIV seroconversion illness

Most patients do not have any clinical illness at the time of seroconversion. However, glandular fever-like illness, hepatitis, meningitic illness and thrombocytopenia have been described as a part of seroconversion illness. There is a high level of HIV viraemia at this time.

Asymptomatic chronic infection

After acute infection a steady state evolves between the virus and the immune system. The infected CD4 cells that die are replaced rapidly. This stage may last for 5–15 years and is characterized with low viral load and a normal CD4 lymphocyte count. Some patients may develop persistent generalized lymphadenopathy (PGL).

AIDS

This is heralded by an increase in HIV viral load and a decrease in the CD4 lympho-cytes, which leaves the patient open to opportunistic infections and other conditions associated with immune deficiency states. The so-called AIDS defining illnesses can be grouped under the following headings.

Infections

Bacterial

- Tuberculosis: *Mycobacterium tuberculosis* (pulmonary, gastrointestinal); *Mycobacterium avium complex* (gastrointestinal, lymph nodes, skin and other sites).

Fungal

- *Pneumocystis jirovecii* (pneumocystis pneumonia (PCP)).
- *Candida albicans* (oral, oesophageal thrush).
- *Cryptococcus neoformans* (meningitis).

Viral

- Cytomegalovirus (CMV) (retinitis, gastrointestinal infection, central nervous system (CNS) infection).
- Varicella-zoster virus (VZV) (shingles).
- JC polyoma virus (CNS infection).
- Herpes simplex virus (HSV) (skin, mucus membrane, genital).
- Epstein–Barr virus (lymphadenopathy, hairy oral leukoplakia).

Other

- *Toxoplasma gondii* (CNS infection, lymphadenopathy).
- *Cryptosporidium* (chronic gastrointestinal infection).

Malignancies

- Kaposi's sarcoma (endothelial sarcoma driven by human herpes virus 8 (HHV8)).
- Epstein–Barr virus driven lymphomas.

Table 11.3. *Laboratory diagnosis of HIV infection.*

Clinical indication	Test	Significance
Acute HIV infection or suspected seroconversion	HIV antibody and antigen HIV RNA	Positive result indicates infection. Result must be confirmed by testing a repeat follow-up specimen.
HIV screening	HIV antibody (must use the most sensitive available assay)	The initial positive assay result must be confirmed by other tests and by testing a repeat follow-up specimen.
Neonatal HIV infection	PCR for HIV pro-viral DNA or HIV RNA	Positive result indicates infection. Test should be repeated for confirmation. (Presence of HIV antibody alone before 18 months of age is NOT diagnostic of neonatal infection as it may be maternal in origin.)
Follow-up of infected patients	Quantitative HIV RNA PCR (viral load)	High level is indication for treatment. Positive PCR in patients on treatment and with previously undetectable virus may indicate viral drug resistance or non-compliance to therapy.

- Non-Hodgkin's lymphoma.
- Carcinoma of the uterus or cervix.
- Skin carcinomas.

Neurological
- Aseptic meningitis.
- Human immunodeficiency virus encephalopathy.
- Intracranial mass or lesion.
- Wasting or unexplained weight loss.

Death is usually as a consequence of one of the AIDS defining illnesses rather than HIV infection per se.

Laboratory diagnosis

See Table 11.3.

HIV antibody
Human immunodeficiency virus is a chronic infection in 100% of cases and the virus persists in the presence of antibody, so antibody positivity is indicative of infection and HIV antibody tests are used as the screening test for infection. Because no test is
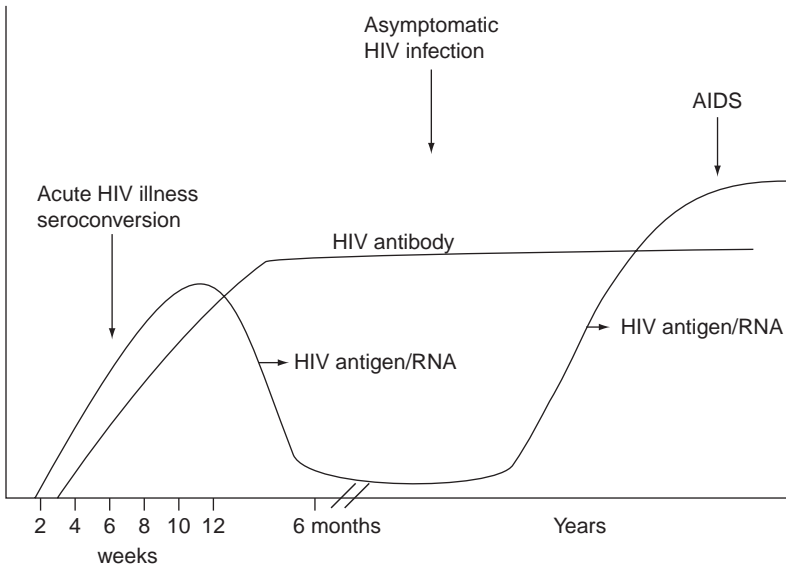
Fig. 11.1. Serological markers in HIV infection.

100% specific positive results *must* be confirmed by a battery of tests and by testing a repeat follow-up sample.

HIV antigen
This appears 3–7 days before the antibody, and is therefore helpful in making an early diagnosis in acute HIV infection (Fig. 11.1). Testing for HIV antigen reduces the so-called 'window period', which is the time from infection to a positive HIV antibody test (Fig. 11.1).

HIV RNA PCR
This is used to diagnose acute infection and then to monitor the progression of disease and treatment response. All infected patients are monitored at three-monthly intervals. The goal of treatment is complete suppression of viral replication (as denoted by negative PCR); a positive HIV RNA PCR in patients on treatment may indicate non-compliance to therapy or drug resistance and a change of drug regimen.

HIV RNA PCR is done on an EDTA blood sample. The plasma must be separated within 6 hours for this test, so inform the laboratory before taking samples.

HIV pro-viral DNA PCR
This looks for the viral DNA integrated in the cells and is used to diagnose infection in neonates as the antibody detected in neonates may reflect maternal antibody. This is now being replaced by HIV RNA PCR as it is equally sensitive in diagnosing infection.

Diagnosis of congenital or vertical HIV infection in neonates

HIV RNA or pro-viral DNA PCR should be tested for at birth, 6 weeks and 12 weeks of age followed by an antibody test at 18 months to show clearance of maternal antibody. *A positive PCR or persistence of antibody beyond 18 months is indicative of vertical transmission.*

Management

Treatment

Human immunodeficiency virus infection

Not all infected patients need be on treatment. The *indicators for treatment* are the clinical status (AIDS defining illness), high HIV viral load and/or low CD4 count. There are several antiretroviral drugs available now for treatment of HIV (Chapter 50). As the virus develops drug resistance rapidly to single drugs, these drugs are used in combination as triple therapy referred to as *highly active antiretroviral therapy (HAART)*. The drug combinations contain at least one nucleoside analogue and one protease inhibitor. The treatment should be discussed in detail with the patient, and drugs chosen to maximize compliance so as to avoid development of drug resistance.

Patients are monitored for response to therapy by regular testing for HIV RNA (viral load). Viral load falls rapidly within 4–6 weeks of the start of treatment, and the *aim of the therapy* is to maintain the viral load at an undetectable level. The fall in viral load is accompanied by a consequent improvement in the immune system due to a rise in CD4 cell count. Drug resistance due to viral mutations is heralded by a rise in viral load and calls for a change in drugs being used.

Patients need to be on the antiretroviral drugs for life, but their use has changed the clinical outcome of infection with most patients living a normal life.

Intercurrent infection or disease

Treatment of opportunistic infections and malignancies is equally important and depends upon the presenting infection or disease.

Prophylaxis

There is no effective HIV vaccine. Vaccine research has been going on for many years, but the biggest barrier to development of a successful vaccine is the inability of the host to develop protective antibody to the virus, the genetic variability of the virus and its ability to mutate rapidly.

Antiretroviral drugs are used as *post-exposure prophylaxis (PEP)* for healthcare workers sustaining accidental exposure or needle-stick injuries from HIV infected patients, or those having at-risk sexual exposure. Triple therapy is given for 4 weeks.

Antiretroviral therapy of pregnant mothers from 14 weeks onward and at labour, followed by *prophylactic treatment of the newborn* for 6 weeks, has reduced the incidence of vertical infection from about 25% to <3% provided that breast feeding is also avoided.

Infection control

The mainstays of prevention are:
- screening of all blood, organ and tissue donors and excluding the infected from donating
- 'safe sex' and use of a barrier method for sexual intercourse
- needle exchange schemes for intravenous drug users.

Useful website

www.avert.org

12 Human herpes viruses types 6, 7 and 8 (HHV 6, 7 and 8)

The viruses

Human herpes viruses 6, 7 and 8 all are double-stranded DNA viruses and belong to the family Herpesviridae.

- HHV6 (beta herpesvirus)
- HHV7 (beta herpesvirus)
- HHV8 (gamma herpesvirus)

Epidemiology

Route of spread

- HHV6: aerosol transmission and saliva from mothers to babies and breast milk.
- HHV7: aerosol transmission and saliva from mothers to babies and breast milk.
- HHV8: there is some evidence of sexual spread via semen and possibly vertically from mother to child. HHV8 has been transmitted to transplant recipients from donor organs.

Prevalence

- HHV6 infection is ubiquitous and occurs worldwide. Infection often occurs after 4 months of age, as maternally acquired immunity wanes.
- HHV7 infection is ubiquitous and occurs worldwide. Most children (95%) acquire the infection by 5 years of age.
- HHV8 infection is more prevalent in Italy, Greece, Israel and Saudi Arabia than in northern Europe. These countries have a higher prevalence of Kaposi's sarcoma. In the UK, the HHV8 antibody prevalence is <5% in blood donors and 30–50% in HIV-positive men who have sex with men (MSM). Human herpes virus 8 antibody prevalence is 85% in patients with Kaposi's sarcoma.

At-risk groups

Immunocompromised patients are at increased risk of more severe infection and clinical disease.

Clinical

Symptoms

- HHV6 causes sixth disease (or roseola infantum), usually in infants between 4 months and 2 years of age. It is also known as exanthum subitum (sudden rash).

Children usually have a sudden spiking high fever (39–40 °C), followed by a mild maculopapular rash. The fever can cause convulsions. Rare infection in adolescents and adults has been associated with seizures, glandular fever-like illness and hepatitis, particularly in immunocompromised patients. These are usually reactivated infections of latent virus in association with CMV reactivation. There are two genetically distinct variants of HHV6 (HHV6A and HHV6B). HHV6A has not been associated with disease; HHV6B is associated with the symptoms listed above.
- HHV7 causes similar symptoms to HHV6 but is less pathogenic.
- HHV8 infection is associated with Kaposi's sarcoma in HIV-positive and HIV-negative persons.

Laboratory diagnosis

These viruses are rarely diagnosed in clinical microbiology and virology laboratories, except in immunocompromised patients and very young children with meningitis or encephalitis. Molecular assays are available in some laboratories for testing cerebrospinal fluid samples. Other testing is available in reference laboratories (antibody tests, virus culture).

Management

Treatment
There is no proven antiviral treatment, although some studies have suggested that ganciclovir may be beneficial (HHV6 and 7 are closely related to CMV).

Prophylaxis
There are no vaccines available.

Infection control

There are no recommendations for infection control precautions with patients infected with HHV 6, 7 and 8.

13 Human T-cell leukaemia virus (HTLV)

The viruses

Human T-cell leukaemia viruses 1 and 2 are retroviruses (like HIV) and belong to the family Retroviridae. However, they belong to the genus oncovirinae (onco = oncogenic), whereas HIV belongs to a separate genus of lentivirus (lenti = slow). Like HIV they possess a reverse transcriptase enzyme, which converts the viral RNA into DNA in the first step of the replication cycle. This pro-viral DNA is capable of integrating in the cellular DNA.

Epidemiology

Human T-cell leukaemia virus 1 was first isolated accidentally in 1979 from a human T-cell line, during experiments to stimulate cells so they could be maintained in cell culture for a longer period of time. The virus was quickly associated as the cause of adult T-cell leukaemia (ATL), which had been described in 1977, and because of a clustering of cases in southern Japan it was suspected to have an infectious aetiology. It was the first human retrovirus to be isolated (pre-dating the isolation of HIV). A few years later the second human retrovirus HTLV 2 was also isolated in the human T-cell line.

Human T-cell leukaemia viruses 1 and 2 are closely related, with some serological cross-reactivity between the two.

Route of spread

Both HTLV 1 and 2 are blood-borne viruses with essentially similar routes of spread as HIV. See Table 13.1.

Prevalence

Human T-cell leukaemia virus 1

About 10 million people are infected worldwide, and most infection is asymptomatic. The vast burden of infection is in Japan (southern), Caribbean, central and south America, and Africa. The prevalence of antibody in southern Japan is about 15% in those over 40 years of age. The prevalence in the young is very low (1%), this is due to a cohort effect whereby the high prevalence in the older age group is due to the high

Table 13.1. *Routes of spread of HTLV.*

Route of spread[a]	HTLV 1	HTLV 2	Comments
Vertical (mother to baby)			
In utero	Yes, uncommon	Not known	Breast feeding accounts for most cases of vertical transmission of HTLV 1, and 5% of all HTLV 1 infections in Japan are through this route. The exact risk of HTLV 2 through breast milk is not known but it has been isolated from breast milk, so can potentially be transmitted through this route.
Breast feeding 20% of breast fed will acquire infection as compared to 1–2% of bottle fed.	Yes, commonly	Probable	
Sexual			
Heterosexual	Yes, 10 times higher risk of transmission from male to females than vice versa	Probable	Ulcerative genital lesions and multiple sexual partners increase the risk of acquisition of infection.
Homosexual	Yes	Probable	
Parenteral			
Blood/blood products	Yes	Yes	Risk is highest where cellular blood components are involved. Plasma alone has very little or no risk.
Intravenous drug use	Yes	Yes	Sharing of equipment.

Note:
[a]Risk of transmission is highest from those with a high viral load.

rate of transmission when they were born, and the low rate in the young now is due to a reduction in transmission rates due to interventions (see 'Infection control' below).

In the Caribbean, central and south America, and Africa the prevalence varies from 5–15%.

In the USA and Europe there is very low (<0.1%) prevalence, infection being mostly identified in immigrants from endemic countries.

Human T-cell leukaemia virus 2

This has a restricted distribution, primarily in the Americas and Africa. In the USA and Europe infection is limited to intravenous drug users (IVDU), with a reported prevalence of 10–15% in this group.

Incubation period

As most infection is asymptomatic it is difficult to define the time of infection from exposure, but it is believed to be about 1–2 months for both HTLV 1 and 2.

Infectious period

Both HTLV 1 and 2 cause chronic infection, therefore infectivity is life long.

At-risk groups

As indicated by transmission routes these include:
- children born to infected mothers especially if breast fed
- sexual partners of infected individuals, especially female partners of infected males
- those who receive infected blood products (containing cellular components)
- intravenous drug users, especially those sharing equipment.

Clinical

Both HTLV 1 and 2 infect the T lymphocyte cells.

Human T-cell leukaemia virus 1

Although most infected patients will remain symptom free, there are two major clinical illnesses associated with HTLV 1.

Adult T-cell leukaemia or lymphoma (ATL)

Human T-cell leukaemia virus is an oncogenic virus, and is therefore capable of transforming the cells (T-cells) that it infects. This is the common clinical presentation of HTLV 1 in Japan. Typically ALT takes 30–50 years to develop after HTLV 1 infection, and is commonly seen in those who have acquired the infection vertically. About 3–5% of those with HTLV 1 infection will develop ATL; this accounts for about 2500 to 3000 cases of ATL per year, most of which are in Japan or affect those of

Japanese descent. Adult T-cell leukaemia is an aggressive form of leukaemia/lymphoma, and may take an acute or chronic clinical course.

HTLV associated myelopathy (HAM) or tropical spastic paraparesis (TSP)

In the Caribbean, HAM or TSP is the clinical disease associated with HTLV 1. The *pathogenesis* is immune mediated causing *demyelination of the long motor neurones* of the spinal cord. Patients present with motor symptoms of: stiff gait, progressive spasticity and weakness of lower limbs, and back pain.

The onset is normally insidious, and some sensory symptoms such as numbness, tingling and burning may also be present. The infection is more common in adults and females. The latent period from acquiring infection to development of HAM/TSP is usually months to years. It is believed that HAM/TSP usually follows those who acquire infection through a sexual route, therefore female predominance is probably due to the high rates of sexual transmission in females.

Human T-cell leukaemia virus 2

So far there has been no specific disease associated with HTLV 2, but HAM/TSP has been described in some patients.

Laboratory diagnosis

Serology is the mainstay of diagnosis as the virus cannot be easily cultured. There is cross-reactivity between HTLV 1 and 2 viruses, therefore HTLV 1 and 2 enzyme-linked immunosorbent assays (EIAs) are used as screening tests. Positive reaction must be confirmed with more specific western blot (WB) tests, which have the advantage of distinguishing between the two infections.

In HAM/TSP the serum HTLV antibody can be demonstrated in the CSF, although the virus cannot be detected as the disease is immune mediated.

Polymerase chain reaction for HTLV 1 can detect the virus genome in the blood and can be used to confirm infection. In ATL, the virus is expressed in the infected tumour cells.

Management

Treatment

There is no effective treatment, and treatment is of the clinical disease e.g. ATL (treated as other similar leukaemia/lymphoma). As HAM/TSP is immune mediated steroids have been tried with some benefit.

Prophylaxis

There is no effective vaccination or other prophylaxis, and prevention is the mainstay (see 'Infection control' below).

Infection control

Preventative measures are as follows:
- Reducing vertical transmission by avoidance of breast feeding. This intervention has virtually eliminated vertical transmission in Japan.
- Screening of all blood or organ donors – highly effective in endemic countries, but of doubtful benefit in countries (such as the UK) with very low prevalence.
- Safe sex using a barrier method.
- Avoidance of sharing drug injecting equipment.

14 Influenza viruses

The viruses

Influenza A and B viruses are RNA viruses and belong to the family Myxoviridae. The RNA genome is split into eight segments, which allows the influenza A strains to exchange genetic information with each other giving rise to new strains all the time.

Both influenza A and B viruses have got two important surface proteins, namely haemagglutinin (H), which is responsible for attaching the virus to the cell surface, and neuraminidase (N). These two proteins are used in the nomenclature of strains (e.g. H2N3 and H5N1).

Epidemiology

Some influenza A strains infect other animals such as birds and pigs. Infections can spread from these animals to humans, sometimes causing an outbreak. We are most familiar with H5 (haemagglutinin type 5) and H7 (haemagglutinin type 7) strains transmitting from birds to humans. Usually, these infections are associated with single cases or clusters of cases in humans. There is always the fear that these avian viruses will mutate, becoming much more infectious to humans and causing a worldwide pandemic.

Influenza viruses are RNA viruses that mutate regularly (especially influenza A virus). Viruses causing outbreaks one year are rarely the same as those causing outbreaks the following year. This is why the composition of influenza virus vaccines is different each year. This gradual change in RNA composition is called *antigenic drift*. It is thought that some new pandemics of influenza A arise because of *antigenic shift*, which usually occurs when two different strains of influenza A virus infect the same cell (especially in pigs, which can be infected with human strains). The two infecting viruses are able to exchange RNA segments in a process called reassortment, resulting in new progeny viruses. If these new viruses were pathogenic for humans, because they were new strains previously unknown to humans, a new worldwide pandemic could result.

Route of spread
Influenza viruses are spread by the respiratory route.

Prevalence
Influenza viruses are constantly mutating. Influenza B viruses are more stable and do not change their antigenic make up regularly. By contrast, influenza A viruses are

constantly mutating, with different strains appearing each year. H5N1 influenza A virus has been creating anxiety in the twenty-first century because of frequent outbreaks in birds, especially in the Far East, but spreading worldwide, with some human infections. The fatality rate in these human cases has been over 50%, and there is close surveillance of these strains in case the virus mutates and becomes more infectious for humans.

The prevalence of human immunity and the incidence of infection varies from year to year, depending on the influenza virus strain circulating in the community. Most people are not immune to the current circulating strain, unless they have received vaccination in the last year. Infection usually occurs between October and March.

Incubation period
1–2 days.

Infectious period
Patients are infectious while they have respiratory symptoms (especially when coughing).

At-risk groups
Immunocompromised patients, elderly persons (>65 years old), patients with chronic heart and lung disease and diabetes.

Clinical

Symptoms
Influenza A and B have similar clinical presentations. However, gastric symptoms such as abdominal pain may be a prominent feature of influenza B infection; therefore it is also referred to as 'gastric flu'.

Primary influenza illness presents with fever, malaise and muscle aches, which are primarily due to an interferon-mediated host immune response. These are often accompanied by respiratory symptoms.

Avian influenza in humans can present as any other influenza case. It can also present as conjunctivitis.

Primary influenza pneumonia may occur in the immunocompromised, but the most serious complication of influenza is secondary bacterial lung infection (e.g. with pneumococcus, streptococcus or staphylococcus). This often results in severe or fatal infection, especially in at-risk groups.

Differential diagnosis
Any respiratory infection can be confused with influenza, although severe cases, with significant malaise, fever, chills and myalgia, are usually correctly diagnosed as influenza.

Table 14.1. *Laboratory diagnosis of influenza virus infection.*

Specimen	Test	Interpretation of test results
Nose and throat swab in virus transport medium	PCR (sensitive and rapid)	If positive, indicates current infection
	Virus culture (takes 1 week to get a result)	If positive, indicates current infection
	Immunofluorescence test (rapid but not very sensitive)	If positive, indicates current infection
	Rapid test device	If positive, indicates current infection
Nasopharyngeal aspirate (in very young children) or bronchoalveolar lavage (if primary influenza pneumonia suspected)	PCR (sensitive and rapid)	If positive, indicates current infection
	Virus culture (takes 1 week to get a result)	If positive, indicates current infection
	Immunofluorescence test (rapid but not very sensitive)	If positive, indicates current infection
	Rapid test device	If positive, indicates current infection
Serum	Complement fixation test (not good for acute diagnosis – it takes about 10 days for antibody to become detectable)	High titres (>64) are suggestive of recent infection (or vaccination). Four-fold rise in antibody titre indicates recent infection (or vaccination)

Laboratory diagnosis

See Table 14.1.

Management

Treatment

Oseltamivir treatment (75 mg bd) or zanamivir started as soon as possible, but not later than 48 hours after onset of symptoms, reduces the morbidity and duration of illness and is recommended by the National Institute of Health and Clinical Excellence (NICE) in the UK. Treatment should be started on the basis of clinical diagnosis in the 'influenza' season. Out of the peak influenza season laboratory confirmation of disease should be sought as most of the cases are likely to be due to respiratory viruses other than influenza. (Note: see the latest national guidance and drug data sheets for drug doses and for suitable patients to treat.)

Prophylaxis

Pre-exposure prophylaxis

Annual influenza vaccination of at-risk groups is recommended. This is a killed vaccine, recommended for those persons at greatest risk of severe infection. It confers 70% protection in vaccinated populations. In addition, healthcare workers (HCWs) and those working in other emergency services should be offered vaccination. As the circulating influenza strains change constantly, the strains included in the current vaccine are selected on the basis of surveillance of the strains most recently in circulation. The influenza A virus components (currently H3N1 and H1N1) change almost every year. The influenza B virus components change every few years.

Post-exposure prophylaxis

The National Institute of Health and Clinical Excellence recommends giving oseltamivir (75 mg od) or zanamivir as post-exposure prophylaxis.

Infection control

Influenza is spread by the airborne route and can be transmitted via hands. It causes outbreaks in hospitals and the community. In hospitals infected patients should be put into single rooms (with the door closed) or cohorted until they are asymptomatic. Staff should wear aprons, gloves and face masks, and should wash their hands with soap and water before and after patient contact. Staff with influenza-like symptoms should not work with patients, especially those with a higher risk of severe symptoms.

If a patient is suspected of having avian influenza, they should be kept in isolation in a negative pressure room with full barrier precautions, including an FFP 2 face mask. A respirator should be worn while performing procedures that are likely to generate aerosol of respiratory secretions. Healthcare staff and others in contact with these patients should be offered seasonal influenza vaccine and prophylactic oseltamivir, and monitored for signs of infection. Special tests are required (usually PCR) for testing for avian influenza virus infection.

15 Measles virus

The virus

Measles is an RNA virus belonging to the family Paramyxoviridae.

Epidemiology

Route of spread
Measles is highly infectious with a high secondary infection rate in contacts, especially household contacts. The infection is spread by the respiratory droplet route.

Prevalence
Measles has a worldwide prevalence with most infections occurring in childhood. In the Western world infection below the age of one year is unusual, due to protection offered by maternal antibody. In the developing world, however, due to poor acquisition of maternal antibody, measles under one year is common and has a high mortality rate because of secondary bacterial infection and poor nourishment. Measles was endemic in the UK with epidemics occurring every 2–3 years prior to the introduction of the childhood measles, mumps and rubella (MMR) vaccination programme in the mid 1980s. However, outbreak clusters have occurred recently because of the fall in the uptake of measles vaccination. Humans are the only host and the World Health Organization estimates that worldwide there are over a million childhood deaths due to measles each year, and has declared measles as one of the infections to be eradicated from the world.

Incubation period
10–15 days, an average of two weeks.

Infectious period
Prodromal period (2–3 days before the rash appears) to about 4 days after the rash appears.

At-risk groups
All susceptible individuals, but especially those who are immunocompromised or pregnant.

Clinical

Symptoms

The typical measles rash is preceded by a 2–3 day prodromal illness, which consists of cough, fever (38°C and above), conjunctivitis and rhinitis. At this stage, typical white lesions called *Koplik's spots* can be seen in the inside of cheek buccal mucosa in a proportion of cases; these are diagnostic of measles. Patients are highly infectious in the prodromal stage and the virus is shed and spread from *respiratory secretions*. The prodromal stage is followed by the appearance of a maculopapular rash, which first appears on the face and neck and then spreads to the trunk and limbs. The rash and fever fade by 4–5 days.

Complications

Secondary bacterial infection

Causing otitis media, laryngotracheitis, bronchopneumonia. These are common in children with measles in developing countries due to poor nourishment, and the cause of high measles mortality rates there.

Encephalitis

- *Acute post-infectious measles encephalitis*: This typically occurs about a week or 10 days after the rash disappears. It is accompanied by headache, irritability, loss of consciousness and fever. This is due to demyelination as a result of auto-immune reaction to the measles virus and therefore the virus cannot be found in the central nervous system. It is relatively uncommon (1 in 1000 cases of measles) and has a high mortality rate.
- *Subacute sclerosing panencephalitis (SSPE)*: This is a rare condition with an incidence of 1 in a million measles cases, but is invariably fatal. Typically symptoms appear several years (10–15 years) after the initial acute attack of measles in early childhood. The first signs are deterioration in intellect (poor performance at school) followed by motor dysfunction and seizures. A defect in the measles virus allows it to persist in the brain by 'hiding' from the immune system. Virus can therefore be found in the brain and cerebro-spinal fluid (CSF) in SSPE by molecular techniques and this confirms the diagnosis.

Immunocompromised patients

Such patients do not develop a rash at all or may have an atypical measles rash. Measles pneumonitis called *giant cell pneumonitis* is common, and may be present without a measles rash. Diagnosis can be confirmed by detecting the virus in respiratory secretions. Measles pneumonitis has a high mortality rate.

Laboratory diagnosis

See Table 15.1.

Table 15.1. *Measles: laboratory diagnosis.*

Clinical indication	Specimen	Test	Significance	Essential information for the laboratory
Acute measles infection	Venous blood OR saliva (in young children)	Measles IgM	Positive result indicates recent infection	Date of onset, symptoms
Acute measles infection	NPA and/or urine	Measles PCR	Positive PCR confirms current infection	Date of onset, symptoms
Past measles infection	Venous blood	Measles IgG	Positive IgG (in absence of IgM) indicates past infection and immunity	If present, history and date of contact with suspected case of measles
Post-vaccination antibody check	Is not indicated as there is no consensus regarding the level of antibody that is consistent with immunity			
Subacute sclerosing panencephalitis	CSF; brain biopsy if done	Measles PCR	Positive result confirms diagnosis	Detailed clinical history including past history of acute measles and vaccination

NPA, nasopharyngeal aspirate.

Management

Treatment

There is no effective treatment for measles. Anecdotally, ribavirin (Chapter 50) has been used to treat measles pneumonitis in the immunocompromised and SSPE, but is of doubtful efficacy.

Prophylaxis

Pre-exposure

Live attenuated measles vaccine as triple vaccine with mumps and rubella (MMR) is recommended at 13–15 months (to allow maternal antibody to disappear as otherwise it may interfere with vaccine take) with a pre-school booster (see Chapter 51). High levels of vaccine coverage (approximately 90%) are required for interruption of spread, and due to the falling uptake in MMR as a result of bad publicity over the past decade several localized outbreaks of measles have occurred in the UK recently. There is no evidence that MMR vaccine is associated with autism and it is regarded as a safe and effective vaccine.

Post-exposure

The MMR vaccine can be given within 72 hours of exposure as post-exposure prophylaxis. Normal immunoglobulin should be given as post-exposure prophylaxis to those at risk in whom MMR is contraindicated (e.g. pregnant and immunocompromised patients) or those who present within 6 days of at-risk exposure.

Infection control

Measles is one of the most highly contagious infections with attack rates of >80% in household contacts. As it is spread by the respiratory route, respiratory precautions (Chapter 52) should be instituted for those at risk. Susceptible healthcare workers (HCWs) who work with at-risk patients should be excluded from work during the incubation period if exposed to measles. All infected HCWs should be excluded from work during the infectious period.

16 Mumps virus

The virus

The mumps virus is a single-stranded RNA virus and belongs to the family Paramyxoviridae.

Epidemiology

Route of spread
Infection is spread by aerosol or hand and fomite contact with infected salivary or respiratory secretions.

Prevalence
Mumps is an endemic childhood infection worldwide. Cases occur all year round, though in temperate climates they tend to peak in colder months. Mumps is highly infectious and outbreaks occur in institutionalized settings such as schools and universities provided there are sufficient numbers of susceptible individuals to allow the infection to spread.

Incubation period
10–21 days, average of about 2 weeks.

Infectious period
Virus is shed in the saliva and respiratory secretions, maximum infectivity is at 48 hours prior to appearance of parotitis, but patients are infectious from about a week before to after the appearance of parotitis. The virus can be shed in the urine for much longer than this.

At-risk groups
All those who are susceptible, particularly post-pubertal males as 20–30% may develop acute mumps orchitis.

Clinical

Acute parotitis
Up to 50% of acute cases of mumps infection in children may be subclinical (i.e. asymptomatic). When symptoms develop they comprise uni- or bilateral parotid

Table 16.1. *Laboratory diagnosis of mumps.*

Clinical indication	Specimen	Test	Significance	Essential information
Acute mumps	Venous blood – clotted	Mumps IgM	Positive result indicates recent infection. Test may take up to a week to become positive so may be negative in first week of infection.	Clinical symptoms, date of onset, relevant epidemiology e.g. history of contact, outbreak etc.
Acute mumps	Parotid or salivary swab, urine	Mumps PCR or mumps culture	Positive result indicates current infection.	As above.
Mumps immunity	Venous blood – clotted	Mumps[a] IgG	Positive IgG (in the absence of IgM) indicates past infection.	History of at-risk contact with date etc.

Note:
[a]It is not possible to test reliably for post-vaccination immunity to mumps because there is no consensus on the amount of antibody that is consistent with immunity. Post-vaccination mumps immunity tests are therefore not recommended.

gland swelling (parotitis); other salivary glands may also be involved. There is usually a 24-hour prodrome of fever and malaise preceding the parotitis.

Complications

The following complications may occur with or without clinical parotitis.

Orchitis develops in 20–30% of young adult or adolescent males. It follows 4–5 days after parotitis (if present) and may involve pain and swelling in one or both testes, which is often accompanied by headache and fever. The resulting severe testicular pain may raise testicular torsion as a differential diagnosis, especially if mumps orchitis is not preceded by parotitis (clinical mumps). However, the symptoms of mumps orchitis subside in 3–4 days. Infertility is a rare occurrence, but testicular atrophy may follow in about 30% of cases.

Similarly inflammation of ovaries (*oophoritis*) may occur in post-pubertal women, but this is much less common (5%). Rarely mumps *pancreatitis* may occur.

Central nervous system complications

Meningitis is the most common complication and may occur in up to 15% of mumps cases. It is normally self-limiting, but may spread to the brain to cause more serious *meningoencephalitis*. Sensorineural deafness in a small number of cases may result as

a consequence of this infection. Central nervous system infection can be difficult to diagnose clinically, especially in the absence of parotitis.

Laboratory diagnosis

See Table 16.1.

Management

Treatment

There is no treatment. Treatment is supportive with pain-killers etc.

Prophylaxis

Mumps vaccine is a component of the childhood vaccination MMR (see Chapter 51), and in countries where MMR is incorporated in childhood vaccination programmes mumps infection has declined. Unfortunately, in the 1980s the mumps component was withdrawn from the UK vaccine due to vaccine-induced mumps meningitis. This has led to a large cohort of mumps-susceptible young adults, resulting recently in several large mumps outbreaks in the university student population of the UK, some of which were controlled by offering mass vaccination to university students.

Infection control

Respiratory droplet precautions (Chapter 52) over the infectious period.

17 Noroviruses

The viruses

Noroviruses are single-stranded RNA viruses and belong to the family Caliciviridae. There are three genogroups of noroviruses. New variants emerge every few years.

Epidemiology

Route of spread

Noroviruses most frequently spread by the ingestion or inhalation of vomit. Patients frequently have no prior warning that they are about to vomit, which results in environmental contamination.

Noroviruses are also transmitted by contaminated food (e.g. bivalve molluscs, such as cockles and oysters, contaminated by human sewage in sea water). Symptomatic food handlers can also contaminate food, resulting in outbreaks.

Prevalence

Norovirus infection is common and 90% of adults have been infected at some time in their lives. Immunity lasts for less than a year, and reinfection can occur with the same or different strains.

Incubation period

24–48 hours after contact with a contaminated environment or eating contaminated food.

Infectious period

From onset of symptoms to 48 hours after symptoms stop.

At-risk groups

All ages.

Clinical

Symptoms

Noroviruses are associated with diarrhoea and vomiting (especially projectile vomiting).

Outbreaks

Noroviruses cause large outbreaks in hospitals, cruise ships and in the community, especially in schools and nursing homes. Outbreaks occur more frequently in the winter (winter vomiting disease), but when new variants emerge outbreaks in the summer occur.

Differential diagnosis

In very young and old persons, sporadic cases and outbreaks of diarrhoea and vomiting can be caused by rotaviruses (especially between December and March). Other enteric viruses such as astroviruses, adenoviruses and sapoviruses (newly identified viruses belonging to the family Caliciviridae) can cause sporadic diarrhoea and vomiting, but seldom cause outbreaks.

Laboratory diagnosis

Liquid faeces samples taken up to 3 days after the onset of symptoms. Samples should be taken as soon after the onset of symptoms as possible. Reverse transcription polymerase chain reaction (RT-PCR) is the preferred laboratory method, but samples can be tested by electron microscopy (Chapter 37) or EIA.

Management

Treatment

There is no antiviral treatment for norovirus infections. Replacement of fluid in severe cases should be considered.

Infection control

- In hospitals, isolation or the cohorting of infected patients is very important. Patients are infectious until 48 hours after the last symptoms.
- Exclusion of symptomatic staff until 48 hours after the last symptoms is also important.
- Do not move patients from a ward with symptomatic patients to other wards or care homes. Do not admit new patients to an infected ward.
- Restrict staff movement.
- Thoroughly clean the ward when the outbreak has finished (48 hours after the last symptomatic case) with diluted hypochlorite or hot soapy water before admitting new patients.
- In cruise ships, where norovirus outbreaks are a big problem, increased passenger awareness, exclusion of symptomatic passengers and prompt decontamination of public areas are the principal tools used to reduce the risk of outbreaks.

18 Parainfluenza viruses

The viruses

Parainfluenza viruses 1–4 are single-stranded RNA viruses and members of the Paramyxoviridae family.

Epidemiology

Route of spread
Parainfluenza viruses are spread by the respiratory route.

Prevalence
Most people experience parainfluenza virus infection several times during their lives. Infections occur throughout the year (parainfluenza virus 3 infections usually occur in the summer, the others usually occur in the winter).

Incubation period
1–3 days.

Infectious period
Patients are infectious while they have respiratory symptoms (especially when coughing).

At-risk groups
Immunocompromised patients (especially bone-marrow transplant recipients). These viruses cause severe and fatal infections in bone-marrow transplant recipients and cause outbreaks in bone-marrow transplant units.

Clinical

Symptoms
Parainfluenza virus infection is associated with fever, respiratory symptoms and pneumonia.

Differential diagnosis
It is impossible to diagnose parainfluenza virus infections clinically and to distinguish infection from many other respiratory viruses and bacteria.

Table 18.1. *Laboratory diagnosis of parainfluenza virus infection.*

Specimen	Test	Interpretation of positive result
Nose and throat swab in virus transport medium	PCR (sensitive and rapid)	If positive, indicates current infection
	Virus culture (takes 1 week to get a result)	If positive, indicates current infection
	Immunofluorescence test (rapid but not very sensitive)	If positive, indicates current infection
Nasopharyngeal aspirate (in very young children)	PCR (sensitive and rapid)	If positive, indicates current infection
or bronchoalveolar lavage (in immunocompromised patients and those in ITUs)	Virus culture (takes 1 week to get a result)	If positive, indicates current infection
	Immunofluorescence test (rapid but not very sensitive)	If positive, indicates current infection

ITU, intensive therapy unit.

Laboratory diagnosis

See Table 18.1.

Management

Treatment

The antiviral drug ribavirin is used to treat infected bone-marrow transplant recipients. Expert advice should be sought, as parainfluenza viruses cause fatal infections and outbreaks in this group of patients.

Infection control

Parainfluenza is spread by the airborne route, and can cause outbreaks in hospitals and the community. In hospitals, infected patients should be put into single rooms (in a negative pressure room or with the door closed) or cohorted until they are asymptomatic. Staff should wear aprons, gloves and eye and face masks (if involved in procedures likely to generate respiratory aerosols) and should wash their hands with soap and water before and after patient contact.

19 Papilloma and polyoma viruses

The viruses

Human papilloma viruses (HPV) and polyoma viruses are DNA viruses and belong to the family Papovaviridae. There are over a hundred known genotypes of HPV, some of which are oncogenic.

The envelope proteins E6 and E7 are transforming proteins and associated with initiating cancer by the oncogenic HPV genotypes.

Papilloma viruses

Epidemiology

Route of spread
- Sexual: the main route of spread for genital warts is sexual, and therefore it is a sexually transmitted infection.
- Vertical: laryngeal papilloma or warts in children are usually due to transmission to the baby at the time of delivery if the mother has genital warts.
- Direct contact with infected material: usually introduced through abraded skin (e.g. sharing towels, swimming pools, walking barefoot). Common skin warts are normally transmitted by this route.

Prevalence
Infection is prevalent worldwide. Human papilloma viruses 1–4 cause skin lesions, HPV 4 typically causes plantar warts and HPV 1 papillomatous lesions on fingers and trunks. Human papilloma viruses 6 and 11 are associated with genital warts and cause respiratory papilloma in children. Human papilloma viruses 16, 18 and other higher numbered genotypes also cause genital infection, which is directly linked to cervical cancer.

Most of the HPV prevalence figures are around genital infection. Human papilloma virus infection is the commonest sexually transmitted infection, and 25–40% of women between the ages of 15–25 years have evidence of HPV infection. There are an estimated 400 million cases of genital HPV infection worldwide. It is estimated that 250 000 women die of cervical cancer each year with 500 000 new diagnoses each year, 80% of which occur in the developing world.

Table 19.1. *Human papilloma viruses and their associated lesions.*

	Lesion	Associated HPV genotype
Non-malignant lesions	Common warts	1, 2, 4
	Flat warts	3
	Genital warts	6, 11
	Laryngeal papilloma	6, 11
Premalignant lesions	Epidermodysplasia verruciformis	2, 3 and others
Malignant lesions	Cervical cancer	16, 18, 31, 33, 35 and others

Incubation period
- Warts: genital warts normally appear 3 months after exposure to an infected partner.
- Cancer: there is usually a latency period of several years from the acquisition of infection to the development of cervical cancer.

Infectious period
Lesions when present are highly infectious; asymptomatic shedding of the virus from the genital tract may occur. Lesions from skin once they disappear are no longer infectious.

At-risk groups
The virus infects both sexes and all age groups. Warts may recur with waning immunity, therefore those who are immunosuppressed and the elderly may have frequent recurrences and extensive lesions.

Clinical

Human papilloma viruses cause infection of the mucus membrane and skin. The virus infects the rapidly replicating epithelial cells and therefore may cause lesions both on the skin and mucus membrane. Different genotypes may be associated with different clinical and anatomical sites of infection although there is an overlap. See Table 19.1.

The most serious clinical manifestation of HPV infection is *cervical carcinoma.* Human papilloma viruses 16, 18, 31, 35 and some of the other higher numbered genotypes are associated with cervical cancer and are called the oncogenic HPV genotypes.

The oncogenic HPV genotypes may cause other squamous cell cancer, e.g. carcinoma of the prepuce in males and vaginal cancer. Rarely it may cause squamous cell carcinoma on other parts of the skin.

Skin
Common warts (verrucae vulgaris) HPV types 1, 2, 4
Small in size, these occur in large numbers anywhere on the body, but most commonly on hands and feet, and have a roughened surface. Patients' complaints are

related mostly to the cosmetic appearance; however, because of the pressure on the warts they are painful when they occur on the soles of the feet.

Flat warts (verrucae planae) HPV types 3
These are flat and smooth and generally affect children.

Epidermodysplasia verruciformis 2, 3 and up to 20 other HPV genotypes
This condition is characterized by the appearance of multiple flat lesions all over the body, which may persist. It is associated with specific T-cell deficiency and is a premalignant condition.

Mucus membrane
Genital warts HPV types 6, 11
Ninety per cent of genital warts are due to HPV genotypes 6 and 11. Genital warts (condylomata acuminata) are the most common sexually transmitted infection (STI) and commonly occur in association with other STIs. The lesions may appear as papules or papillomatous, and the size may vary from small to very large especially when several lesions coalesce into one.

Affected areas in *men*:
- penis – mostly around the glans and prepuce
- urethra
- anus and rectum – especially in those who practise receptive ano-rectal sex, e.g. men who have sex with men (MSM).
  Affected areas in *women*:
- vulva
- vagina
- cervix – typically flat lesions
- anus and perineum.

Laryngeal warts HPV types 6, 11
These occur in the mouth and larynx, especially in small children as a result of vertical transmission at delivery from the mother's genital infection.

Carcinoma
Cervical cancer HPV types 16, 18, 31, 33, 35 and higher genotypes
There is incontrovertible evidence now that cervical cancers are related to HPV infection, and about 70% of all HPV associated cancers are due to genotype 16 and 18, the rest are due to the other HPV genotypes. See also Chapter 44.

Other cancers
Squamous cell carcinoma of the penis, vulva, vagina and some laryngeal carcinomas are also associated with HPV infection.

Figure 1 Herpes simplex virus skin blisters on a patient's arm.

Figure 2 Chickenpox showing cropping lesions.
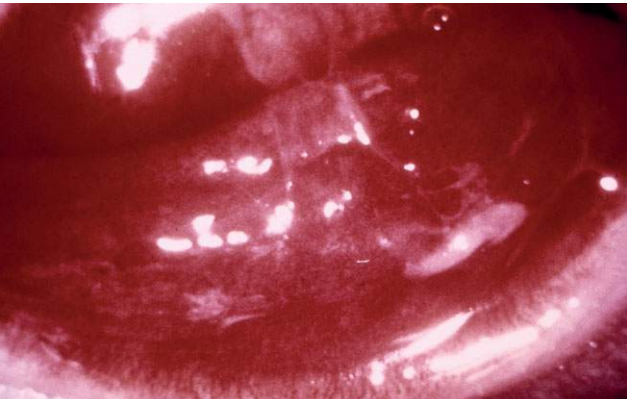
Figure 3 *Chlamydia trachomatis* conjunctivitis.
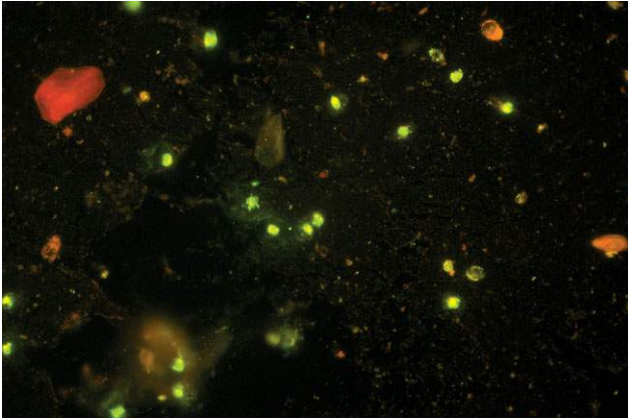
Figure 4 Parainfluenza virus type 3 positive immunofluorescence.

Figure 5 Maculopapular rash.

Figure 6 Orf lesion on hand.
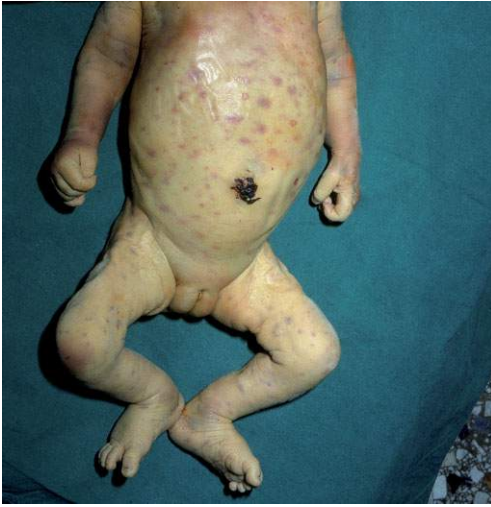
Figure 7 Congenital CMV.

Figure 8 Enzyme-linked immunosorbent assay (EIA) plate.
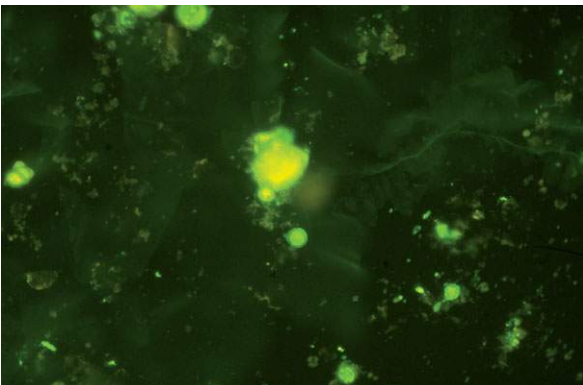
Figure 9 Varicella-zoster virus immunofluorescence.

Figure 10 Uninfected Graham 293 cells.
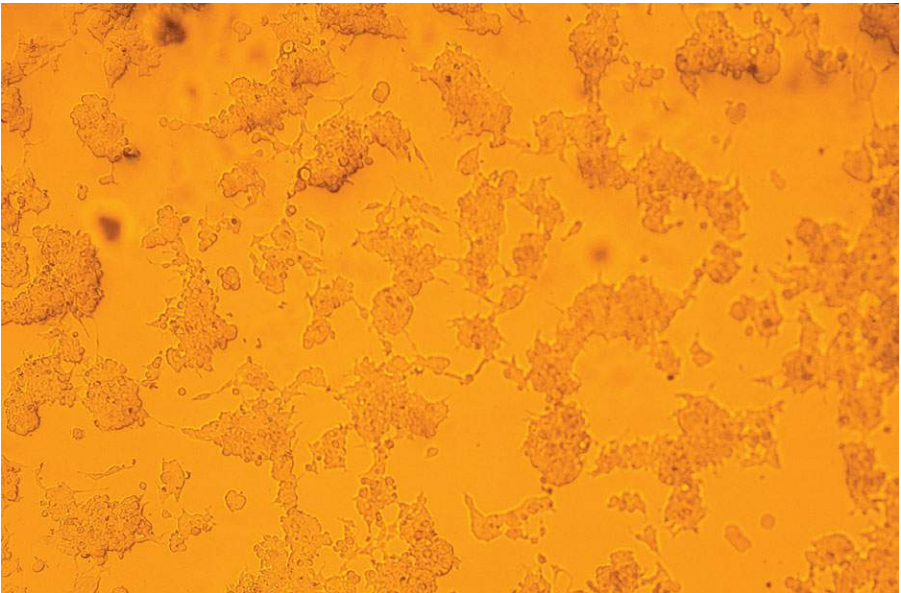
Figure 11 Graham 293 cells showing adenovirus cytopathic effect.

Laboratory diagnosis

Routine laboratory diagnosis is not available and the diagnosis is on the basis of clinical history and appearance of the lesions on examination.

Human papilloma virus can be detected in the lesion biopsy or cervical swab (in the case of cervical lesions) by PCR. This, however, is not recommended for making routine diagnosis for genital warts, which remains clinical. There are several trials going on at present to evaluate the role of HPV PCR testing as a screening tool for cervical cancer. Human papilloma virus testing, although not yet integrated in screening for cervical cancer, is likely to become an integral part of it once the results of ongoing trials are known. There are arguments both in favour of and against using it as a primary screen to identify women at risk of cervical cancer.

Management

Treatment
Warts

There is no specific treatment, as the lesions are self-limiting and normally recede in 6–12 months. If required then ablative treatment with podophylin or liquid nitrogen can be offered.

Cervical cancer

Cervical cancer requires management by the gynaecological oncologists.

Prophylaxis

Two vaccines have recently been licensed for prophylaxis of HPV. Gardasil, which offers protection against four HPV genotypes (6, 11, 16 and 18), and Cervarix, which protects against the two most important oncogenic HPV types (16 and 18). The vaccination schedule for both is of 3 doses spread over 6 months, and both offer good protection for the HPV types included in the vaccine. Both vaccines protect against the oncogenic HPV 16 and 18; in addition Gardasil will protect against types 6 and 11, which are responsible for up to 90% of all genital warts. It is recommended that girls between the ages of 13–25 be offered HPV vaccine. In the UK all pre-pubertal girls aged between 11–13 years of age will now be offered HPV vaccine with a catch-up programme for girls up to 19 years of age.

The effectiveness in the older age groups has not been established yet, and trials are ongoing to determine the safety and cost-effectiveness of vaccinating older women. Similarly, at present the vaccination of boys is not recommended, but it is likely that vaccinating boys would protect them from genital infection and would also have the indirect benefit of reducing the pool of infected males and hence preventing the spread to females who are at risk of developing cervical cancer later in life as a result of HPV infection.

Infection control

Barrier methods should be used during sexual intercourse to prevent infection. Warts should be covered, especially while swimming. Towels should not be shared; walking barefoot on floors in public areas, such as swimming pools, should be avoided.

Polyoma viruses

Polyoma viruses also belong to the family Papovaviridae. There are two viruses that cause infection in humans: polyoma virus hominis 1 and 2 (BK and JC virus).

Polyomavirus hominis 1 or BK virus

This was named after the initials of the patient from whom it was first isolated. It is a common infection of childhood but a specific disease has not been associated with the virus. Most infections are likely to be subclinical, although virus has been isolated in urine from children with cystitis and evidence of infection has been demonstrated in children with acute respiratory illness. The virus reactivates in immunosuppressed patients, especially in renal transplant patients where it causes urethral strictures and in bone-marrow transplant patients where it gives rise to haemorrhagic cystitis.

Treatment comprises reducing immunosuppression where possible. Cidofovir (Chapter 50) is the only antiviral agent that may be effective and has been used to treat severe cases.

Infection can be diagnosed by detection of the virus in urine and blood by PCR. Regular monitoring for BK virus by testing of urine and blood by PCR may help identify infection early. Quantitative PCR (Chapter 49) is particularly helpful as a high or rising viral load, especially in blood, is predictive of clinical illness.

Polyomavirus hominis 2 or JC virus

This was also named after the initials of the patient it was first isolated from. Antibody to the virus is highly prevalent in the general population, but so far it is not clear what primary illness the virus causes. Its clinical importance is in patients who are immunosuppressed due to T-cell dysfunction in whom the virus reactivates to cause progressive multifocal leucoencephalopathy (PML). Progressive multifocal leucoencephalopathy is a progressive degenerative brain disease, which occurs as a result of demyelination and loss of oligodendrocytes. The disease usually begins insidiously with changes in intellect, affectation of motor function or sensory loss. It rapidly progresses to give rise to multifocal neurological signs, and it invariably leads to death within a year.

Prior to effective antiretroviral therapy for AIDS, PML developed in 2–4% of AIDS patients.

There is no effective treatment for PML. Laboratory confirmation of clinical diagnosis is by finding JC virus in the CSF or brain biopsy by PCR.

Simian virus 40 (SV 40)

This is a monkey virus and does not cause human infection. However, in the 1950s it was inadvertently introduced with some contaminated batches of killed polio vaccine grown in monkey kidney cells; all affected individuals have been followed up with no evidence of any associated SV 40 disease.

20 Parvovirus B19

The virus

Parvovirus B19 is a small DNA virus, which belongs to the genera erythrovirus in the family Parvoviridae; it is the only known human parvovirus. Many other mammalian species including dogs have parvoviruses, but they don't cause infection in humans.

The virus replicates in the erythroid precursor cells, which it infects by attachment to one of the blood group antigens (P antigen) expressed at the surface of the cells which act as a receptor for the virus.

Epidemiology

Route of spread

The virus replicates initially in the respiratory mucosa and is spread by droplet (rather than aerosol) transmission by the respiratory route. Attack rate is about 50% in susceptible household contacts, but much lower in the community setting.

There is a short period of viraemia before a rash appears; therefore occasional transmissions by blood transfusion have been recorded where a donor has donated in the prodromal period.

Prevalence

Parvoviruses have worldwide prevalence. Parvovirus is a childhood infection with the prevalence of antibody rising with age; about 50% of young adults show evidence of previous infection.

Incubation period

Is about 12–18 days.

Infectious period

The highest infectivity period is in the prodromal phase, which is 2 days before the rash appears, but patients are not infectious after the rash appears.

At-risk groups

Pregnant women, immunocompromised patients and those with haemolytic anaemia.

Clinical

Erythema infectiosum

This is also called *fifth disease*. About 50% of infections, especially in childhood, are asymptomatic. Symptomatic infection is characterized by a biphasic illness of fever, malaise and upper respiratory symptoms for a few days followed by a fine maculo-papular rash, which is immune mediated. Typically the rash is on the cheeks (malar eminences) hence the name of *slapped cheek syndrome* as the child has the appearance of having been slapped on both cheeks. A generalized rash on the limbs and body may occur; this is usually very transient but a persistent rash for up to 2–3 weeks has been described. *Joint pains (arthralgia)* occur in up to 30–50% of adults with parvovirus infection and may be the only presenting feature. These may persist for several weeks; generally the large joints are involved but small joints may be involved. True rheumatoid factor positive *arthritis* may occasionally occur as a result of infection.

Complications

Transient infection of the erythroid precursor cells leads only to a transient fall in red cells, which does not clinically manifest itself as anaemia in healthy immunocompetent children or adults. However, in the following at-risk groups complications occur due to manifestations of severe anaemia of an aplastic nature.

Infections in pregnancy

Fetal transmission may occur in up to 30% of cases, but congenital malformation or birth defects are not associated with it. Fetal loss occurs in about 7–10% of infected women if infected prior to 20 weeks' gestation. The most severe fetal complication is *hydrops fetalis*, which occurs in 2–3% of infected women. The condition is due to fetal oedema and ascites as a result of severe fetal anaemia, and is managed by giving the fetus an intra-uterine blood transfusion until the condition resolves in a few weeks.

After 20 weeks of gestation, although fetal infection may occur it is not accompanied by untoward fetal outcome.

Evidence also suggests that asymptomatic infection in pregnancy has a higher risk of transmission to the fetus as compared to symptomatic infection, as the former suggests a poor host immune response and failure to clear the virus effectively.

Infection in immunocompromised patients

May result in *chronic parvovirus infection* due to the failure of the immune system to clear the virus. The patient develops chronic intractable aplastic anaemia.

Infection in patients with haemolytic anaemia

Aplastic crisis develops due to red blood cell death and a sharp fall in red blood cells and haemoglobin. The patient is normally viraemic at the time of the aplastic crisis. Once the immune response is mounted, the patient recovers from the aplastic crisis with a reticulocytic response. Typically these patients do not develop a rash.

Table 20.1. *Laboratory diagnosis of human parvovirus B19 infection.*

Clinical indication	Specimen	Test	Significance	Essential information for the laboratory
Diagnosis of acute parvovirus infection	Serum	Parvovirus IgM	Positive result denotes recent infection.	Clinical symptoms, date of onset, any history of any risk factor e.g. pregnancy, immuno-compromised or aplastic crisis.
Diagnosis of acute infection in the immunocompromised and in patients with aplastic crisis	Serum	Parvovirus DNA PCR	Positive result indicates recent or chronic infection. Specific IgM may be negative in immuno-compromised patients due to poor immune response.	Clinical details and symptoms with risk factors if any, date of onset.
Diagnosis of fetal infection	Cord blood by cordocentesis	Parvovirus DNA PCR and IgM if fetus is more than 20 weeks	Positive IgM and/or PCR indicates fetal infection.	Gestational age of the fetus, presence of hydrops.
Check immune status	Serum	Parvovirus IgG by EIA	A positive IgG in the absence of parvovirus-specific IgM indicates past infection.	History of and date of recent contact if any, risk factors for infection.

Laboratory diagnosis

See Table 20.1.

Management

Treatment

There is no specific treatment in immunocompetent patients; the treatment is supportive.

- *Immunocompromised patients and those in aplastic crisis.* Blood transfusions are given to improve and maintain the haemoglobin level. Use of intravenous IgG has been shown to be effective in resolving infection.
- *Hydrops fetalis.* Pregnancy should be monitored by regular ultrasound and intra-uterine blood transfusions should be given to manage fetal anaemia in cases of hydrops fetalis. The hydrops resolves itself once the fetus is able to limit the infection. There is no evidence of long-term damage to the fetus and such pregnancies successfully go to term with a normal outcome.
- *Pregnancy.* Pregnant women with acute parvovirus infection should be referred to an obstetrician so that the pregnancy can be followed and managed appropriately (see above) if hydrops fetalis develops.

Prophylaxis

There is no specific prophylaxis or vaccine.

Pregnant women who are in contact with a known case of parvovirus B19 infection should be tested for parvovirus IgG to establish immunity. Those found to be susceptible should have a repeat test 4 weeks after contact to ensure that they have not had a subclinical infection (50% of adults have subclinical infection).

Infection control

Patients should be isolated, where possible, with respiratory precautions (Chapter 52). Patients with haemolytic anaemia in aplastic crisis do not normally develop a rash and have a prolonged period and a high level of infectivity.

Advice to avoid exposure to infection should be given to patients at risk of parvovirus complications. Patients with infection should also be advised to avoid contact with pregnant women and those who are immunocompromised or suffer from haemolytic anaemia. If in contact with the virus, patients at risk of complications from parvovirus infection should be screened for immunity and observed if susceptible, and managed appropriately if signs of infection develop.

Healthcare workers who have had significant exposure to parvovirus B19 infection either at work or at home, and who work with the at-risk group of patients, should be excluded from work from 7 days to 3 weeks after exposure to cover the incubation period.

21 Pox viruses

The viruses

Orthopox and *parapox* viruses are double-stranded DNA viruses. They are the largest in size of all known viruses.

Introduction

Pox virus infections, with the exception of molluscum contagiosum, are very rare in the UK. Smallpox was eradicated from the world in 1977. The most commonly diagnosed infections in the UK are molluscum contagiosum, cowpox (most often acquired from cats) and orf (transmitted by sheep) and milker's node (acquired from cows). Other pox viruses, such as monkeypox, are endemic in a few tropical and sub-tropical countries, occasionally causing outbreaks in the Western world due to imported animals. All these viruses cause characteristic pustular skin lesions, which develop into large scabs that can leave permanent pock marks. These skin lesions and their distribution are different, facilitating clinical diagnosis. However, clinical diagnosis is not foolproof – with monkeypox, smallpox and chickenpox being mistaken for each other before smallpox eradication in Africa. Laboratory diagnosis used to be made by electron microscopy and via culture in embryonated eggs. Although diagnosis can still be made by electron microscopy, molecular methods, especially for pox viruses, are becoming the most commonly used.

Smallpox

Smallpox is transmitted from human to human through the respiratory route, after close contact with an infected person. Although the virus can be transmitted to and between monkeys, there is no animal reservoir of the virus.

Smallpox has been eradicated from the world after a concerted international vaccination campaign co-ordinated by the World Health Organization (WHO). The last case occurred in Africa in 1977, and the virus is held in two high-security units in the USA and in Russia. There has been some concern about the remote possibility that the virus could be used by terrorists.

Smallpox has an incubation period of 10–12 days. Patients are infectious after the rash has appeared. Once the rash has formed scabs, patients are not infectious. Although virus can be found in scabs, they are not a significant source of infection.

There are two forms of smallpox – variola major, which causes a mortality rate of 20–30% and variola minor, with a case fatality rate of 1%. The most characteristic

feature of smallpox is the rash, which evolves over several days from macule to vesicle to pustule. Finally, a scab forms, which falls off, leaving a pock mark. The rash first appears on the face, then on the arms, and later, on the lower limbs. It is usually more profuse on the face and limbs than on the trunk.

The first symptoms are a sudden onset of fever, headache and backache. The fever often falls on the second or third day, as the rash appears and rises again as the rash becomes pustular. Immunosuppression, pregnancy and malnutrition are likely to be associated with more severe infection.

Chickenpox would be the major differential diagnosis if the disease were ever to emerge again. The chickenpox rash is similar, but is more prevalent on the body (trunk) than on the face and limbs. Smallpox lesions tend to be larger. There are several other pox viruses (e.g. cowpox), which cause vesicular lesions on the skin.

There are no really effective antiviral drugs available to treat smallpox. Smallpox was eliminated from the world by use of the smallpox vaccine. Vaccination in the UK is restricted to those personnel who would be involved in an emergency response to a deliberate release of the virus by terrorists.

Suspected smallpox cases should be treated in strict isolation in negative pressure isolation facilities, preferably in designated specialist units. Staff caring for infected patients must be vaccinated.

Cowpox

Cowpox is a pox virus. The virus is a close relative to the vaccinia virus used for smallpox vaccination. Cowpox used to be commonly transmitted to farmworkers, often milkmaids, from cows. This is now a rare transmission route and human cases these days are usually acquired from cats. Infection can also rarely be caught from contact with bank voles, wood mice and field voles. Cats often acquire infection from rodents and pass it on to humans.

The incubation period is 9–10 days and, usually, just one large pustular skin lesion is most commonly found on the face and hands, reflecting the point of contact with the infected cat. The skin lesions eventually crust over; when the crust falls off, patients are no longer infectious. Patients can sometimes have more systemic symptoms including headache and malaise as well as localized skin redness, swelling and local lymph node involvement. The illness usually lasts from 6–12 weeks. Occasional deaths from cowpox have been recorded and infection can be more severe in atopic patients and immunocompromised patients, who often have a more generalized and widespread infection. There is no antiviral treatment. Occasionally infection can be misdiagnosed as orf or milker's node.

Monkeypox

Monkeypox is also caused by an orthopox virus. It is a rare disease, which most commonly occurs in west and central Africa. Rats, mice, squirrels and rabbits can also be infected by monkeypox virus. Infection outside Africa is rare; there was an outbreak of monkeypox in the USA in 2003 after human contact with pet prairie dogs.

Monkeypox produces an illness similar to smallpox, but milder. Monkeypox infection is associated with the swelling of lymph nodes. Inguinal lymphadenopathy can be pronounced, more so than in smallpox. The incubation period is 7–17 days, after which patients experience fever, headache, backache, malaise and muscle ache. The vesicular rash appears about 3–5 days later, becoming pustular and then scabbing over. The illness usually lasts for 2–4 weeks. In Africa, mortality rates are 1–10%. As in smallpox, infection can spread from human to human via the respiratory route or infected fomites (infected bedding etc.). Smallpox vaccination will protect against monkeypox.

Molluscum contagiosum

Molluscum contagiosum is caused by an orthopox virus. It is the most common pox virus infecting humans worldwide. Infection is most common in children. It causes small (2–6mm) wart-like lesions on the skin, often in clusters on exposed areas of skin (hands, arms, face, neck, chest, abdomen and eyelid margins). They are raised dome-shaped areas of skin with a central dimple. They eventually form a crust and then heal up. Patients rarely have any other symptoms.

Molluscum contagiosum is infectious and is usually spread among young children by direct contact. It can also be transmitted via toys. Although infectious, no exclusion from school, work or swimming pools is necessary, although sharing of towels and sponges should be avoided for those infected. There is no antiviral treatment but squeezing individual lesions will result in the molluscum body, full of infectious virus, to be forced out of the central dimple in the lesion; this will result in the lesion resolving. This is easier after a bath. Freezing (cryotherapy) and burning (diathermy) can also be used. Piercing the lesions with a sharp object dipped in podophylin or phenol is sometimes used for treatment, but this can leave scars.

Orf and milker's node

These diseases have an identical clinical presentation and are acquired by close contact with sheep (orf) and cows (milker's node). They are caused by a parapox virus (Fig. 41.2), which has a different morphological appearance to orthopox viruses (Fig. 41.4) from which it can be distinguished easily. See Chapter 41.

They produce large (1–2cm) vesicular lesions (Fig. 41.3), which become pustular and then scab over. They are often surrounded by a red erythematous area, which can be quite tender to touch. Patients with a severe form of the disease can have symptomatic symptoms such as headache, malaise and fever as well as swollen lymph nodes. There is no treatment and infection cannot be passed on to other humans. Although the lesions may often appear severe, patients can be reassured that symptoms will resolve in 2–3 weeks.

Laboratory diagnosis

Several laboratory methods can be used to diagnose pox and parapox virus infections. Polymerase chain reaction can distinguish between different viruses and some

Table 21.1. *Laboratory diagnosis of pox virus infections.*

Specimens	Test	Interpretation of positive result
Vesicle fluid, vesicle swab or scab	PCR	Specific virus infection
	Electron microscopy	Pox virus or parapox virus infection

are so specific that they can differentiate different strains of the same virus. Electron microscopy can easily distinguish between pox (Fig. 41.4) and parapox (Fig. 41.2) viruses by morphology, but only experienced electron microscopists could accurately distinguish between smallpox, vaccinia and molluscum contagiosum viruses. See Table 21.1.

Varicella-zoster virus tests should also be conducted as part of the differential diagnosis (see Chapter 28).

22 Rabies virus

The virus

Rabies virus belongs to the family Rhabdoviridae.

Epidemiology

Route of spread

Rabies is a zoonotic disease that is transmitted from animals (particularly dogs, foxes, wolves, jackals, monkeys and bats) to man. Infection can be transmitted from a bite or scratch via a puncture wound through the skin, or through a lick on an open wound or sore.

Prevalence

Rabies occurs in every region of the world, but there are some countries, such as the UK, Hawaii, Panama and Australia, that have eradicated the infection. Rabies is common in India, Russia, Africa, the Phillipines, Central Europe, China and Japan. Rabies can be reintroduced into countries that have eradicated it, so it is always wise to check if it is present in countries you are visiting (so you can be aware of the risk and the need for prophylactic rabies vaccine).

Incubation period

The incubation period in man is usually 1–3 months, but it can be as short as 10 days and as long as 2 years, following exposure. The incubation period in the dog is usually from 14 to 60 days, but it may be much longer.

Infectious period

Once infected animals remain infectious via infected saliva. Rabies is usually a fatal infection in animals but asymptomatic infection, especially in bats, is recognized. The latter may provide a long-term reservoir of infection.

At-risk groups

People are at risk when they have not received prophylactic vaccine and they are bitten or scratched by an infected animal, or licked on an open wound, in a country where rabies is prevalent.

Clinical

Symptoms

For the first 2–4 days, patients usually develop malaise, fever, headache, sore throat and lack of appetite. The virus first multiplies in the tissue around the site of inoculation. It then moves into local nerves. Pain and tingling around the site of inoculation in the infected limb is usually the first indication that the virus has entered the nervous system. These symptoms usually travel up the limb or spread around the face or neck, depending on the site of infection. Jerky movements and increased muscle tone may well follow. Dilation of the eye pupils and excessive secretion of tears and saliva often occur next. The patient may next become anxious and frightened when examined or disturbed, and the patient's temperature rises to 38–40°C. Localized paralysis may follow, resulting in difficulty in swallowing and in the patient being terrified of drinking. The fear of drinking water (hydrophobia) is very suggestive of rabies. Patients may be very excited or apathetic. With very few exceptions, patients die within a week of the onset of symptoms. Tetanus can cause similar convulsions.

Laboratory diagnosis

Several laboratory methods and clinical specimens can be used to diagnose rabies; all the tests should be performed in a high-security specialist laboratory. In life, a hairline biopsy is usually tested for presence of rabies virus by PCR or immunofluorescence in a reference laboratory. After death, additional specimens such as a brain biopsy can be tested for rabies virus by PCR or immunofluorescence. Negri bodies (rabies virus inclusions in the neuronal cells) are typically seen on brain histology.

Management

Treatment

Once symptoms have become established, there is no effective treatment other than supportive care.

Prophylaxis

Pre-exposure prophylaxis is with 3 doses of rabies vaccine. Post-exposure prophylaxis is either by 5 doses of rabies vaccine, over a period of a month, or, if the risk of rabies exposure is likely, by means of vaccine and human anti-rabies immunoglobulin (half injected around the site of inoculation and half given intramuscularly). It is very important to seek urgent medical advice in the case of a bite or a lick or scratch from a suspect animal abroad, especially if it was behaving aggressively. Even in the case of previous rabies vaccine, it is strongly advised to have post-exposure vaccine where a significant risk of exposure has occurred.

Infection control

Rabies does not spread from human to human, but gloves and an apron should be worn when treating patients with suspected rabies. Healthcare workers caring for an infected patient should be offered rabies vaccination.

23 Respiratory syncytial virus (RSV)

The virus

Respiratory syncytial virus is a single-stranded RNA virus belonging to the family Paramyxoviridae.

Epidemiology

Route of spread
Respiratory syncytial virus is spread readily by direct contact with respiratory secretions, fomites and large droplets through the nose and eyes (but not the mouth). Nosocomial infections are common.

Prevalence
Respiratory syncytial virus has a worldwide distribution. In the developed world it occurs in epidemics in mid winter (November to February in the UK). Infection is common in young children; 70% are infected and 30% have clinical illness in their first year of life. Two per cent of infants have severe lower respiratory tract symptoms. All children are infected by 3 years of age, some having had more than one infection. Immunity is short lasting – just a few weeks or months. In families of pre-school age children as the primary case, 50% of family members will be infected. There are higher attack rates in nurseries and playschools.

Incubation period
3–6 days.

Infectious period
- Children are infectious for 9 days on average, but this can be much longer.
- Adults are infectious for about 2 days.
- Immunocompromised patients can be infectious for several weeks.

At-risk groups
Immunocompromised patients (e.g. those with severe combined immunodeficiency syndrome, bone-marrow transplant recipients, those on chemotherapy, HIV infected patients).

Table 23.1. *Laboratory diagnosis of RSV infection.*

Specimens	Test	Comments
Nasopharyngeal aspirate and bronchoalveolar lavage	PCR	Very sensitive. Can have results in a few hours.
	Immunofluorescence	Less sensitive than PCR. Results in 1–2 hours.
	Culture	Less sensitive than PCR. Results in 5–10 days.
	Rapid test device	Rapid (less than 1 hour) but less sensitive than PCR.
Nose and throat swab in virus transport medium	PCR	Very sensitive. Can have results in a few hours.
	Culture	Less sensitive than PCR. Results in 5–10 days.

Clinical

Symptoms

Respiratory syncytial virus produces a range of symptoms from asymptomatic infection and mild afebrile respiratory symptoms, to severe bronchiolitis and pneumonia. In young children with symptoms, 50–90% have bronchiolitis and 5–40% have pneumonia. Pneumonia occurs in 50–60% of immunocompromised patients, with a mortality rate of 20–80%. Lower respiratory tract symptoms are more common in children under 3 years of age.

- Children have bronchiolitis with expiratory wheezing; 50% have fever. Hypoxia is common in hospitalized children.
- Adults often have non-specific upper respiratory tract symptoms, sore throat, cough, nasal congestion and hoarseness.
- Elderly patients often have an influenza-like illness, but with less fever.

Differential diagnosis

Influenza, parainfluenza, adenovirus and other respiratory viral infections. Respiratory syncytial virus infections in nursing homes can mimic influenza.

Laboratory diagnosis

Several laboratory methods and clinical specimens can be used in diagnosing RSV infection. Serology is not helpful. See Table 23.1.

Management

Treatment

Ribavirin is given as aerosolized particle inhalation for severe cases of bronchiolitis in children, especially in patients with underlying heart or lung conditions and

ex-premature babies. Immunocompromised adults (e.g. bone-marrow transplant recipients) should also be treated. As ribavirin is potentially teratogenic pregnant healthcare workers should avoid exposure to the aerosolized drug particles.

Prophylaxis

Palivizumab is a monoclonal antibody indicated for preventing RSV infection in infants of high risk of mortality (e.g. ex-premature babies and children under 2 years of age who have received treatment for bronchopulmonary dysplasia or severe congenital heart disease). It is licensed for monthly use in the RSV season.

Infection control

The spread of RSV can be reduced by strict handwashing after patient contact. The use of gloves, aprons, face masks and goggles will reduce the risk of transmission. Isolation in single rooms or cohort nursing reduces the risk to other patients. During the RSV season many paediatric centres screen for RSV before admission so they can cohort nurse the infected babies separately from those who are not infected.

24 Rhinoviruses

The viruses

Rhinoviruses are single-stranded RNA viruses and belong to the Picornaviridae family.

Epidemiology

Route of spread

Rhinoviruses are spread readily by direct contact with respiratory secretions, fomites and large droplets through the nose and eyes. Nosocomial infections are common. The name rhinovirus derives from the fact that these viruses infect the nasal passages, and they are one of several causes of the 'common cold'. There are over 100 serotypes of rhinovirus.

Prevalence

Rhinoviruses have a worldwide distribution. In the developed world they occur in epidemics in autumn, winter and spring, with peaks of infection at these times of the year. Infection occurs in people of all ages, but the incidence is higher in children than adults.

Incubation period

1–3 days.

Infectious period

Infected individuals are usually infectious for about 5 days, when they are sneezing and have a nasal discharge.

At-risk groups

Immunocompromised patients (e.g. those with severe combined immunodeficiency, bone-marrow transplant, chemotherapy and HIV patients) are at greatly increased risk of developing potentially fatal pneumonia.

Clinical

Symptoms

Most (75%) rhinovirus infections are associated with clinical illness. Infections with various serotypes begin in early childhood and continue throughout life, usually

Table 24.1. *Laboratory diagnosis of rhinovirus infections.*

Specimens	Test	Comments
Nasopharyngeal aspirates and bronchoalveolar lavages	PCR	Very sensitive. Can have results in a few hours.
	Culture	Less sensitive than PCR. Results in 5–10 days.
Nose and throat swab	PCR	Very sensitive. Can have results in a few hours.
	Culture	Less sensitive than PCR. Results in 5–10 days.

resulting in typical 'common cold' symptoms. The infection has no prodrome; sneezing and nasal discharge are usually the first symptoms to become apparent. The nasal passages, paranasal sinuses, oropharynx, eustacian tubes, middle ear, larynx and large airways can all be involved. Symptoms include sneezing, nasal obstruction, sore throat, facial pressure, hoarseness, cough, headache, malaise and fever. Symptoms usually last for about 5 days. Complications such as acute bacterial otitis media and acute bacterial sinusitis may occur, but in a minority of those infected.

Differential diagnosis
Influenza, parainfluenza, RSV, adenovirus and other respiratory viral infections.

Laboratory diagnosis

Diagnosis is usually clinical and laboratory investigations are normally not indicated. If required several laboratory methods and clinical specimens can be used to diagnose infection (Table 24.1). Serology is not helpful.

Management

Treatment
There are no specific antiviral treatments available, although compounds with anti-rhinovirus activity have been identified in the laboratory. Treatments for headache, nasal congestion, cough and sore throat are appropriate.

Prophylaxis
There are no viral vaccines available for preventing rhinovirus infections.

Infection control

The spread of rhinoviruses can be reduced by strict handwashing after patient contact. Use of gloves, aprons, face masks and goggles will reduce the risk of transmission. Isolation in single rooms or cohort nursing reduces the risk to other patients.

25 Rotavirus

The virus

Rotavirus is a double-stranded RNA virus belonging to the family Reoviridae. It is called rotavirus because by electron microscopy the virus particle resembles a wheel (see Fig. 25.1).

Epidemiology

Route of spread

Rotavirus spreads among humans by the faecal–oral and respiratory routes. There are seven different groups (A–G). Group A rotaviruses are the major cause of human infection, but groups B and C also infect humans. Rotavirus infections occur in most animal species, and although they can infect humans, are mostly associated with mild or no human disease, and no onward transmission.

Prevalence

Rotavirus infections are common in childhood and have a high morbidity with associated mortality in poor developing countries. In the UK, by the age of 5 years 90% of children have been infected. Reinfection can occur throughout life, but only the first infection after loss of maternal protection is associated with severe symptoms, and reinfections in older children and adults tend to be mild or asymptomatic. Infection usually occurs between November and March.

Incubation period

The incubation period of rotavirus is 1–2 days.

Infectious period

Patients are most infectious when symptomatic with diarrhoea and vomiting.

At-risk groups

Infection most frequently occurs in very young children under the age of 2 years. Reinfection occurs throughout life, but elderly persons over 60 years in age are particularly susceptible to symptomatic reinfection because of declining immunity.
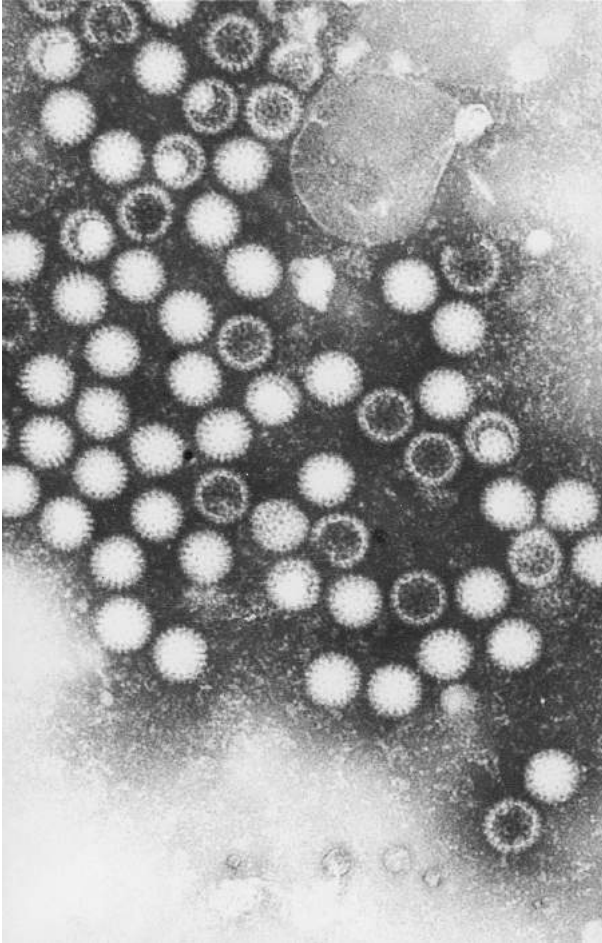
Fig. 25.1. Electron micrograph of the rotavirus.

Immuno-compromised persons are more likely to have more severe and persistent symptoms, with prolonged diarrhoea and virus excretion.

Clinical

Symptoms
Rotavirus infection is associated with watery diarrhoea and vomiting.

Differential diagnosis
Other viruses such as noroviruses, astroviruses, sapoviruses and adenoviruses can cause sporadic cases of diarrhoea and vomiting. Rotaviruses are seldom associated with outbreaks of diarrhoea and vomiting, but outbreaks can occur in very young and old patients.

Table 25.1. *Laboratory diagnosis of rotavirus infections.*

Specimen	Test	Interpretation of results
Faeces	RT-PCR	If positive, indicates current infection.[a]
	EIA	If positive, indicates current infection.
	Dip stick/rapid test device	If positive, indicates current infection.
	Electron microscopy	If positive, indicates current infection.

Note:
[a]The increased sensitivity of the RT-PCR for rotavirus detection means that asymptomatic infection, characterized by low viral loads, can be detected, and results must be interpreted with caution.

Laboratory diagnosis

See Table 25.1.

Management

Treatment
There is no antiviral treatment. Rehydration is appropriate in severe cases, especially in very young children.

Prophylaxis
There are oral vaccines, which can prevent rotavirus associated disease, but none are licensed in the UK or the West. These vaccines are being trialled in countries with a high incidence of rotavirus infection in children e.g. countries in the Indian subcontinent and Africa.

Infection control

Rotaviruses are spread by the faecal–oral route and can cause outbreaks in hospitals and in the community. In hospitals, infected patients should be put into single rooms (with the door closed) or cohorted until they are asymptomatic. Staff should wear aprons and gloves, and should wash their hands with soap and water before and after patient contact.

26 Rubella virus

The virus

Rubella virus is a single-stranded RNA virus, which is the only member of the genus *Rubivirus* within the family Togaviridae. The outer envelope protein E1 is the viral haemagglutinin protein responsible for binding to the cell receptors to initiate infection.

Epidemiology

Prevalence

Rubella has a worldwide prevalence. Before the introduction of vaccination, it circulated in epidemic form with an epidemic cycle every 6–8 years. In countries with effective childhood rubella vaccination programmes this pattern has been interrupted, as has been the number of reports of endemic cases. In countries without vaccination programmes it remains an infection of childhood. About 15–20% of young adults remain susceptible, putting them (especially pregnant women) at risk of acute infection as the virus is endemic and continues to circulate in the community.

Route of spread

Infection is spread via respiratory secretion droplets. The virus is highly infectious with attack rates of 50–80% in susceptible individuals in communities during outbreaks.

Incubation period

The rash usually develops 16–18 days after exposure, but the incubation period may range from 14–21 days. Infection is first initiated in the respiratory epithelium and then spreads and replicates in the regional lymph node. This is then followed by viraemia and dissemination of the virus to multiple sites.

Infectious period

Maximum viral shedding from the respiratory tract of infected individuals occurs from 5 days before to 7 days after the appearance of the rash.

At-risk groups

Pregnant women, especially those in the first trimester of pregnancy (see below).

Clinical

Postnatal rubella

Around 50–80% of infections are asymptomatic; infections in childhood are likely to be asymptomatic. Symptoms are usually mild and consist of fever and a maculopapular rash, which may be transient. Arthralgia (joint pains) or frank arthritis may occur in up to 30% of adolescents and young adults with rubella, but are less common in children. Usually big joints are involved and pain may be fleeting in nature. Development of post-auricular shotty lymph nodes is almost pathognomic of rubella.

Congenital rubella

Sir Norman Gregg, an Australian ophthalmologist, was the first to describe congenital rubella syndrome (CRS), which consists of the classical triad of bilateral cataract, microcephaly and sensorineural deafness. Other features are hepatosplenomegaly, thrombocytopaenia and a purpuric rash.

The risk of fetal malformation is highest (80%) after maternal rubella in the first trimester especially in the first 6 weeks of pregnancy. The risk of fetal malformation decreases from the second trimester onwards, and maternal infection after 20 weeks of gestation although leading to fetal infection has little risk of fetal abnormality (i.e. congenital malformation), although a minority of infants may develop sensorineural deafness later on; therefore long-term follow up is advisable.

Complications

Postnatal acute rubella is a self-limiting illness; in adults rare complications are rubella hepatitis and encephalitis.

Acute infection, especially in the first trimester of pregnancy, leads to fetal infection and congenital infection (see above).

Laboratory Diagnosis

See Table 26.1.

Management

Treatment

- Postnatal rubella: there is no treatment and acute rubella is a self-limiting illness; complications are rare and management is supportive.
- Congenital rubella: prognosis depends upon the fetal age at acquisition of congenital infection. The neonate should be followed as late sequelae of congenital infection, especially deafness (not apparent at birth), may develop. There is no specific treatment, and treatment will depend upon the management of the presenting condition (e.g. sensorineural deafness, cataract etc.).

Table 26.1. *Laboratory diagnosis of rubella infection.*

Clinical indication	Specimen	Test	Significance	Essential information for the laboratory
Diagnosis of acute rubella infection in children and adults	5–10ml of clotted venous blood	Rubella IgM Rubella IgG avidity	Positive IgM result denotes recent infection. Spurious positive IgM result may occasionally occur therefore result should be confirmed by rubella IgG avidity test – mature (high avidity IgG) antibody indicates that infection has occurred more than 3 months ago.	Clinical symptoms, date of onset, history of contact, if pregnant then period of gestation.
Diagnosis of congenital infection in neonates	As above	Rubella IgM	Presence of rubella IgM in a newborn is indicative of congenital infection as IgM does not cross the placental barrier.	History of suspected or confirmed maternal rubella infection. Clinical signs and symptoms.
Diagnosis of fetal infection	Fetal blood by cordocentesis (taking of fetal cord blood under ultrasound guidance)	Rubella IgM Rubella PCR	Positive result indicates fetal infection. Positive IgM must be confirmed.	History of suspected or confirmed maternal rubella infection.
Check for past infection or immunity	5–10ml of clotted venous blood	Rubella IgG	Positive result indicates immunity due to past infection or vaccination.	History of vaccination.

Prophylaxis

Post-exposure

Pregnant women with suspected rubella contact should have a blood test for rubella IgG antibody to determine their immune status. Those who are found to be susceptible should have a second blood test 4 weeks after the suspected contact to ensure that they have not acquired the infection.

Pre-exposure

Rubella immunization programmes are well established in many countries especially in the West. Most countries follow a universal childhood vaccination programme.

In the UK universal vaccination as combined mumps, measles and rubella (MMR) is offered at 12–15 months, followed by a second dose before school entry at 3–5 years.

This is supplemented by a screening programme for rubella immunity in the first trimester of pregnancy, and any woman found to be susceptible is offered vaccination in the post-partum period as rubella vaccination is contraindicated in pregnancy. Inadvertent administration of rubella vaccine in pregnancy is *not* an indication for therapeutic intervention as there has been no association to date of rubella vaccine virus causing fetal malformation.

Infection control

Respiratory precautions (Chapter 52) should be applied. Rubella can be shed for a long period in the urine of congenitally infected babies. Hand washing and wearing of gloves when dealing with infected secretions should be practised. Healthcare workers should be excluded from work during the infectious period.

Rubella immunization remains the mainstay of infection control. Healthcare workers and women working with small children who do not have a documented vaccination history should be screened and immunized.

27 SARS CoV and other coronaviruses

The viruses

Coronaviruses (CoV), including SARS CoV, are single-stranded RNA viruses and belong to the family Coronaviridae.

Epidemiology

Route of spread

Coronaviruses are spread by the respiratory route.

Severe acute respiratory syndrome (SARS) is caused by SARS coronavirus (SARS CoV), which is spread by the respiratory route and through the ingestion of aerosolized faeces via contamination of the hands and environment. Close contact with a symptomatic person poses the highest risk of infection. In the 2003 outbreak, most cases occurred in hospital workers or family members in contact with cases.

Prevalence

Coronaviruses have a worldwide distribution and almost all adults in the UK have been infected by at least one type of coronavirus. Infection usually occurs in winter or spring and is associated with upper respiratory tract infection (a 'cold'). The severity of illness is similar to that of rhinovirus infection, but less severe than infection with respiratory syncitial virus or influenza viruses. Symptoms are usually more severe in elderly persons. Reinfection is common.

SARS CoV caused a worldwide outbreak between March and July 2003, and there was a smaller outbreak, probably associated with laboratory-released SARS CoV, in 2004. There were over 8000 cases reported from 32 countries. There have been no more cases since then. The outbreak originated in Guandong Province in China and is thought to have been transmitted from civet cats (a variety of wild cat) to humans with subsequent human-to-human spread.

Incubation period

2–4 days (SARS has an incubation period of 2–7 days).

Infectious period

Coronaviruses are considered infectious while patients are symptomatic. Patients are most infectious at the onset of respiratory symptoms.

At-risk groups

Coronavirus infection is more severe in elderly persons. The most severe and fatal infections with SARS have been in elderly persons.

Clinical

Symptoms

Coronaviruses produce a range of symptoms from asymptomatic infection to upper respiratory symptoms (a 'cold'), malaise and fever. Brochiolitis and other lower respiratory tract symptoms occur in a few patients of all ages.

Coronaviruses can be found in the human gut, but there is no clear disease association.

SARS CoV causes high fever ($>38°C$), dry cough, shortness of breath, myalgia, headache and diarrhoea. Chest X-rays show pneumonia or respiratory distress syndrome. Symptoms are usually severe enough to warrant hospital admission. The overall fatality rate was 15% in previous outbreaks, higher in elderly patients and those with other respiratory conditions; less than 1% in persons less than 24 years of age, 6% in those aged 25–44 years, 15% in those aged 45–64 years and greater than 50% in persons aged 65 years or older.

Differential diagnosis

Parainfluenza, RSV, adenovirus and other respiratory viral infections have to be considered in the differential diagnosis of respiratory CoV infections.

SARS CoV infection has to be distinguished from influenza and other causes of pneumonia and high fever.

Laboratory diagnosis

Coronaviruses are not usually tested for in most hospital laboratories, although some regional virology laboratories may include coronavirus detection in their respiratory PCR diagnostic test repertoire. They are difficult to grow in cell culture.

SARS CoV is only diagnosed in specialist reference laboratories with Category 4 diagnostic facilities. In England there are two centres of the Health Protection Agency, in London and Porton Down, that are able to undertake this work. Infection can be diagnosed by PCR or serological tests.

Management

Treatment

There is no specific treatment for coronavirus infections, including SARS CoV. Management of the latter requires supportive management of the presenting symptoms.

Infection control

The spread of coronaviruses can be reduced by strict handwashing after patient contact. The use of gloves, face masks, aprons and goggles will reduce the risk of transmission. Isolation in single rooms or cohort nursing reduces the risk to other patients.

Severe acute respiratory syndrome is less infectious than influenza but symptomatic patients should be nursed in side rooms, preferably negative-pressure rooms, with gloves, aprons and a respirator mask conforming to at least European standard EN149:2001 FFP3. If a suitable respirator mask is not immediately available, use a surgical face mask (see latest guidance).

Useful website

Refer to www.hpa.org.uk for more information on diagnosis and infection control for SARS CoV.

28 Varicella-zoster virus (VZV)

The virus

Varicella-zoster virus is a double-stranded DNA virus and a member of the Herpes-viridae family of viruses.

Epidemiology

Route of spread

Varicella-zoster virus is transmitted by the airborne route, from respiratory secretions and from vesicles on the skin. After entry through the respiratory route there is an initial period of viraemia, which seeds the virus in the reticulo-endothelial system. This is followed by a second episode of viraemia resulting in dissemination of the virus throughout the body and manifestations of the typical chickenpox vesicular rash on the skin surface.

Prevalence

Varicella-zoster virus infection occurs worldwide and the prevalence of infection varies considerably. While 95% of people in industrialized countries have had chickenpox by the age of 20 years (although about 20% will have had such a mild infection that they may be unaware of this), in the tropics, only 50% of people have had chickenpox by the age of 20 years.

Incubation period

10–23 days (mean 14 days).

Infectious period

From 2 days before the onset of symptoms until 5 days after the rash or all the skin lesions are fully crusted.

At-risk groups

- Immunocompromised persons
- Pregnant women
- Unborn babies in the first 20 weeks of pregnancy, and babies one week before or after delivery.

Clinical

Symptoms

Chickenpox produces a generalized vesicular skin rash. The lesions normally first appear on the upper part of the body before becoming generalized. The rash involves the whole body (including the scalp), but the lesions are most dense on the central part of the body (the trunk) as compared to the limbs. Lesions of chickenpox continue to appear over the first 48 hours of onset, and lesions at various stages of development can be seen in clusters (cropping). It is usually a fairly mild infection in children, but severe infection can occur, particularly in immunocompromised children. Adults are at much higher risk of severe or fatal chickenpox, particularly if they develop varicella pneumonitis, which is much more common in smokers than non-smokers. Rarely encephalitis may occur as a complication. Symptoms are more severe in immuno-compromised adults, and haemorrhagic chickenpox (almost always fatal) with multi-organ involvement can occur in transplant recipients.

Shingles (zoster) results when VZV reactivates from a dorsal root ganglion; the virus then travels down a sensory nerve to the skin supplied by that nerve (derma-tome). It usually produces a group of fluid-filled blisters (vesicles) on the skin. Sometimes vesicles do not appear on the skin, but patients experience pain in the affected dermatome (zoster sine herpete). Shingles is often associated with pain (post-herpetic neuralgia), particularly in older persons, and prompt antiviral treat-ment given less than 48 hours after the onset of the symptoms is indicated in these patients.

Infection in pregnancy

Chickenpox can produce problems in pregnancy. Pregnant women are more likely to have severe symptoms than other adults. Chickenpox in the first 20 weeks of preg-nancy can result in severe infection in the fetus (congenital varicella syndrome) in 1–2% cases. Always seek expert advice from a specialist if a pregnant woman presents with chickenpox or she has had recent contact with a person with chickenpox or shingles. Zoster immune globulin (ZIG) or aciclovir can be given prophylactically to pregnant women who have no evidence of previous VZV infection (VZV antibody negative).

Chickenpox in the last few days of pregnancy can be problematic for the baby. Babies born to mothers who develop chickenpox seven days or less before delivery are at significant risk of severe or fatal chickenpox. They must be given prophylactic ZIG and/or aciclovir.

Differential diagnosis

Vesicular skin lesions caused by VZV can be mistaken for HSV infection. Chickenpox usually causes widespread lesions, especially on the body, with vesicles at various stages of development in one cluster (Fig. 28.1). Shingles vesicles are usually confined to an area of skin (dermatome) on one side of the body served by a sensory nerve (although immunosuppressed patients can have much more extensive lesions).
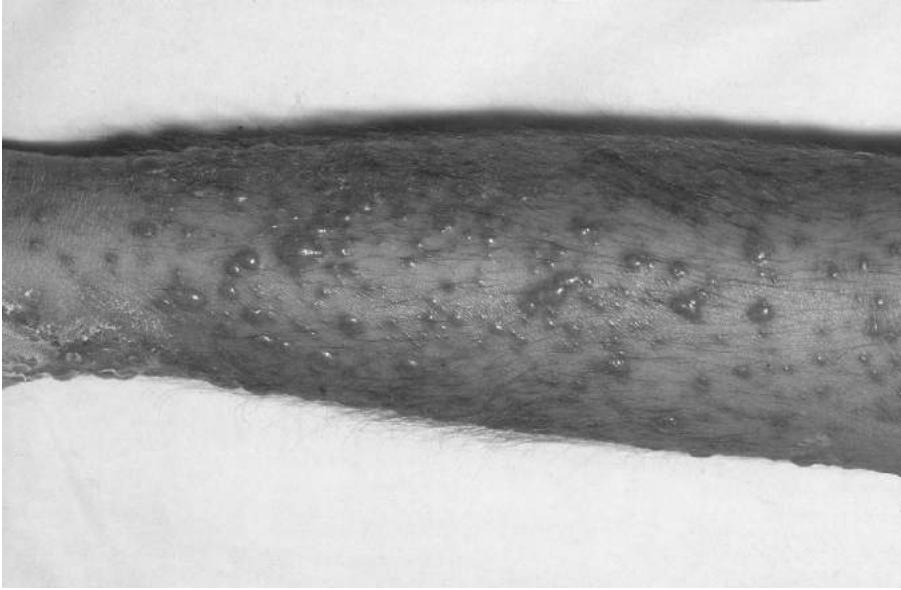
Fig. 28.1. Chickenpox showing cropping lesions. (See Fig. 2 in colour plate section)

Herpes simplex virus lesions are usually all at the same stage of development in the same cluster.

Laboratory diagnosis

Several laboratory methods and clinical specimens can be used to diagnose VZV infection. See Table 28.1.

Management

Treatment

Several drugs are available for treating VZV infections. (Always refer to nationally agreed protocols and drug data sheets for the latest recommended treatment regimes.) See Table 28.2.

Prophylaxis

Zoster immune globulin or oral aciclovir can be given prophylactically to reduce the severity of infection or prevent diseases after exposure (seek expert advice). These should be given less than 10 days after exposure to infection.

Infection control

Varicella-zoster virus is a very infectious virus, which can damage unborn babies and cause fatal infection particularly in immunocompromised patients. Patients with

Table 28.1. *Laboratory diagnosis of VZV infection.*

Clinical indication	Specimens	Test	Interpretation of a positive result
Chickenpox	Vesicle fluid	Electron microscopy	Indicates a herpes virus infection (all herpes viruses look alike in the EM, so cannot distinguish between VZV and HSV)
		PCR	Indicates VZV infection
	Vesicle fluid swab of the base of the lesion in virus transport medium	Virus culture	Indicates VZV infection (takes 10–14 days to grow)
	Clotted blood taken at least 7 days after onset	VZV IgM	Indicates recent VZV infection
Shingles	Vesicle fluid	Electron microscopy	Indicates a herpes virus infection (VZV or HSV)
		PCR	Indicates VZV infection
	Vesicle fluid in virus transport medium	Virus culture	Indicates VZV infection
	Clotted blood	VZV IgM	Indicates recent VZV infection (but may be negative in cases of shingles)
	Paired clotted blood samples (first taken in first 5 days of illness)	VZV IgG	A significant rise in VZV IgG titre indicates recent shingles
Encephalitis/meningitis	CSF	PCR	Indicates VZV CNS infection
Has the patient had VZV infection before?	Clotted blood	VZV IgG	Indicates previous VZV infection.

Table 28.2. *Antiviral drugs for treating chickenpox and shingles.*

Clinical indication	Drug
Chickenpox	oral aciclovir
Severe chickenpox (encephalitis or pneumonitis)	iv aciclovir
Severe chickenpox in immunocompromised patients	iv aciclovir
Shingles	oral aciclovir
	oral valaciclovir
	oral famciclovir
Severe shingles in immunocompromised patients	iv aciclovir

chickenpox and zoster should be nursed in isolation. Expert infection control and patient management advice should be sought if a pregnant woman, immunocompromised person or healthcare worker in contact with these patients develops chickenpox or shingles or is in contact with a case of chickenpox or shingles.

Section 2 – Other related agents

29 Chlamydia

Chlamydia are obligate intracellular Gram-negative bacteria. They have a dimorphic growth cycle of *elementary bodies (EB)*, which are electron-dense infectious structures and *reticulate bodies (RB)*, which are non-infectious, intracellular forms. Elementary bodies attach to the cell to initiate cell infection. Once inside the cells they differentiate into RBs; RBs divide by binary fission and subsequently differentiate back to EBs to be released from the cell to initiate further infection.

Chlamydia belong to the family Chlamydiaceae, which has two genera:

1. *Chlamydia* – which has one species *C. trachomatis. C. trachomatis* is further subdivided into serovars.

   Serovars A, B, Ba and C cause trachoma (a tropical eye infection).

   Serovars D–K cause genital infection.

   Lymphogranuloma venereum (LGV) 1, 2, 3 cause genital infection with inguinal lymphadenopathy in the tropics.

2. *Chlamydophila* – species in the genus are:

   Ch. psittaci – natural infection in birds, both psittacine (parrots, budgerigars etc.) and other birds (e.g. pigeons). Human infection is acquired as a zoonosis from birds.

   Ch. pneumoniae – is a human pathogen.

   Ch. abortus – primarily infects sheep and causes abortion in pregnant ewes (hence the name), human infection is accidental from sheep.

   Ch. caviae – causes infection in guinea pigs, but does not cause human infection.

Epidemiology

Both chlamydia and chlamydophila are prevalent worldwide. Trachoma is a disease of underdeveloped and developing countries, and the most important cause of blindness in these parts. Genital *C. trachomatis* infection is the most common bacterial sexually transmitted infection (STI) in the UK, with between 10 and 15% of all 15 to 25 year-olds being infected at any given time. Lymphogranuloma venereum is limited purely to those who have partners from tropical countries as their sexual contacts.

Chlamydophila psittaci and *Ch. pneumoniae* are prevalent worldwide; about 60–80% of people worldwide acquire *Ch. pneumoniae* infection, the incidence being 1–2% per year.

Lymphogranuloma venereum and trachoma are limited to tropical countries.

Table 29.1. *Infections due to* Chlamydia *and* Chlamydophila *species.*

Agent	Clinical infection	Route of spread
C. trachomatis A, B, Ba, C	Trachoma	Infected fomites, flies
C. trachomatis D–K	Genital chlamydia, adult inclusion conjunctivitis, ophthalmia neonatorum	Sexual Mother to baby
LGV 1, 2, 3	Genital ulcers and enlarged inguinal lymph nodes	Sexual
Ch. psittaci	Febrile illness, atypical pneumonia, rarely endocarditis	Respiratory
Ch. pneumoniae	Upper respiratory tract infection or atypical pneumonia	Respiratory
Ch. abortus	Febrile illness, miscarriage in pregnancy	Respiratory

Clinical

See Table 29.1.

Chlamydia trachomatis
Trachoma

This is an infection of childhood in the tropics. Trachoma is spread as a result of poor hygiene through infected fomites or close personal contact. Flies are an important route of spread for trachoma, as they can carry the bacteria from person to person. Active trachoma presents as follicular conjunctivitis. Reactivation and reinfections occur resulting in severe fibrosis of eyelids and inward turning of eyelid (entropian) due to contracture. This in turn results in the eyelashes constantly rubbing against the cornea (trichiasis) and leads to blindness in adult life.

Genital chlamydia infection

Those who have unprotected casual sexual intercourse with multiple partners are the most at risk.

Male genital infection is mostly asymptomatic. Clinical infection presents as *urethritis*. Chlamydia infection is the commonest cause of non-specific urethritis (NSU) in males. Infection may spread to the upper genital tract and cause *epididymo-orchitis* and *prostatitis* and may cause male infertility. Inclusion *conjunctivitis* (Fig. 29.1) and *proctitis* occur in the case of eye and rectal infection.

Female genital infection: as in males more than 50% of infection is asymptomatic. Clinically, *cervicitis* with cervical discharge is the most common presentation, urethritis being relatively uncommon in females. If untreated, ascending infection can lead to *salpingitis* (infection of the Fallopian tubes) and pelvic inflammatory disease (PID). *Fitz-Hugh-Curtis syndrome* is the name given to chlamydia perihepatitis and is a rare
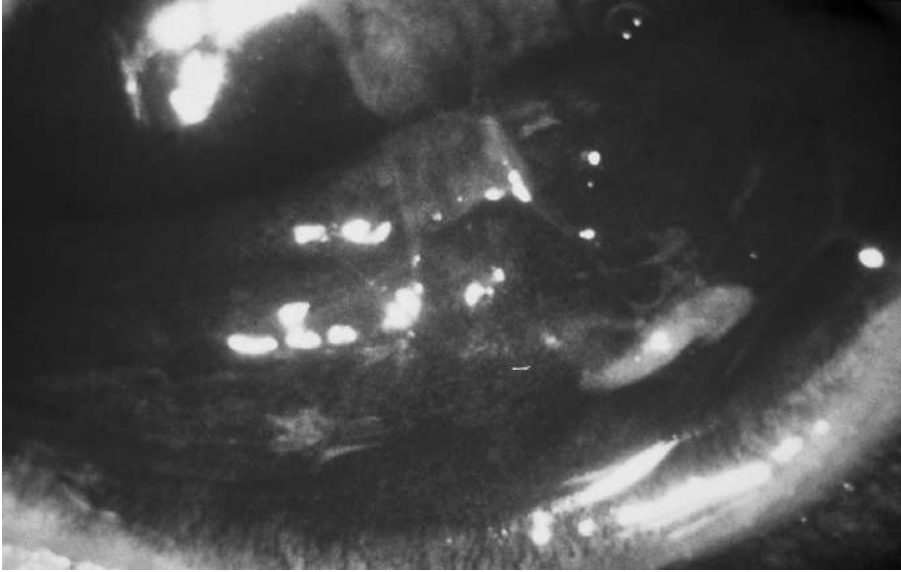
Fig. 29.1. *Chlamydia trachomatis* conjunctivitis. (See Fig. 3 in colour plate section)

complication of intra-abdominal extension of PID. Infertility may occur due to block-age of Fallopian tubes as a result of salpingitis or infection of ovaries (*oophoritis*).

Ophthalmia neonatorum

This is neonatal conjunctivitis, which typically presents between 5–15 days of age due to acquisition of infection from the mother at the time of birth. Approximately a third of the babies will have nasopharyngeal carriage of chlamydia, therefore it is essential to treat the infection with systemic antibiotics. Untreated infection may give rise to chlamydial pneumonia, which presents around 6 weeks of age or later.

Lymphogranuloma venereum

This causes genital ulcers and inguinal lymphadenopathy. Inguinal buboes may be a feature.

Chlamydophila

Ch. psittaci

This presents clinically as atypical pneumonia (Chapter 36). Infection may be asymp-tomatic or present as febrile influenza-like syndrome with general malaise, sore throat, headache and photophobia. Rare complications are endocarditis, myocarditis, arthritis or meningo-encephalitis. The infection is acquired from birds and should be suspected on epidemiological grounds. Pigeon and bird fanciers, and those who keep birds as pets or work in bird pet shops, are most at risk.

Table 29.2. C. trachomatis *diagnosis.*

Clinical presentation	Specimen type for NAAT test	Serology
Trachoma, inclusion conjunctivitis and ophthalmia neonatorum	Conjunctival swab.	Not indicated.
Female genital tract infection	Cervical swab or first void urine sample (FVU). Other swabs as indicated by clinical presentation.	Only useful for diagnosis of pelvic inflammatory disease, otherwise not indicated.
Male genital tract infection	First void urine specimen (FVU). Other swabs as indicated by clinical presentation.	Not indicated.

Ch. pneumoniae

This is a human chlamydial infection and a common cause of community-acquired pneumonia. Outbreaks in young institutionalized adults (e.g. military recruits) occur. Infection may also present as pharyngitis, sinusitis and bronchitis. *Ch. pneumoniae* has been detected in atheromatous plaques in blood vessels leading to suggestions that infection may lead to heart disease. There is, however, no confirmed proof of this association as yet.

Ch. abortus

This is an infection of sheep where it causes abortion in ewes. Farmers and those coming in contact with sheep, especially at lambing time, are at risk of infection as the bacteria are present in high concentration in the sheep placenta. Infection in pregnant women may lead to miscarriage, therefore it is advisable to avoid contact with pregnant ewes at lambing time.

Laboratory diagnosis

Laboratory diagnosis of *C. trachomatis* is by demonstration of chlamydia in swabs taken from the relevant sites (Table 29.2). Although chlamydia culture and antigen detection methods such as EIA and immunofluorescence tests (IFT) (Chapter 48) have been the mainstay of diagnosis, recently they have been replaced by nucleic acid amplification techniques (NAATs) such as strand displacement assay (SDA), polymerase chain reaction (PCR) and transmediated amplification (TMA) (Chapter 49). The chlamydia NAAT tests are usually able to detect all of *C. trachomatis* serovars including those that cause trachoma and LGV.

Ch. psittaci and *Ch. pneumoniae* infection are diagnosed serologically by demonstration of rising antibody titre in *paired acute and convalescent serum samples.* As the bacteria are intracellular they cannot be cultured on the traditional bacterial medium

in the laboratory. Nucleic acid amplification technique tests on respiratory secretions are being developed to aid laboratory diagnosis.

Management

Treatment

Chlamydia (genital and respiratory) infections respond to treatment with antibiotics. Tetracyclines are the first line drugs for treatment. Erythromycin should be used in pregnancy and in children as tetracyclines are contraindicated in them.

Azithromycin is a new drug, which is equally effective against chlamydia. It is available as a single dose treatment for *C. trachomatis* and hence results in better patient compliance.

The UK National Chlamydia Screening Programme (NCSP) for genital chlamydia infection aims to identify the pool of infected 15 to 25 year-old young adults. The aim is to reduce the burden of genital infection and thus the associated complications of PID and infertility, by targeting at least 50% of this population through opportunistic screening, identifying the infected and offering them and their partners treatment.

Infection control

Good personal hygiene, and avoidance of unprotected sexual intercourse with casual partners by the use of a barrier method of protection. *Ch. psittaci* and *Ch. abortus* infections are by zoonosis, and human-to-human spread does not occur. However, since these infections can be more severe in pregnant women and their unborn children, pregnant women should not come into contact with sheep and goats who are giving birth or who have recently done so. *Ch. pneumoniae* is a common respiratory infection in the community and so it is difficult to control.

30   *Toxoplasma gondii*

The organism

Toxoplasma gondii is a coccidial parasite.

Epidemiology

Route of spread

Toxoplasma gondii is transmitted to humans through the ingestion of cat faeces (containing oocysts) or undercooked meat (containing tissue cysts). Pregnant women (and their unborn babies) and immunocompromised persons are particularly susceptible to severe infection.

Prevalence

Toxoplasma gondii is a parasitic infection, which infects approximately 10–20% of people in the UK before the age of 50. *Toxoplasma gondii,* after primary infection, becomes dormant in humans as bradyzoites in tissue cysts (especially in muscles) and can reactivate, especially in immunocompromised patients, producing symptomatic infection.

Incubation period

4–21 days (mean 10 days).

Infectious period

Humans cannot acquire *Toxoplasma gondii* infection from other humans.

At-risk groups

Immunosuppressed persons (transplant recipients, HIV positive patients) and unborn babies whose mothers have active *Toxoplasma gondii* infection in pregnancy.

Clinical

Symptoms

Most *Toxoplasma gondii* infections are asymptomatic. Those persons who do have symptoms experience pyrexia, lymphadenopathy, myalgia and malaise. The frequency of lymphadenopathy varies with age and sex; it is more prevalent in boys

Table 30.1. *Laboratory diagnosis of* Toxoplasma gondii *infection.*

Sample	Laboratory test	Result interpretation
Clotted blood (serum)	*Toxoplasma gondii* IgG	If positive, indicates infection at some time.
	Toxoplasma gondii IgM	If positive, indicates recent infection. This needs confirmation in a Reference Laboratory in pregnant women, neonatal and immunocompromised patients.
	Toxoplasma gondii dye test	The gold standard test. Only done in a Reference Laboratory. If positive, indicates infection at some time.
EDTA blood	*Toxoplasma gondii* DNA	If positive, indicates active infection.

under the age of 15 years old, and more prevalent in women than men. The peak age group in both sexes is 21–25 years old. The most common sites are neck (65%), axillae (24%) and groin (11%). In most persons (60%) lymphadenopathy lasts less than 2 months, but it can last for 2–6 months (33%) or longer in 6% of cases.

Immunocompromised persons (see Chapter 43) can experience severe and life-threatening infection (encephalitis, pneumonia, myocarditis and retinitis), both as primary and reactivated infection.

Babies can be infected in utero (see Chapter 42) and this can cause damage to the baby at any stage of pregnancy. In the first trimester of pregnancy, 25% of babies will have congenital infection. The rates for the second and third trimesters are approximately 54% and 60–70% respectively. Infection of the placenta is a prerequisite for congenital transmission. The severity of symptoms in the baby depends on the trimester in which the infection occurred. Infection acquired in the first trimester of pregnancy leads to congenital damage in 75% of infected fetuses, infection later in pregnancy is less likely to cause fetal damage with virtually no damage associated with infections acquired in the third trimester. Congenital symptoms include hydrocephalus, meningoencephalitis, intracranial calcifications, chorioretinitis, hepatosplenomegaly, jaundice, petechial rash, anaemia and thrombocytopenia.

Differential diagnosis
Epstein–Barr virus and cytomegalovirus. Adenovirus (see Glandular fever-type illness, Chapter 40) and lymphoma.

Laboratory diagnosis
See Table 30.1.

Management

Treatment
Infections can be treated with antimicrobials (combination of pyrimethamine and sulphadiazine). Specialist advice should be sought for the treatment of *Toxoplasma*

gondii infections, especially in pregnant women, neonatal babies, or immunocompromised persons.

Prophylaxis

Some patients (notably those with HIV infection or those who have received transplanted organs or bone marrow) may require antimicrobial prophylaxis to prevent donor-acquired infection or symptomatic reactivation.

Infection control

There are no infection control issues with *Toxoplasma gondii* infection. It does not spread from person to person. Infection prevention advice, such as avoidance of eating uncooked or undercooked meat, wearing gloves and an apron while gardening and clearing cat litter, and strict hand washing after such activities, should be given to all at increased risk (as listed above) of toxoplasma infection.

31 Transmissible spongiform encephalopathies (CJD and vCJD)

Transmissible spongiform encephalopathies (TSE) are a group of agents that give rise to spongiform degeneration in the brain. These agents do not possess any nucleic acid (DNA or RNA) and are very resistant to inactivation. They consist of only a glycoprotein core and the term *prion* or *prion protein* (PrP) has been coined to describe them. They infect both humans and animals, and have recently been shown to cross the species barrier, e.g. vCJD crossed into humans from cattle. See Table 31.1.

Epidemiology

The first agent to be described was *scrapie.* Scrapie has been known to cause infection in sheep in the UK for more than a hundred years. In the late 1980s and 1990s there was an outbreak of a bovine form of scrapie, namely *bovine spongiform encephalopathy* (BSE), which had previously not been described. This led to destruction of thousands of cattle in the UK and a public health crisis in the confidence of beef for human consumption.

Creutzfeldt–Jakob disease (CJD) is the human form of prion disease, and has been known to occur throughout the world since 1920. *Kuru* is the name given to the infection that was limited to only parts of Papua New Guinea. In the 1990s, a new form of CJD was described for the first time in the UK as a result of BSE transmission; this was named as *variant CJD* (vCJD) to distinguish it from the already existing CJD.

Human prion disease can be acquired through either an inherited or an infectious route. To understand this, and to understand how an agent consisting of protein only can be 'infectious', it is important to understand the pathogenesis of prion disease.

Pathogenesis of prion disease

A cellular form of PrP exists naturally in cells; this cellular 33–37 kDa protein is a referred to as *PrP^c* (c for cellular). Mutations in the cellular protein (PrP^c) lead to changes in its conformational (folding pattern) structure and make it resistant to protease enzyme. This mutated protein is 27–30 kDa in size and referred to as *PrP^Sc* (Sc for scrapie) or *PrP^Res* (Res for resistant).

As this PrP^{Sc} is resistant to protease enzyme it is not destroyed and accumulates in the brain. Even though the exact mechanism is not clear, this accumulation initiates the process of spongiform brain degeneration (encephalopathy). Folded PrP^{Sc} or *scrapie fibrils* can be demonstrated by electron microscopy in the infected brain tissue.

Table 31.1. *List of animal and human TSEs.*

TSE	Route of transmission
Animal	
Sheep, goats (scrapie)	Grazing on infected pastures. Vertical from mother to newborn.
Cattle (BSE)	Feeding on infected bone-meal. Vertical from mother to newborn.
Domesticated elk, deer, minks, domestic cats (wasting transmissible encephalopathy)	Feeding of contaminated food.
Human	
Sporadic CJD	Probably due to chance mutation of the cellular prion protein. Occurs in older individuals.
Iatrogenic CJD	Infection acquired as a result of medical intervention.
Kuru	Ritualistic cannibalism, children and women affected.
vCJD	Consumption of contaminated beef, blood transfusion.
GSS and FFI	Autosomal inherited.

There is considerable experimental evidence to show that when this PrP^{Sc} is injected into a normal brain it can induce the normal cellular PrP^{c} to change to the resistant PrP^{Sc} by contact, thus explaining the infectious aetiology of prion disease.

Route of spread

Transmissible spongiform encephalopathies in humans can be acquired as an inherited (due to the inheritance of the defective gene causing the PrP^{c} mutation) or infectious form.

The main route of infectious spread is through consumption of infected meat, or exposure of cuts and abrasions to infected material.

Iatrogenic spread of CJD through the use of pituitary growth hormone, dura mater and corneal grafts, and through contaminated neurosurgical instruments has been well documented. Variant CJD has also been shown to be transmitted via blood transfusion.

In animals, the vertical route of transmission (e.g. from mother to newborn) has been shown for both BSE and scrapie.

Prevalence

Scrapie is known to exist in many other countries besides the UK; Australia is considered as a scrapie free country. Although the BSE outbreak occurred in the UK, sporadic cases in cattle have been identified in France, Germany and other European countries.

Sporadic CJD has an incidence of 1 per million population, and probably occurs because of chance mutation of the PrP^c to PrP^{Sc}. Familial forms are due to inheritance of the defective gene, have higher incidence than sporadic CJD and are limited to family clusters or certain races. Over a hundred cases of vCJD have occurred in the UK since the BSE outbreak.

Incubation period
The incubation period is prolonged, and varies from months to years depending upon the species and clinical presentation of the prion disease.

Infectious period
Infectivity lasts throughout the period of infection, and is highest in the neural tissue especially in the central nervous system. It is likely that both animals and humans are infectious in the incubation period, before any symptoms appear.

At-risk groups
Some forms of CJD have been shown to occur in family clusters. For vCJD, consumption of infected beef (especially prior to safety measures being instituted) and blood transfusions from potentially infected donors, are also risk factors.

Clinical

Animal prion disease
Scrapie
As the name implies, this disease presents as intense itching, which results in the sheep scraping themselves against objects; this is normally accompanied with ataxia.

Bovine spongiform encephalopathy
In cattle BSE presents as ataxia, excessive response to sensory stimuli and aggressive behaviour; this gave it the popular name of 'mad cow disease'. The BSE outbreak is likely to have been started by the feeding of scrapie-infected bone-meal to cattle. There is some debate, though, that sporadic low-level BSE already existed, and that the outbreak was due to BSE infected bone-meal getting into the food chain due to changes in the process of bone-meal extraction. The outbreak was bought under control by the slaughter of hundreds of thousands of potentially infected cattle, and by the banning of bone-meal as cattle feed.

Human prion disease
Creutzfeld–Jakob disease (CJD)
Sporadic CJD has an incidence of 1 case per million, and is a slowly progressive disease with a long incubation period (decades) and occurs after 50 years of age. Disease onset starts with tremors, insomnia and depression, progressing to ataxia and dementia. It is invariably fatal, death normally occurring within a few months to years after onset. Diagnosis is clinical, and at autopsy the brain biopsy shows spongiform

degeneration. Several different forms have been described, one of which, *Kuru*, was limited to the Fore tribe of Papua New Guinea who practised ritualistic cannibalism. It was mainly seen in the women and children, as the brains of the dead elders were consumed mostly by them. The disease was eradicated in the 1950s subsequent to the banning of cannibalism in the country.

Iatrogenic CJD is similar to sporadic CJD but acquired as a result of some medical intervention (see routes of spread above).

Variant CJD is directly linked to BSE and the consumption of infected beef. The prion of vCJD and BSE has been shown to have the same structure. Variant CJD has a longer clinical course than CJD, and affects a younger age group with an average age of around 25 years. *Gerstmann–Straussler–Scheinker* disease (GSS) and *fatal familial insomnia* (FFI) are familial forms of the disease.

Laboratory diagnosis

There are no specific laboratory tests, except for histology on brain biopsy. However, tests to detect PrP^{Sc} in blood, tonsillar tissue and cerebro-spinal fluid are being developed and look promising.

Diagnosis is clinical. Histology on brain biopsy is the only definitive diagnosis, and shows spongiform degeneration of brain with astrocytosis and an absence of inflammatory response. Amyloid-like plaques in the brain are a feature of most of the TSEs; the folded PrP^{Sc} protein or scrapie fibrils can be seen by electron microscopy in these plaques.

Management

No effective treatment or prophylaxis exists, and all the TSEs are invariably fatal.

Infection control

The BSE epidemic was controlled by the banning of bone-meal as cattle feed, and by the slaughtering of infected herds (i.e. all herds with any infected cows).

There are strict guidelines to prevent the iatrogenic spread of CJD and vCJD, these include:

- single-use neurosurgical instruments on high-risk patients
- removal of leucocytes from blood to be transfused (to reduce the risk of vCJD)
- sourcing plasma from countries free of vCJD.

Section 3 – Clinical syndromes

32   Central nervous system viral infections

Clinical

There are several viruses that can cause meningitis and/or encephalitis. Listed below are the viruses most commonly associated with these symptoms. However, it must be remembered that any virus (e.g. rubella virus and rotavirus) can cause encephalitis rarely. For more details on individual viruses, refer to virus-specific pages.

Viral encephalitis

- Herpes simplex virus encephalitis is caused by HSV type 1 or rarely type 2. Symptoms include fever, severe headache, drowsiness, fits and/or unconsciousness. Prompt antiviral treatment with intravenous aciclovir is essential, since herpes encephalitis can have a mortality rate of 70% when untreated. Patients very rarely have HSV-type vesicles on the skin. Even when prompt treatment is given, about 10–30% of patients will be left with some sort of neurological deficit.
- Varicella-zoster virus can cause meningitis or meningo-encephalitis as a result of reactivation of the virus in the brain. As with HSV, few patients have VZV lesions on the skin. Patients are usually experiencing zoster with no external manifestations. One of the most feared but rare complications of chickenpox is encephalitis, which can be fatal, especially in pregnant women, and should be treated promptly with high dose intravenous aciclovir.
- Other viruses, such as arboviruses (e.g. Japanese encephalitis virus) or rabies virus cause potentially fatal encephalitis, almost always acquired abroad. Any virus can cause encephalitis and the clue to the causal virus often lies in the other symptoms (e.g. rubella rash or rotavirus diarrhoea and vomiting) or their travel history.

    Neonates can be born with encephalitis as a result of congenital infection. Herpes viruses (HSV, VZV, CMV) are usually the cause, but rubella virus and *Toxoplasma gondii* can also be responsible.

Post-infectious encephalitis

Infection with several viruses (e.g. measles virus, rubella virus, mumps virus and varicella-zoster virus) can rarely be associated with post-infectious encephalomyelitis. This syndrome can also be caused by vaccination against these infections, but this is much less likely. For example, the risk of post-infectious encephalomyelitis with rubella virus is 1 in 6000, whereas the risk after receiving rubella vaccine is less than one in a million.

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                    ┌─────────────────┐
                    │ Take CSF sample │
                    └────────┬────────┘
           ┌─────────────────┴──────────────────┐
  ┌────────┴────────┐                   ┌────────┴────────┐
  │  Immunocompetent│                   │Immunocompromised│
  │     patient     │                   │     patient     │
  └────────┬────────┘                   └────────┬────────┘
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| HSV PCR | VZV PCR | Enterovirus PCR | | HSV PCR | VZV PCR | Enterovirus PCR | CMV PCR | EBV PCR |
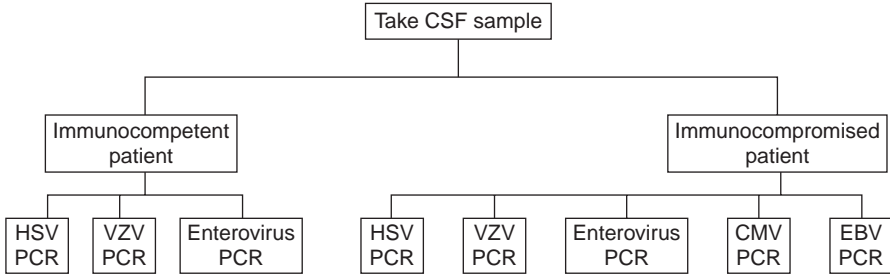
Note: this algorithm assumes that, when clinically indicated, appropriate investigations will also be carried out by culture, antigen detection and PCR to exclude bacterial pathogens, fungal pathogens and parasitic infections.

Fig. 32.1. Investigation of viral encephalitis or meningitis.

Acute post-infectious encephalitis typically occurs about a week or 10 days after the viral symptoms appear. In measles, this is usually 10 days after the rash disappears. It is accompanied by headache, irritability, loss of conciousness and fever. This is due to demyelination as a result of auto-immune reaction to the virus and therefore the virus cannot be found in the central nervous system (CNS). It is relatively uncommon (e.g. 1 in 1000 cases of measles) and has a high mortality rate.

Subacute sclerosing panencephalitis (SSPE)
This is a rare condition, with an incidence of one in a million measles cases, but is invariably fatal. Typically symptoms appear several years (10–15 years) after the initial acute attack of measles in early childhood. The first signs are deterioration in intellect (poor performance at school) followed by motor dysfunction and seizures. A defect in the measles virus allows it to persist in the brain by 'hiding' from the immune system. Virus can therefore be found in the brain and cerebro-spinal fluid (CSF) in SSPE, by molecular techniques, and confirms the diagnosis.

Guillain–Barré syndrome
This is an acute ascending symmetrical paralytic disease associated with flaccid paralysis, which can be triggered by various viral and bacterial infections (e.g. CMV, EBV, HIV, Japanese encephalitis virus and *Campylobacter jejuni*). Guillain–Barré syndrome is more common in adults than in children. Overall, 80% of those affected by this syndrome recover to lead normal lives, but some are left with permanent disability.

Viral meningitis
Viral meningitis is usually less severe than bacterial meningitis (such as meningococcal meningitis), which can be fatal and needs prompt treatment. The most common causes of viral meningitis are enteroviruses (especially echoviruses and coxsackie A and B viruses), HSV type 2 virus and mumps virus.

A typical presentation is a young adult consulting his primary care physician or being admitted to hospital with fever, severe frontal headache and meningism or

Table 32.1. *Laboratory diagnosis of viral encephalitis and meningitis.*

Virus	CNS symptoms	Best specimen	Other useful specimens to take if CSF is not available
HSV types 1 & 2	Encephalitis	CSF	—
HSV type 2	Meningitis	CSF	—
VZV	Encephalitis or meningo-encephalitis	CSF	Clotted blood taken at least 7 days after onset of symptoms for VZV IgM tests
Enteroviruses • Echoviruses • Coxsackie A viruses • Coxsackie B viruses	Meningitis	CSF	Faeces taken in the first 7 days of infection can be cultured for viruses and tested by PCR
• Enterovirus type 71	Encephalitis	CSF	As for other enteroviruses
• Poliomyelitis viruses	Poliomyelitis	CSF	As for other enteroviruses
Mumps	Meningitis or meningo-encephalitis	CSF	Clotted blood taken at least 3 days after onset of symptoms for mumps virus IgM tests Throat swab/parotid gland mouth swab in virus transport medium for virus culture or PCR
HHV type 6	Meningitis in neonates and young children, petechial rash	CSF	—
Measles	Encephalitis	CSF	Clotted blood taken at least 3 days after onset of rash for measles virus IgM tests
Rabies	Encephalitis and death	Skin biopsy from hairline	—

meningitis. On questioning, he reveals that his young child has a mild respiratory infection and has been slightly unwell. The father has caught the enterovirus infection from the child, but adults often have far more severe symptoms than children. Symptoms normally resolve in a few days with conservative treatment. There is no antiviral treatment.

Laboratory diagnosis

Figure 32.1 and Table 32.1 show the laboratory diagnosis of viral encephalitis and meningitis.

It is widely believed that white blood cells are usually found in the CSF of persons with viral encephalitis and meningitis, but early in infection white cells may be absent in the CSF. Cerebro-spinal fluid from patients with encephalitis or meningitis should be tested by molecular techniques such as polymerase chain reaction (PCR) for virus infections (HSV, VZV, enteroviruses), which should include CMV and EBV in immunocompromised patients.

33 Viral eye infections

There are several viruses that can cause infections in or around the eye. These are best considered according to what symptoms they cause.

Conjunctivitis

Conjunctivitis is inflammation of the conjunctiva and is sometimes called 'red eye'. Virus infections can cause these symptoms but it can also be caused by other conditions, e.g. allergies such as hay fever. Viral conjunctivitis is very infectious and can cause sizeable outbreaks. Although several viruses can cause these symptoms, adenoviruses and enteroviruses are the most likely causes.

Adenovirus conjunctivitis used to be called 'shipyard eye' because one of the earliest outbreaks of this condition occurred in a shipyard in the north of England. Occupational health staff inadvertently spread the infection between metal workers, who were attending to have pieces of metal removed from their eyes. The forceps used for this purpose were inadequately sterilized between patients, thus causing an outbreak.

Several enteroviruses (especially enterovirus 70 and coxsackie virus A24) can cause conjunctivitis. These viruses can cause extensive outbreaks and are very infectious. Enterovirus 70 used to be called 'Apollo eye' after a large outbreak in Africa, which it was alleged was a result of people staring at the sky to look at the Apollo spacecraft.

Keratitis

Keratitis is corneal inflammation and ulceration, which can lead to blindness. Herpes simplex virus is the most significant virus associated with keratitis. Primary infection can produce ulcers on the cornea, which should be treated with aciclovir. When the primary infection subsides, the virus becomes latent. The virus can reactivate, producing another episode of corneal ulceration. Successive episodes of corneal ulceration can produce extensive corneal scarring and even blindness. Prompt diagnosis and treatment is essential.

These and other eye conditions associated with virus infection are shown in Table 33.1. In addition, *Chlamydia trachomatis* causes both conjunctivitis and keratitis (in trachoma). These are discussed in Chapter 29.

Table 33.1. *Diagnosis and treatment of viral eye infections.*

Symptoms	Virus	Special clinical features	Diagnosis	Treatment
Conjunctivitis	Adenovirus	Follicular and pseudomembranous conjunctivitis	Conjunctival swab for virus culture or PCR	None
	Enteroviruses Enterovirus 70 and coxsackie A24	Acute haemorrhagic conjunctivitis (very infectious)	Conjunctival swab for virus culture or PCR	None
	Herpes simplex virus	Follicular conjunctivitis	Conjunctival swab for virus culture or PCR	Aciclovir ointment and oral aciclovir if severe infection
	Measles virus	Mucopurulent keratoconjunctivitis	Conjunctival swab for virus culture or PCR	None
	Influenza A	Follicular conjunctivitis (especially Avian influenza)	Conjunctival swab for virus culture or PCR	Oseltamivir if clinically indicated
Corneal inflammation and keratitis	Herpes simplex virus	Dendritic and geographic corneal ulcers and disciform keratitis	Conjunctival swab for virus culture or PCR	Aciclovir ointment and oral aciclovir if severe infection
	Varicella-zoster virus	Epithelial disease and disciform keratitis	Conjunctival swab for virus culture or PCR	Aciclovir ointment and oral aciclovir if severe infection
	Adenoviruses	Keratitis	Conjunctival swab for virus culture or PCR	None
	Measles virus	Epithelial keratitis	Conjunctival swab for virus culture or PCR	None
Scleritis	Herpes simplex virus	Scleritis	Conjunctival swab for virus culture or PCR	Aciclovir ointment and oral aciclovir if severe infection

Retinitis and neuritis	Varicella-zoster virus	Scleritis	Conjunctival swab for virus culture or PCR	Aciclovir ointment and oral aciclovir if severe infection
	Cytomegalovirus	Necrotizing retinitis and optic neuritis especially in HIV infection (AIDS)	Clotted blood for CMV IgM and IgG or retinal biopsy for CMV PCR	Intravenous or intra-ocular ganciclovir (foscarnet, cidofivir if ganciclovir is not indicated)
	VZV	Retinitis	Clotted blood for VZV IgM and IgG or retinal biopsy for VZV PCR	Intravenous aciclovir
	Toxoplasma gondii	Retinitis, choroiditis and uveitis	Retinal biopsy for Toxoplasma gondii PCR	Pyrimethamine and sulphadiazine
Eyelid and periocular skin infection	Molluscum contagiosum	Molluscum nodules	Histology or PCR	
	VZV	Ophthalmic zoster	Vesicle fluid or swab for VZV PCR	Aciclovir, famciclovir or valaciclovir
	HSV	Vesicular blepharo-conjunctivitis	Vesicle fluid or swab for HSV PCR	Aciclovir, famciclovir or valaciclovir
	Papilloma viruses	Papillomata on lid and conjunctiva	Clinical but if unsure biopsy for papilloma virus PCR	
	Human herpes virus 8	Kaposi's sarcoma in HIV positive patients	Clinical but if unsure biopsy for HHV 8 PCR	

Management

The management of viral eye infection is supportive. As sunlight is painful, the infected eye may be protected with dark glasses while going out in the sun. The eye can be washed with tepid water to keep it clean and the condition usually clears up in 3–4 days. Pain-killers may be used if the pain is severe. Specific treatment is not available for most eye infections; HSV and VZV infections should be treated with aciclovir as indicated (see Table 33.1).

Control of infection

Viral conjunctivitis is highly infectious and as already described can result in large outbreaks. Personal hygiene with hand washing is of utmost importance. Sharing of eye wear, face towels and handkerchiefs should be avoided. Iatrogenic spread is avoided by using sterilized or disposable eye instruments (including droppers for eye drops) for each patient and strict hand washing between each patient.

34 The common cold

The viruses

The main viruses associated with the common cold are rhinoviruses (over 100 types), coronaviruses, influenza viruses, respiratory syncytial virus and parainfluenza viruses.

Epidemiology

Route of spread
The mechanism of transmission of the common cold is different for different viruses. There are three main routes of transmission – direct contact (the virus is transmitted by skin contact from handling an infected object and transmission to the mouth or nose), via small particle aerosols (these hang around in the air and can be highly infectious) and/or via large particle aerosols (created by coughing and sneezing).

Prevalence
As its name suggests, the common cold occurs throughout the year. It is most prevalent in children, especially in younger children. Pre-school or primary school children have about 3–8 colds a year, whereas adults usually have 2–4 colds per year. Parents, teachers and others in frequent contact with young children have more colds than those with minimal contact. Women have more colds than men, probably reflecting their increased contact with children.

The common cold is more prevalent in winter months (usually caused by rhinoviruses or parainfluenza types 1 and 2 virus). Summer colds are more likely to be caused by coronaviruses or parainfluenza virus type 3. Quite why parainfluenza viruses type 1 and 2 cause winter infections and parainfluenza virus type 3 causes summer infections is a mystery! It is a myth that colds are more likely to be acquired in cold and wet weather.

Incubation period
1–3 days.

Infectious period
Persons are infectious when they are symptomatic, especially if they are coughing and sneezing. They are likely to be most infectious in the first few days of the illness.

Table 34.1. *Laboratory diagnosis of common cold virus infections.*

Clinical indication	Specimens	Test	Interpretation of a positive result
Severe respiratory infection in hospitalized patients	Nose and throat swab in virus transport medium	Virus culture	Indicates infection with a particular type of respiratory virus
		PCR	Indicates infection with a particular type of respiratory virus
	Nasopharyngeal aspirate in children <2 years old or bronchoalveolar lavages in patients in intensive care	Immunofluorescence test (especially for RSV and parainfluenza and influenza viruses)	Indicates infection with a particular type of respiratory virus
		Virus culture	Indicates infection with a particular type of respiratory virus
		PCR	Indicates infection with a particular type of respiratory virus
	Clotted blood	Serology for atypical pneumonia antibody detection	Indicates infection with a particular atypical pneumonia bacteria

Clinical

Symptoms

A sore throat is often the first symptom. Nasal congestion, nasal discharge and sneezing usually follow. Laryngitis sometimes occurs and 30% of people will develop a cough (often after the nasal symptoms have gone). Some will have sore eyes. Low grade fever is often present. Headache and muscle pain are more frequent in cases of influenza, but mild influenza can present with common cold symptoms.

Sinusitis and lower respiratory tract infections caused by bacterial superinfection are the most common complications in adults. Sinusitis occurs in 0.5–2% of adults and older children. Lower respiratory tract infection occurs more frequently in elderly persons, immunocompromised patients and those with asthma, chronic obstructive airway disease and in smokers. Lower respiratory tract infection may be a result of

community-acquired pneumonia (*Mycoplasma pneumoniae, Chlamydophila psittaci, Chlamydophila pneumoniae, Coxiella burnetii* or *Legionella pneumophila*) (see Chapter 36), which should be investigated because appropriate treatment is usually with different antibiotics than other bacterial chest infections and there may be environmental and public health issues that need to be explored.

Laboratory diagnosis

If patients present with typical common cold symptoms, laboratory investigation is not recommended. If they are admitted to hospital, swabs for virus investigation should be sent to the laboratory, especially if patients are immunosuppressed. Patients with suspected community-acquired pneumonia should be investigated. See Table 34.1.

Management

Treatment

There is no antiviral treatment for the common cold, but analgesics can be used to treat fever, headache and muscle aches. Atypical pneumonia and bacterial infections should be treated with appropriate antibiotics.

Infection control

Patients with the common cold admitted to hospital should be isolated in single rooms or cohorted in isolation bays, if possible.

35 Respiratory virus infections

Clinical

Individual respiratory virus infections are difficult to diagnose clinically because they all cause similar symptoms. They often occur in outbreaks, at certain times of the year and in certain age groups, which increases the accuracy of clinical diagnosis. For example, respiratory syncytial virus (RSV) infection most frequently occurs in children under the age of 18 months from November to February each year and is associated with bronchiolitis, sometimes requiring hospital admission.

Several viruses, such as rhinoviruses, coronaviruses, enteroviruses, respiratory adenoviruses and parainfluenza viruses are causes of the 'common cold' (see Chapter 34). It is interesting that types 1 and 2 parainfluenza viruses cause outbreaks in the winter while parainfluenza 3 viruses cause summer colds.

Some of these viruses (especially parainfluenza viruses and RSV) can cause pneumonia.

Influenza

Influenza viruses are the most feared cause of respiratory viral infection. As a result of the profound malaise and myalgia associated with influenza, clinical diagnosis is more accurate than with the other viral respiratory infections. Influenza occurs each year in the UK from October to April. Nobody can predict exactly when an outbreak of influenza will occur each year, which virus will be involved, how severe it will be and which age group will be worst affected. If patients acquire a bacterial lung infection on top of influenza, this can result in severe or fatal infection. There is an extensive surveillance programme in the UK for influenza, which involves general practitioners, the Health Protection Agency (HPA) and the Department of Health. This gives impending warning of the first influenza cases of the season, and monitors each evolving national outbreak. There are two influenza viruses (influenza A virus and influenza B virus) that cause influenza outbreaks in the UK. Influenza B virus is genetically fairly stable and does not change antigenically significantly from year to year. By contrast, influenza A virus is constantly mutating and the virus strain causing infection one year is unlikely to be the same one causing influenza A the following year. There are currently two types of influenza A viruses circulating in the UK – H3N2 (haemagglutinin type 3 and neuraminidase type 2) and H1N1 (haemagglutinin type 1 and neuraminidase type 1) viruses. The haemagglutinin and neuraminidase are antigens on the virus surface against which neutralizing protective antibodies are made.

These are the vital constituents of influenza vaccine (which currently contains influenza A virus types H1N1 and H3N2 and influenza B). The influenza viruses circulating in the southern hemisphere in our summer determine the influenza viruses in our vaccine for the next influenza season.

Influenza can be treated with antivirals such as oseltamivir or zanamivir, but to be effective, treatment should be started less than 48 hours after the onset of symptoms. Influenza vaccine is available each year and is offered to those members of the community most susceptible to severe infection (the elderly, immunosuppressed persons and those with chronic conditions such as renal and heart disease and diabetes). Healthcare workers in patient contact should seriously consider annual influenza vaccination, in order to minimize the risk of infecting vulnerable patients.

Avian influenza is an ongoing threat and there is a comprehensive surveillance and regional diagnostic strategy in place in the UK to respond rapidly to this threat.

Parainfluenza viruses

Most people experience several parainfluenza virus illnesses in their lives. There are no particular distinguishing features to enable accurate clinical diagnosis. Infection can be severe or fatal in immunocompromised patients, especially in those having received a bone marrow transplant. Parainfluenza 1 and 2 viruses cause infections in the colder months of the year, while parainfluenza 3 virus infection usually causes infections in the summer. There is no specific antiviral treatment, except in immunocompromised patients, who can be given ribavirin.

Respiratory syncytial virus

Respiratory syncytial virus (RSV) causes respiratory symptoms in people of all ages usually between November and February, but most characteristically causes severe respiratory symptoms, especially bronchiolitis, in young children less than 2 years old. Infection can be more severe and fatal in immunocompromised patients, especially in bone marrow transplant recipients. Ribavirin treatment is available for children and immunosuppressed patients.

Other respiratory viruses

Coronaviruses and rhinoviruses have many different serotypes and cause 'common cold' symptoms. People have several infections with each of these viruses during their lifetime. It is difficult to distinguish them clinically. There are no antivirals for treatment.

Adenoviruses can cause respiratory symptoms, but other symptoms such as conjunctivitis, maculopapular rash and lymphadenopathy can occur concurrently. Infections can be severe or fatal in immunocompromised patients, especially in children and in bone marrow transplant recipients. Immunosuppressed patients can be treated with cidofovir.

Enteroviruses can also cause respiratory symptoms as well as meningitis, maculopapular rashes and conjunctivitis.
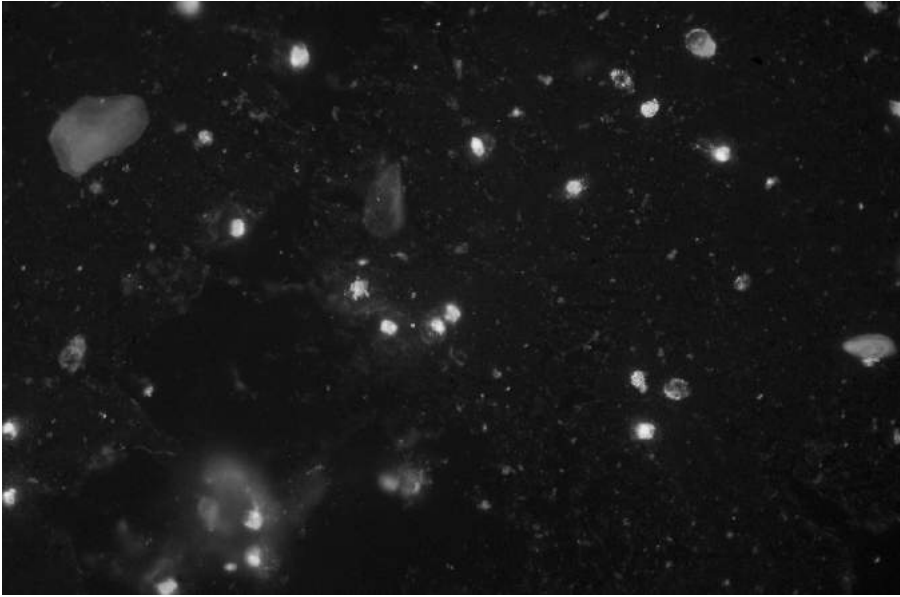
Fig. 35.1. Parainfluenza virus type 3 positive immunofluorescence. (See Fig. 4 in colour plate section)

Laboratory diagnosis

In young children under 2 years of age, the best sample to take is a nasopharyngeal aspirate, which can be tested in the laboratory in the immunofluorescence test in under 2 hours. The same assay, by use of specific monoclonal antibodies, can distinguish between influenza A and B viruses, parainfluenza types 1–4 viruses and respiratory adenoviruses. Figure 35.1 shows a positive parainfluenza type 3 immunofluorescence assay result.

Virus culture is a sensitive technique, requiring inoculation onto cell cultures in the laboratory, but it usually takes at least a week to obtain a specific diagnosis.

Increasingly, laboratories (especially regional virus laboratories) are employing molecular methods such as PCR to test for respiratory viruses. This is the most sensitive method available and results can be available in under 24 hours.

Infection control

Patients in hospitals and nursing homes should be isolated if possible, to prevent infection in others. Special care should be taken in immunocompromised (e.g. bone marrow transplant recipients) and elderly patients, in whom these infections can be fatal. Prophylactic antiviral agents are available to protect against influenza virus and RSV infection in patients at high risk of severe disease, and influenza vaccines are available for staff and high-risk patients.

36 Atypical pneumonia

Epidemiology

Atypical pneumonia is caused by bacteria rather than viruses, but it is included in this book because laboratory tests for evidence of infection with these organisms are normally carried out in virology laboratories. They are called 'atypical' because in general they produce less severe and more protracted symptoms than other bacterial pneumonias; however, atypical pneumonias can be severe and can be fatal.

Atypical pneumonia is caused mainly by five different bacteria. Prompt diagnosis of infection is important because these organisms can produce severe or fatal infection and they are all susceptible to antibiotic treatment. The five organisms are *Mycoplasma pneumoniae*, *Chlamydophila psittaci*, *Chlamydophila pneumoniae*, *Coxiella burnetii* and *Legionella pneumophila*.

Laboratory diagnosis

All of these infections can be diagnosed by testing clotted blood for specific antibodies. Antibody may be present at the time of presentation (especially *M. pneumoniae*) but may not be detectable until 10 days after the onset of symptoms (up to a month for *L. pneumophila*). Urine taken in the first 5 days (for antigen detection) after the onset of symptoms is the best way to diagnose *L. pneumophila* infection. To identify outbreaks of *L. pneumophila* infection, it is important to culture respiratory samples on specialized media so that strains can be characterized.

Mycoplasma pneumoniae

Mycoplasma pneumoniae causes respiratory symptoms from mild to severe pneumonia. Primary infection usually occurs in school-age children but immunity only lasts for about 6 years, so individuals can be infected several times during their life. Over 95% of patients have a cough and 25% of patients have a maculopapular rash, which starts on the trunk and then moves to the limbs but not the face. Other symptoms such as haemolytic anaemia and neurological complications (e.g. meningitis and Guillain–Barré syndrome) can occur about 2 weeks after the onset of symptoms. Stevens–Johnson syndrome (erythema multiforme) can also develop 10–14 days after the onset of symptoms.

The infection can be effectively treated with macrolide antibiotics such as clarythromycin or doxycycline and can be diagnosed by serological assays such as the

complement fixation test (CFT) or immunofluorescence tests. The presence of specific IgM or IgA or a fourfold rise in CFT titres indicates recent infection.

Chlamydophila psittaci

Chlamydophila psittaci infection is transmitted from birds to humans but does not transmit from human to human. Symptoms range from mild respiratory to severe pneumonia, which can be fatal, especially in older patients. Patients usually have a severe headache and severe infection is associated with confusion and abnormal liver function tests. Most cases are not diagnosed, but a history of bird contact should be sought in all patients with atypical pneumonia; 70% of patients with *Ch. psittaci* infection have had recent bird contact. Birds carry the infection in their gut and infection is often the result of breathing in dried bird faeces. The most common birds that can transmit infection are parrots, cockatiels, pigeons and budgerigars. The infection can be effectively treated with macrolide antibiotics such as clarithromycin or doxycycline and can be diagnosed by serological assays such as the CFT. People with severe respiratory symptoms in contact with birds should consult their primary care physician and inform them about the bird contact. This is because antibiotics used to treat community-acquired pneumonia may often be different from those used to treat *Ch. psittaci* infection. A fourfold rise in CFT titre is indicative of recent infection but even single titres of 16 or greater should warrant appropriate antibiotic treatment while further blood samples are tested. A specific diagnosis of *Ch. psittaci* infection can be established only by means of specific microimmunofluorescence tests in a reference laboratory. Severe respiratory chlamydial infection with a closely related organism (*Chlamydophila abortus*) can be acquired by inhaling aerosolized sheep products of conception. This is a particular danger for pregnant women and their unborn children; infection can be fatal for both.

Chlamydophila pneumoniae

Chlamydophila pneumoniae infection is transmitted from human to human, with no animal reservoir. The symptoms are similar to those caused by *Ch. psittaci*, but usually less severe. Diagnosis is by serology as for *Ch. psittaci*. Treatment is the same as for *Ch. psittaci*.

Coxiella burnetii

Coxiella burnetii infection (also known as Q fever) is a zoonotic infection transmitted from sheep, cattle and goats to humans, often by breathing in dried faeces or products of conception, but it can also transmit from humans to humans. The organism is very resistant and can survive in the environment for many weeks. It can be blown in the wind and has been associated with large outbreaks, which need to be investigated so that the source of infection can be identified and eliminated. Patients have fever and respiratory symptoms as for the other atypical pneumonias. The most feared complication is endocarditis, which can be fatal. The infection can be treated with tetracycline. Infection can be diagnosed by CFT and titres of 16 or greater should be regarded

as suspicious and confirmed with specific *C. burnetii* phase 1 and 2 immunofluorescence assays.

Legionella pneumophila

Legionella pneumophila is the cause of Legionnaires' disease and is acquired by humans from breathing air contaminated with *L. pneumophila* in water droplets from air conditioning units, spa pools, water features or hot-water systems. The organism is commonly found in the environment but usually causes infection only in humans when present in high concentrations. It causes respiratory symptoms, usually with lobar pneumonia and can have a mortality rate of up to 40%, especially in immuno-compromised and elderly patients. Infection can be diagnosed by the *L. pneumophila* antigen test on urine taken in the first 5 days of symptoms. Specific antibody can be detected by several assays including EIA and immunofluorescence tests. Treatment is with macrolide antibiotics. When infection is diagnosed, the source of infection should be sought urgently and remedial action taken promptly, in order to prevent further cases. Infections should be reported promptly to the appropriate public health bodies (in England, Health Protection Units) so that clusters of cases can be identified, the source of infection identified and prompt action taken.

37 Gastroenteritis viruses

Clinical

Gastroenteritis can be caused by bacteria or viruses. Viral infection can be associated with either diarrhoea or vomiting – or both. Bacterial infections often have a longer incubation period unless illness is caused by bacterial toxins, when the onset is shorter (e.g. 12 hours). Within hospitals, outbreaks involving diarrhoea and vomiting, especially if staff are symptomatic, should be regarded as norovirus outbreaks until proved otherwise.

In foodborne infections (e.g. norovirus) symptoms occur 24–40 hours after eating contaminated food.

Epidemiology

In young children under the age of 18 months, rotavirus infection is the most common cause of diarrhoea and vomiting. Infection in very young children occurs every winter from December to March. Mild infection occurs in adults, but is more severe in the elderly. Rotavirus is infrequently associated with outbreaks, but
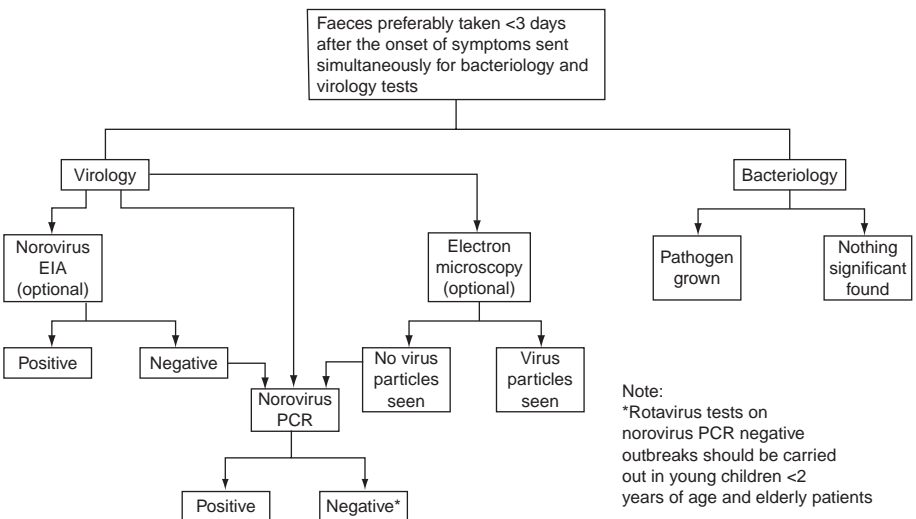
Fig. 37.1. Laboratory investigation of gastroenteritis outbreaks.
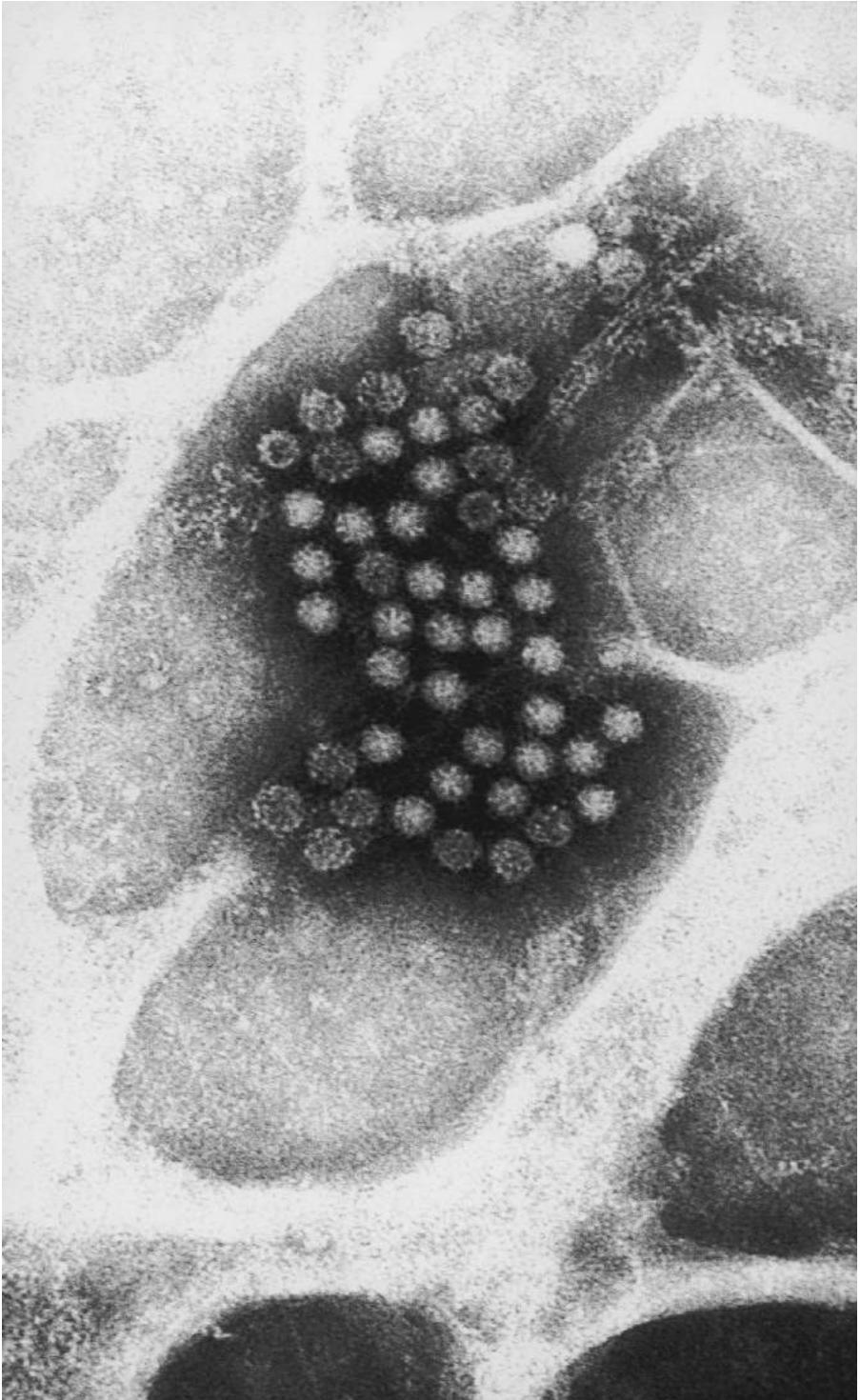
Fig. 37.2. Electron micrograph of noroviruses.

outbreaks can occur in hospitals and nursing homes in elderly or in very young persons (e.g. in nurseries and playgroups).

Noroviruses are the most common causes of diarrhoea and vomiting outbreaks in all ages. Hospitals, care homes, holiday camps and cruise ships are frequent outbreak locations. Outbreaks should be managed with strict infection control procedures such as patient isolation or cohorting, symptomatic staff exclusion and thorough cleaning when the outbreak is over (see local guidelines). Noroviruses mutate frequently, which results in the emergence of new epidemic strains and more extensive outbreaks of diarrhoea and vomiting every few years.

A related group of viruses called sapoviruses has been identified recently. These belong to the same family (Caliciviridae) as noroviruses and cause a clinically similar illness and outbreaks.

Other enteric viruses, such as adenoviruses, astroviruses, sapoviruses and caliciviruses, can cause diarrhoea and vomiting in all age groups. They tend to be associated with sporadic cases, but rare outbreaks do occur.

Foodborne infection

Foodborne infection is usually caused by noroviruses. Contaminated shellfish (cockles, oysters) are frequently the cause, but infection can be transmitted via food when infected symptomatic food handlers do not wash their hands properly before handling food.

Laboratory diagnosis

Laboratory diagnosis is performed on faeces samples, preferably taken in the first 3 days after the onset of symptoms. See Fig. 37.1 for details of how to diagnose gastroenteritis outbreaks. Laboratory diagnosis techniques include RT-PCR, EIA, agglutination and electron microscopy. Figure 37.2 shows an electron microscope picture of a norovirus.

Treatment

There is no antiviral treatment for viral gastroenteritis other than the replacement of fluids in severe cases.

38 Viral hepatitis

Viral hepatitis is a clinical diagnosis and presents as a systemic infection primarily affecting the liver or as part of a general systemic infection. Hepatitis A, B, C, D and E viruses are all hepatotropic viruses and primarily cause hepatic infection, whereas Epstein–Barr virus (EBV), cytomegalovirus (CMV) and other viruses may cause hepatitis as part of a more generalized systemic infection. The differential diagnosis should also include non-viral causes such as leptospirosis.

Clinical

The clinical features of hepatitis include nausea, vomiting, lack of appetite and dark urine, and these may be accompanied by pain in the right upper quadrant. This is normally preceded by prodromal symptoms, which may include fever, arthralgia, myalgia, headache and rash. Clinically it is not possible to distinguish the etiological agent, although there may be clues in the epidemiology (Table 38.1). The majority of cases of acute viral hepatitis, especially in children, may be asymptomatic e.g. not accompanied by clinical jaundice. About 50% of adults with acute hepatitis A (HAV) and B (HBV) virus infections and 70% with acute hepatitis C (HCV) virus infection develop an asymptomatic infection. Diagnosis is only made by chance or due to investigations of non-specific symptoms or during follow up after known exposure. The main abnormal finding is elevated liver function tests (LFTs) with peak alanine aminotransferase (ALT) levels of >1000 U/L, especially in hepatitis A and B virus infections. Peak ALT levels tend to be lower in acute hepatitis C virus infection.

Both HBV and HCV may fail to clear after acute infection leading to persistent/chronic hepatitis, cirrhosis and in some cases hepatocellular carcinoma; chronic infection with HAV or hepatitis E (HEV) virus does not occur. Hepatitis D or delta (HDV) virus causes both acute and chronic infections, but only in conjunction with HBV co-infection as it requires the outer protein coat of HBV to infect.

Differential diagnosis

- Viral causes of hepatitis
  - Infection with hepatotropic viruses:
    hepatitis A virus
    hepatitis B virus
    hepatitis C virus

Table 38.1. *Clinical and epidemiological differential diagnosis of hepatitis A to E.*

	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Range of incubation period (mean)	2–6 weeks (4 weeks)	2–6 months (6–12 weeks)	2–12 weeks (6 weeks)	1–6 months (2–3 months)	2–8 weeks (6 weeks)
Clinical	Acute onset <5 years 90% asymptomatic, >5 years 50% asymptomatic. No chronic infection.	Acute or insidious onset, <5 years 90% asymptomatic, >5 years 50% asymptomatic. 5–10% would develop chronic infection, more likely in very young or immunocompromised.	Insidious onset. 70% asymptomatic, 70–80% develop chronic infection.	Acute or insidious.	Acute. Mostly symptomatic. No chronic infection.
Transmission					
Blood	No	Yes	Yes	Yes	No
Vertical (perinatal transmission from mother baby)	No	Yes, 30–90% risk	Yes, <5% risk	Yes	No
Sexual	Anal–oral sex	Yes, moderate to high risk	Yes, low risk	Yes	No
Faecal–oral/enteric	Yes, person to person, food- and waterborne.	No	No	No	Yes. Waterborne outbreaks. Sporadic cases.

Risk groups	Travellers to endemic countries, sewage workers, intravenous drug users (IVDUs) because of preparing drugs for use in contaminated water.	IVDUs, healthcare workers (HCWs), sex workers, men who have sex with men (MSM), body piercing/tattoo.	IVDUs, body piercing/tattoos, HCWs.	IVDUs, body piercing and tattoos.	Travellers, sporadic cases in West as zoonosis (from pigs).
Prevalence/distribution	Worldwide, high in Asia, Africa, south America.	Worldwide, >200 million infected.	Worldwide, 200 million infected.	Mediterranean countries.	Asia, Africa, South America, Eastern Europe.

Table 38.2. *Laboratory markers of viral hepatitis.*

Virus	Acute	Chronic	Past	Monitoring treatment
Hepatitis A	HAV IgM +ve HAV IgG +ve/−ve	Not applicable	HAV IgM −ve HAV IgG +ve	Not applicable
Hepatitis B[a]	HBs Ag +ve Anti-HBc IgM +ve	HBs Ag +ve Anti-HBc IgM −ve Anti-HBc +ve	HBs Ag −ve Anti-HBc +ve Anti-HBs +ve	HBe Ag/anti-HBe HBV DNA
Hepatitis C	Anti-HCV +ve (may be −ve in early acute infection) HCV PCR +ve	Anti-HCV +ve HCV PCR +ve	Anti-HCV +ve HCV PCR −ve	HCV PCR
Hepatitis D	HDV Ag +ve Anti-HDV +ve	HDV Ag +ve Anti-HDV +ve	HDV Ag −ve Anti-HDV +ve	Not applicable
Hepatitis E	HEV IgM +ve HEV IgG +ve/−ve	Not applicable	HEV IgM −ve HEV IgG +ve	Not applicable

Note:
[a]See Table 7.2 and Figs. 7.2 and 7.3 in Chapter 7 on hepatitis B virus for nomenclature and explanation of the various hepatitis B markers.

    hepatitis D virus
    hepatitis E virus
- Infection with other viruses:
    cytomegalovirus (CMV)
    Epstein–Barr virus (EBV)
    rubella virus
- Infection with 'exotic viruses':
    yellow fever virus
    hantavirus
    Lassa virus
    Marburg and Ebola viruses
    Junin and Machupo viruses
    Kyasanur Forest virus
- Other non-viral infective causes, such as leptospira, rickettsia including Coxiella, bacterial cholangitis
- Non-infective causes, such as drugs, alcohol, metabolic liver disease, autoimmune liver disease, cryptogenic hepatitis, obstructive hepatitis

Epidemiology

Hepatitis B and C infections are distributed worldwide with about 200 million people with chronic infection with each virus. The main route of spread is via exposure to infected blood and blood contaminated secretions, sexual and vertical (mother to baby). Hepatitis C virus is much less efficiently transmitted by sexual or vertical routes (<5%) as compared to HBV. Hepatitis A and E viruses have a faecal–oral transmission route, which may be person to person (uncommon in HEV) or food- and waterborne. Both these infections are endemic, with high prevalence in underdeveloped or developing countries with poor enteric hygiene, e.g. the Indian subcontinent, South East Asia, Africa and some parts of eastern Europe. Food- and waterborne outbreaks, especially of HEV, are not uncommon in these countries. Travellers to endemic countries from low-risk countries (Europe, the USA, Australasia) are at particular risk of infection due to lack of immunity.

Laboratory investigations

Diagnosis is by serology, 5–10ml of clotted blood sample should be submitted to the laboratory with clinical details, a date of onset and appropriate epidemiology, including history of at-risk exposure, if any. The serological tests are based on enzyme linked immunosorbent assays (EIAs). In addition, molecular diagnostic tests such as the polymerase chain reaction (PCR) are used to detect viral RNA (HAV, HCV) and DNA (HBV); quantitative PCR is used to detect the progress of infection and monitor treatment. A negative PCR result is indicative of viral clearance. Table 38.2 shows the interpretation of the laboratory results for hepatitis viruses A–E.

Table 38.3. *Management of viral hepatitis.*

Virus	Treatment	Pre-exposure prophylaxis	Post-exposure prophylaxis	Control of infection
Hepatitis A	No treatment	Vaccinate	<14 days of exposure – normal immunoglobin and/or vaccinate.	Enteric precautions, avoid contaminated food and water, hand washing.
Hepatitis B	Interferon Lamivudine Tenofovir Adefovir	Vaccinate	Vaccinate – accelerated course + hepatitis B specific immunoglobulin if indicated.	Avoid sexual and percutaneous or mucus membrane exposure to blood or blood-contaminated secretions.
Hepatitis C	Pegylated interferon + Ribavirin	None	None	As for HBV
Hepatitis D	Treat as HBV	As for HBV	As for HBV	As for HBV
Hepatitis E	No treatment	None	None	Enteric precautions, avoid contaminated food and water, hand washing.

- For acute hepatitis request serology for:
  HAV (IgM)
  HBV (HBs Ag and anti-HBc IgM)
  HCV (anti-HCV and PCR if patient immunocompromised)
  CMV (IgM)
  EBV (IgM)
- Also consider:
  HDV (anti-HDV) only if IVDA
  HEV (IgM) if travel to endemic countries
  Leptospira antibody
  Coxiella antibody
  Hantavirus antibody
- For chronic hepatitis request tests for:
  HBV (HBs Ag, HBe Ag, anti-HBe, Anti-HBc)
  HDV (anti-HDV) only in intravenous drug users
  HCV (anti-HCV and HCV PCR)
- Also consider:
  Coxiella antibody

Management

Treatment for chronic HBV and HCV infection is successful; with 50–80% of the patients clearing the virus or achieving sustained viral response (SVR) depending on the virus and virus genotype. The treatment has to be continued for at least 6 months or longer, and the drugs used have considerable side effects. Emergence of viral resistance is a particular problem especially with the anti-HBV drug lamivudine. There is no treatment for acute HAV or HEV infection; as acute HBV is a self-limiting infection in 95% of immunocompetent adults treatment is not warranted. There is some evidence that treatment of acute HCV may be of benefit.

The mainstay of management remains prevention of transmission by control of infection, and active prophylaxis by vaccination or passive prophylaxis by use of specific immunoglobulins.

See Table 38.3.

39 Genital tract and sexually transmitted infections (STIs)

True sexually transmitted infections are those that are transmitted only through sexual activity, but there are many in which sexual transmission is one of the routes and others that even though not strictly transmitted via the sexual route may be transmitted through related sexual practices. It is important to remember that many of these patients may not perceive themselves at risk of a sexually transmitted infection, and therefore may present outside the genito-urinary medicine setting.

Clinical

Sexually transmitted viral infections can be divided into two groups:
- those that present with localized genital lesions or symptoms
- those that are systemic infections but may also be transmitted via sexual route or during related sexual activity.

This chapter will consider only those pathogens that cause local genital lesions; refer to the appropriate chapters in the book for those that have a systemic manifestation.

Vesicular or ulcerative genital lesions

Herpes simplex virus is the commonest cause, but occasionally varicella-zoster virus may also cause localized genital lesions, which may be clinically difficult to distinguish from herpes. Clinical examination may reveal a shingles-like distribution along a sensory nerve in a case of varicella-zoster virus infection. The distinction is important to make as a higher dose of aciclovir is required to treat varicella-zoster.

Acute syphilis may present as an ulcerative gummatous lesion.

Non-vesicular or non-ulcerative genital lesions

Papilloma virus or *genital warts* are sexually transmitted, and multiple warts may be present on the genital area. Papilloma virus types 6 and 11 are the commonest cause of warts and are not associated with cervical cancer. Papilloma virus types 16, 18 and the other types associated with cervical cancer do not present as warts.

Molluscum contagiosum is a pox virus, which spreads by close personal contact resulting from sexual encounters. Lesions may be present on genital areas only or may form part of a more generalized skin infection. The lesions are typical and discharge a caseous material when squeezed.

Widespread genital warts and molluscum lesions can occur in immunocompromised patients, especially those with HIV infection.

Table 39.1. *Sexually transmitted infections with local and systemic manifestations.*

Clinical presentation	Infecting agents	Route of transmission
Localized genital lesions vesicular or ulcerative	Herpes simplex virus 1 and 2	Sexual
	Varicella-zoster virus	Local reactivation (zoster) involving sensory nerve supplying genital area.
Localized genital ulcerative lesion	Treponema (syphilis)	Sexual
Localized lesions other than vesicular or ulcerative	Papilloma virus (genital warts)	Sexual
	Molluscum contagiosum	Direct contact with infected lesions.
Cervical/urethral discharge due to cervicitis or urethritis	*Chlamydia trachomatis* including lymphogranuloma venereum (LGV)	Sexual
Systemic infections	HIV	Sexual, co-incidental ulcerative genital lesions aid in transmission.
	HTLV 1 and 2	
	Hepatitis B and D	
	Hepatitis C	
	Hepatitis A	Sexual practices such as anal–oral sex.
	Epstein–Barr virus	Close contact, salivary exchange 'kissing disease'.
	Cytomegalovirus	Close contact with infected saliva.

Localized genital symptoms

See Table 39.1.

Urethritis and urethral discharge

Chlamydia trachomatis is the commonest cause of non-specific discharge and *urethritis* in males. This may be accompanied by some urinary symptoms, and therefore may be misdiagnosed as a urinary tract infection (UTI). Gonococcal infection should be considered in the differential diagnosis and ruled out; many patients have dual infection with both chlamydia and gonococci. Urethral infection and urethritis in females on its own is rare, and usually occurs as an accompaniment to cervical infection.

Cervicitis and vaginal discharge

Bacterial causes including gonococcal infection should be ruled out. Chlamydia is the commonest cause of cervicitis, but about 50% of women have no symptoms; therefore the infection can only be diagnosed by opportunistic screening.

Lymphogranuloma venereum (LGV)

Symptoms are those of *Chlamydia trachomatis* but in addition large *inguinal lymphadenopathy* is present and there is normally a history of sexual contact in the tropics or with someone from the tropics.

Prostatitis and epididymo-orchitis

Chlamydia trachomatis infection if untreated ascends to the upper genital tract to cause prostatitis and epididymitis; this has been associated with male infertility. Mumps virus is the commonest cause of orchitis, which may be bilateral or unilateral.

Pelvic inflammatory disease (PID)

Chlamydia is the most important cause of PID being responsible for most of the cases. Thirty per cent of women with chlamydia if untreated will develop PID resulting in *salpingitis* and *female infertility* and/or *risk of ectopic pregnancy*. A vaginal discharge is often absent.

Fitz-Hugh-Curtis syndrome

Chronic upper genital tract infection in females may lead to pelvic adhesions and *perihepatitis* with the adhesions extending to the liver.

Genital infection in pregnancy

Genital herpes, chlamydia and papilloma virus (genital warts) infection can be passed on vertically to the fetus at the time of delivery.

Genital herpes simplex lesions if due to primary (and not reactivation) infection are a risk factor for neonatal herpes simplex infection due to vertical transmission at the time of delivery; therefore caesarian section is recommended if active lesions of primary HSV infection are present at the time of delivery.

Laboratory diagnosis

Serology

Serological investigations are of limited use. Type specific HSV IgG and IgM can be done in a specialist centre but are of limited value in the diagnosis of acute infection; type specific IgG tests have been used to study the prevalence and epidemiology of genital herpes. Herpes simplex virus type 1- and type 2-specific serology can be useful to determine if sexual couples are discordant with respect to their previous HSV type 1 and type 2 infection.

Chlamydia antibody tests are useful in the diagnosis of pelvic inflammatory disease, as high levels are diagnostic of PID and endocervical swabs for chlamydia may be negative.

Virus detection

- Herpes simplex or varicella-zoster – lesion or ulcer swab in virus transport medium should be sent to the laboratory for virus culture or polymerase chain reaction (PCR).
- Molluscum – Electron microscopic examination of the central caseous-like material in the lesion shows typical pox-like virus.
- Genital wart – clinical diagnosis; laboratory diagnosis is not routinely indicated but PCR can be done on biopsy material if required. Typing can also be done to determine if patients are infected with a potentially cancer-causing papilloma virus genotype.
- Chlamydia – nucleic acid amplification tests (NAATs) on first void urine (FVU) specimen in males and endocervical or vulvo vaginal swab in females should be sent for diagnosis of *lower and upper genital tract* chlamydia infection. First void urine samples in females are also suitable but sensitivity is lower than the other specimen types. Swabs from other sites, such as rectal or pharyngeal, should also be sent depending upon the history of sexual practice.
- In addition, appropriate tissue biopsies and venous blood sample should be sent for diagnosis of *PID* in females.

Management

Good history, examination, diagnosis and treatment of the specific condition is required.

Aciclovir, valaciclovir or famciclovir should be used for treatment of *HSV infections*. Chlamydia is sensitive to treatment by oxytetracycline, but azithromycin is replacing oxyteracycline as the treatment of choice. Erythromycin should be used in pregnant women as the drug of choice.

There is no specific treatment for *molluscum contagiosum* and it is usually a self-limiting condition.

Genital warts are also self-limiting in nature, but if multiple and large lesions are present these can be removed by cryosurgery with liquid nitrogen.

Prophylaxis and control of infection

Contact tracing of sexual contacts, their screening and treatment is the mainstay of control of infection. There is no vaccination for herpes or chlamydia, although two new vaccines are available against papilloma virus strains 16 and 18 responsible for causing cervical cancer. One of these vaccines also incorporates HPV genotypes 6 and 11 so is also protective against genital warts.

40 Glandular fever-type illness

Clinical

Glandular fever is a broad clinical description given to a cluster of symptoms and signs including lymphadenopathy, sore throat, atypical mononuclear cells in the blood, fever and malaise (often prolonged). Epstein–Barr virus and cytomegalovirus symptoms and signs include jaundice and abnormal liver enzyme test results.

Differential diagnosis

This broad clinical syndrome is associated with a number of different infections. Table 40.1 indicates the symptoms and signs most usually associated with different infections. Epstein–Barr virus infection (infectious mononucleosis) is usually, but not always, clinically diagnosed accurately. Other causes of glandular fever (CMV, adenoviruses and *Toxoplasma gondii*) are less easy to diagnose, but Table 40.1 may be a useful guide to the likely diagnosis. To be absolutely certain of the cause, laboratory investigation is required.

Diagnosis

A diagnostic approach is shown in Table 40.2 and Fig. 40.1.

Table 40.1. *Symptoms associated with various infectious causes of glandular fever-like illness.*

Symptoms/signs	Infectious organism			
	EBV	CMV	Adenovirus	*Toxoplasma gondii*
Sore throat	*****	**	**	*
Lymphadenopathy	**	*	***	*****
Fever	***	***	**	**
Malaise	****	****	*	**
Hepatitis	***	****		
Abnormal liver function tests	****	****		
Night sweats	*	*****		
Relapsing illness	*	****		
Prolonged symptoms	****	****	*	****

Table 40.2. *Laboratory diagnosis of glandular fever-like illness.*

	Test to request			
Specimen	EBV	CMV	Adenovirus	*Toxoplasma gondii*
Clotted blood (serum)	EBV IgM and/or EBV VCA and EBNA antibody	CMV IgM	Adenovirus antibody	*Toxoplasma gondii* IgG and IgM
EDTA blood	EBV DNA PCR[a] (in immuno-compromised patients	CMV DNA PCR (in immuno-compromised patients)	Adenovirus DNA PCR (in immuno-compromised patients)	*Toxoplasma gondii* DNA PCR in immuno-compromised patients
Throat swab in virus transport medium	No	No	Yes (for virus culture or DNA PCR)	No

Note:
[a]PCR = polymerase chain reaction, a molecular technique for viral diagnosis.
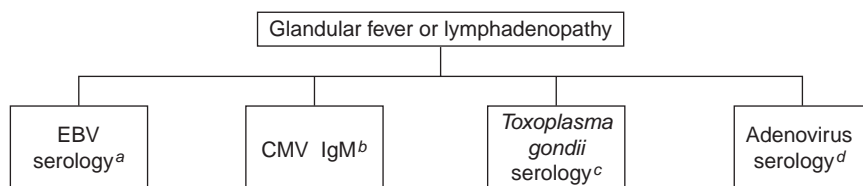
Notes:
[a]Paul Bunnell and monospot tests not suitable for children <16 years old.
[b]This test can be non-specific if weakly reactive results are obtained.
[c]If *Toxoplasma gondii* IgG reactive, refer for *Toxoplasma gondii* IgM test.
[d]Adenovirus serology is usually performed by complement fixation tests. Titres <64 unlikely to be significant.

Fig. 40.1. An algorithm for the diagnosis of patients presenting with glandular fever.

There are also non-virological tests, such as the Paul Bunnell and monospot assays, which can be used to diagnose EBV infection; these tests are not reliable in children under 16 years of age on whose samples specific viral assays should be performed.

41 Viral rashes and skin infections

Clinical

There are several kinds of skin infections caused by viruses, and these are best considered in the four categories that group together similar symptoms for the purpose of differential diagnosis:

- maculopapular rashes
- vesicular rashes
- wart-like lesions
- haemorrhagic rashes.

Maculopapular rashes

These skin rashes can be caused by a variety of different viruses. Clinically it is difficult to distinguish between the viral causes of these maculopapular rashes. Studies have shown that only a small percentage of these rashes are clinically diagnosed accurately. Figure 41.1 shows a typical maculopapular rash. Table 41.1 provides information on the laboratory diagnosis of virus infections associated with maculopapular skin rashes.

Rubella

Rubella is caused by rubella virus. It produces a mild illness with a maculopapular skin rash. It causes severe congenital damage in children born to mothers who acquire infection in the first 12 weeks of pregnancy. Because of this, women should receive rubella virus vaccine before becoming pregnant. They should also seek advice from a healthcare professional if they are in contact with a rubella-like illness in the first 20 weeks of pregnancy. Patients are infectious for one week either side of the onset of rash.

Human parvovirus B19

Infection with human parvovirus B19 can present as a rubella-like rash but the most typical presentation is with a 'slapped cheek' rash, especially in children. It can cause hydrops fetalis in babies when the mother is infected at up to 20 weeks' gestation. Pregnant mothers should seek advice from a healthcare professional if they are in contact with a rubella-like illness in the first 20 weeks of pregnancy. Patients are infectious for one week before the onset of rash but they are not infectious once the rash appears.
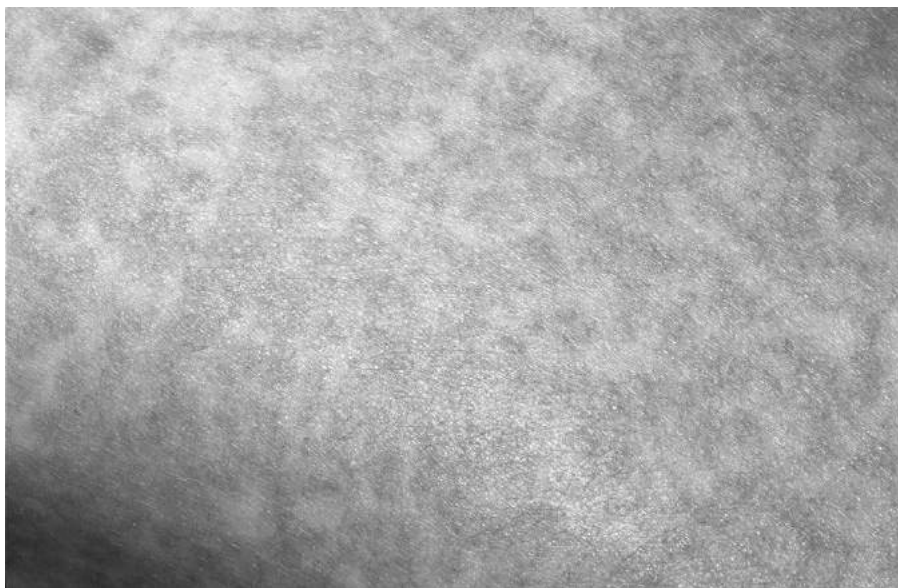
Fig. 41.1. Maculopapular rash. (See Fig. 5 in colour plate section)

Measles

Measles presents with coryza, conjunctivitis, fever and a blotchy skin rash. Since most people in the UK have either had natural measles infection or have received vaccine, infection is uncommon. However, small outbreaks do occur, especially in the spring and summer, due to the inadequate levels of vaccine-induced immunity in the community, largely as a result of the disproven risk of autism linked with the MMR vaccine. Measles is difficult to diagnose clinically, with accuracy rates as low as 5%. Measles is not a cause of congenital infection. It can be severe and 1 in 1000 cases may develop encephalitis, which can be fatal. Severe or fatal infection occurs in immuno-compromised and severely malnourished people.

Enteroviruses

Enteroviruses can produce a non-specific rash, often with respiratory symptoms. Children are most affected, but adults can have more severe symptoms, including meningism and meningitis.

Adenoviruses

Adenoviruses can produce a non-specific rash, often with respiratory symptoms. Adenovirus infection can mimic measles, especially in immunocompromised persons.

Human herpes viruses types 6 and 7

Human herpes viruses types 6 and 7 can give a non-specific rash and fever. They usually produce symptomatic infection in very young children. Allergic reactions (e.g. to drugs) can give similar symptoms.

Table 41.1. *Laboratory diagnosis of virus infections associated with maculopapular skin rashes.*

Virus	Diagnosis	Treatment and prevention
Rubella virus	Clotted blood sample tested for rubella virus-specific IgM	Prevention by giving MMR vaccine. No antiviral treatment available. Always seek medical advice if pregnant.
Human parvovirus B19	Clotted blood sample tested for parvovirus-specific IgM	No vaccine available. No antiviral treatment available. Always seek medical advice if pregnant.
Measles virus	Clotted blood sample tested for measles virus-specific IgM Throat swab in virus transport medium can be cultured or tested by PCR	Prevention by giving MMR vaccine. No antiviral treatment available. Always seek medical advice to investigate the source of infection and to protect those in contact with a case of measles.
Enteroviruses	Throat swab in virus transport medium can be cultured or tested by PCR Can test for enterovirus antibody but tests are not very sensitive	No vaccine available. No antiviral treatment available.
Adenoviruses	Throat swab in virus transport medium can be cultured or tested by PCR	No vaccine available. Consider cidofovir treatment in immunocompromised patients.
Human herpes viruses 6 and 7	EDTA blood for PCR in severely ill children.	No vaccine available. No antiviral treatment available.

Vesicular rashes

Vesicular skin rashes cause vesicles (small fluid filled blisters) on the skin and are usually caused by herpes simplex virus and varicella-zoster virus, although Stevens–Johnson syndrome (erythema multiforme) can give similar symptoms and should be considered in the differential diagnosis. See Table 41.2.

Herpes simplex virus (HSV)

Herpes simplex virus causes a vesicular skin rash. Primary infection in children often presents as mouth and gum infection. Vesicles usually occur in a small group on the skin (Fig. 10.1), mouth or genitals. The virus lies dormant in nerves and can give rise to reactivated infection (e.g. cold sores). Reactivation can lead to encephalitis, but concurrent skin lesions are rare. Herpes simplex virus can cause severe symptoms in immunocompromised patients and those with chronic skin conditions such as eczema. Infection in mothers at the time of childbirth can give rise to severe or fatal

Table 41.2. *Laboratory diagnosis of virus infections associated with vesicular skin rashes.*

Virus	Diagnosis	Treatment and prevention
Herpes simplex viruses (HSV)	Lesion swab in virus transport medium or vesicle fluid for virus culture, PCR or vesicle fluid for electron microscopy.	No vaccine available. Treatment with aciclovir (iv for severe infections in immunosuppressed patients).
Varicella-zoster virus (VZV)	Swab in virus transport medium or vesicle fluid for virus culture, PCR or vesicle fluid for electron microscopy, culture or PCR. Clotted blood sample tested for VZV-specific IgM may be negative in zoster.	There is a vaccine available. Treatment of chickenpox with aciclovir (iv for severe infections (e.g. pneumonia and encephalitis) and in immunosuppressed patients). Zoster can be treated with valaciclovir, famciclovir (or iv aciclovir in immunocompromised patients).
Stevens–Johnson syndrome	Investigate infectious cause.	
Enteroviruses	Enteroviruses can be found in vesicles by electron microscopy and PCR. Some infecting types can be cultured, but inoculation into mice is also employed. Throat swabs in virus transport medium or faeces tested by culture or PCR for diagnosis.	No vaccine available. No antiviral treatment available.
Pox viruses	Lesion swab, vesicle fluid or scab for PCR or electron microscopy.	Smallpox vaccine available. No antiviral treatment available.

infection in neonates (Chapter 42). Antiviral treatment (aciclovir, valaciclovir, famciclovir, foscarnet, etc.) is available.

Varicella-zoster virus (VZV)

Primary VZV infection gives rise to chickenpox. The virus lies dormant in the nerve cells and can reactivate later in life to produce zoster (shingles), which produces clusters of vesicles on one side of the body in the distribution of a sensory nerve. Lesions in one cluster are usually at different stages of development (cropping), which can help in distinguishing infection from HSV (where all lesions are usually at the same stage of development). Varicella-zoster virus can cause severe symptoms in immunocompromised patients. Chickenpox in the first 20 weeks of pregnancy can cause severe or fatal damage in the fetus (Chapter 42). Infection in the last 7 days of

Fig. 41.2. Orf virus.

pregnancy poses a severe risk of neonatal chickenpox in the baby, which can be fatal. Antiviral treatment (aciclovir, valaciclovir, famciclovir, etc.) is available.

Stevens–Johnson syndrome

Stevens–Johnson syndrome can be caused by HSV, *Mycoplasma pneumoniae* and *Chlamydophila psittaci* infection. It produces target-like lesions on the skin, especially on the genitals. It can mimic chickenpox, especially in children (but the presence of a cough in children should suggest a respiratory cause).

Enteroviruses

Certain enteroviruses (especially coxsackie A viruses) cause hand, foot and mouth disease. This is common in young children and is usually a mild infection associated with small hard vesicles on the palms of the hand, soles of the feet and in the mouth. Adults (usually parents) can have similar symptoms, sometimes with meningism or meningitis with an intense frontal headache.

Fig. 41.3. Orf lesion on hand. (See Fig. 6 in colour plate section)

Pox viruses

Cowpox should be suspected in patients with single large vesicular lesions, especially if patients have had contact with cats. Cowpox should always be considered in patients who have a single large vesicular lesion that develops a scab.

Orf is a parapox virus (Fig. 41.2 shows an electron micrograph of the orf virus) and usually produces a single vesicular lesion on an erythematous base, which soon develops a scab. Orf (Fig. 41.3) is common in farmers, acquired from sheep, especially when bottle feeding lambs, and also acquired from cows (milker's node) when milking. The animals also have vesicular skin lesions.

Smallpox (Fig. 41.4 shows an electron micrograph of the smallpox virus) has been eradicated from the world and is therefore an extremely unlikely diagnosis. However, if smallpox infection is suspected, expert medical opinion should be sought.

Other pox virus infection (e.g. monkeypox) is rare and a history of relevant exotic animal contact is important for the diagnosis.

Wart-like rashes

There are many different *papilloma viruses* which cause wart-like lesions on the skin (skin warts, genital warts, plantar warts (veruccas)) (see Chapter 19). Infection can be diagnosed by testing the excised skin lesions by electron microscopy (EM) or polymerase chain reaction (PCR). Warts can be treated with podophylin and other methods such as excision.

There is an effective papilloma virus vaccine against genital warts (and those viruses responsible for cervical cancer) but not the others.
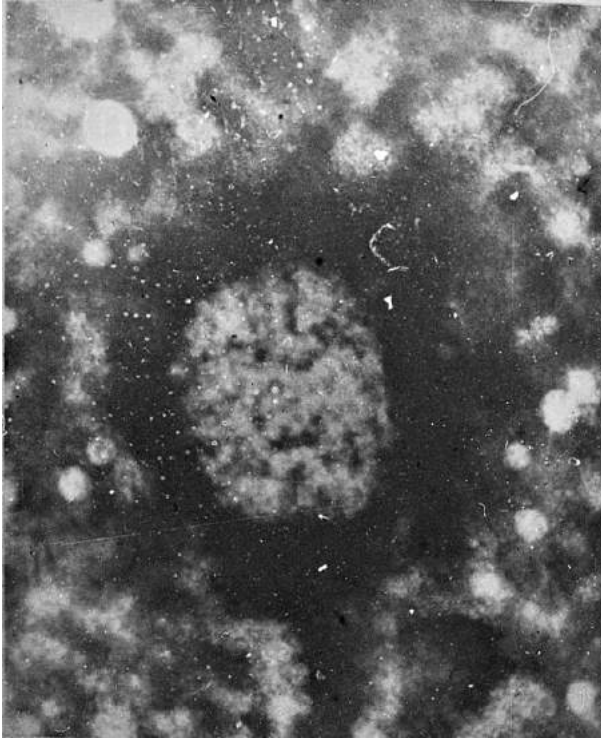
Fig. 41.4. Smallpox virus.

Molluscum contagiosum is a pox virus infection, which causes clusters of small wart-like lesions on eyelid margins, genitals and lower abdominal skin. It is common in children.

Haemorrhagic rashes

Haemorrhagic rashes are usually associated with exotic virus infections such as Lassa fever, Marburg disease, Ebola, Crimean–Congo haemorrhagic fever or dengue fever (see Chapter 2). Patients are often severely ill and give a relevant history of recent travel to tropical countries. A careful history of the exact location of recent travel and other factors (e.g. contact with rodents or monkeys) is very important for the correct diagnosis to be made. Lassa fever can be effectively treated with ribavirin if prompt treatment is given. There are no effective antiviral treatments for the other haemorrhagic fever virus infections. Patients should be isolated in strict isolation facilities until a diagnosis is made. Diagnosis is made in specialist reference laboratories using EDTA blood or throat swabs in virus transport medium.

Rarely, haemorrhagic chickenpox occurs, almost always in immunosuppressed patients. It is usually a very severe or fatal disease, which requires prompt high dose intravenous aciclovir treatment.

42 Infections in pregnancy, congenital and neonatal infections

Infection in the pregnant woman not only has consequences for the mother but for her unborn child as well. The infection may be transmitted to the fetus in utero (*congenital infection*), or at or around the time of birth (*perinatal infection*) or be transmitted some time after birth in the first few weeks of life (*postnatal infection*). See Table 42.1.

Any systemic virus infection in pregnancy may potentially lead to fetal loss, but in this chapter only those infections will be considered that are specifically associated with vertical transmission from the mother to the baby, either in utero or in the peri- or postnatal period.

Congenital infection

The following pathogens cause congenital infection of the fetus. Not all are teratogenic (i.e. cause congenital malformation of the fetus).

- rubella virus
- cytomegalovirus
- *Toxoplasma gondii*
- parvovirus B19
- varicella-zoster virus (chickenpox).

Perinatal infection

Most maternal infections are transmitted to the fetus at or around the time of birth as this is the most vulnerable period. Mixing of feto–maternal blood occurs as the placenta ruptures; also the neonate is exposed to maternal secretions as it comes out of the birth canal. The following pathogens cause perinatal infections:

- HIV
- hepatitis B virus
- hepatitis C virus
- HTLV 1
- herpes simplex virus
- *Chlamydia trachomatis*
- varicella-zoster virus (chickenpox).

Table 42.1. *Important viral and related congenital infections.*

Pathogen	Clinical manifestation			Stage of vertical transmission		
	Congenital malformation	Infection without congenital malformation	Chronic infection	In utero	Perinatal	Postnatal
Cytomegalovirus (CMV)	++ (15% babies will have symptoms)	+++	+ (ongoing infection may occur)	+++		+++ (breast milk)
Rubella virus	+++ (80% risk of severe malformation if maternal infection in first 6 weeks of gestation)	+ (where maternal infection occurs after first trimester)		+++		
Toxoplasma gondii	++	+++		+++		
Varicella-zoster virus	+ (1–3% risk of congenital varicella syndrome after in utero infection in first 20 weeks)	+++ (neonatal chickenpox)		+	+++ (if mother gets chickenpox 7 days before to 7 days after delivery)	
Parvovirus B19 virus		++ (10% risk of fetal loss, hydrops fetalis)		++		

Herpes simplex virus	++ (neonatal herpes simplex infection)		+/–	+++ (80% of all infection acquired at time of birth as a result of primary genital herpes in mother)	++ (20% acquired postnatally from mother or other close relatives via direct contact with infected lesions)
Chlamydia trachomatis	+ (ophthalmia neonatorum)			+ (genital chlamydia infection in mother)	
HIV	++	++	+/–	+++	+++ (breast milk)
Hepatitis B virus	++	+ to +++ (depending on mother's HBe antibody status)	+/–	+++	
Hepatitis C virus	+	+/–	+/–	+	
HTLV 1	+	++	+/–	++	+++ (breast milk)

Postnatal infection

Breast milk is the potential source for transmission to the neonate in the immediate period after birth, and breast feeding is a significant risk factor for vertical transmission of:

- HIV
- HTLV 1
- cytomegalovirus.

Rubella

Maternal rubella infection in the first trimester invariably leads to transplacental transmission and fetal infection with severe malformation, and is an indication for therapeutic termination of pregnancy. The risk of severe fetal malformation is maximum if infection occurs in the first trimester, being about 80% for maternal rubella infection in the first 6–8 weeks of pregnancy. Although fetal infection may occur at any stage of pregnancy it rarely causes severe fetal defects after 17 weeks of gestation.

The classical triad of congenital rubella syndrome (CRS) is congenital bilateral cataract (first associated with congenital rubella infection by an Australian ophthalmologist, Sir Norman Gregg), microcephaly and sensorineural deafness. This is usually accompanied with a purpuric rash (due to thrombocytopenia) and hepatomegaly.

With the introduction of the childhood rubella vaccination programme, rubella and CRS has been virtually eliminated from the UK, USA and from European countries where childhood MMR vaccination programmes are in place. In addition, in the UK, all pregnant women are screened for rubella immunity at their first antenatal visit and those found to be susceptible are offered vaccination in the immediate postpartum period.

Cytomegalovirus (CMV)

Like rubella, CMV is a teratogenic virus, but unlike rubella, CMV can cause damage to the fetus at any stage of pregnancy. Primary CMV infection in pregnancy has an overall 40% risk of transmission to the fetus; however, 85% of these congenitally infected babies will be asymptomatic at birth with only 15% showing congenital stigmata. Cytomegalovirus reactivation in pregnancy has a very low risk of causing congenital infection ($<=1\%$).

Sensorineural deafness is the most common defect. Severe congenital manifestations such as microcephaly, thrombocytopenic purpuric rash and hepatosplenomegaly (Fig. 42.1) occur, but not commonly. Treatment with ganciclovir should be considered for those congenitally infected babies who show signs of central nervous system involvement at birth. Trials are ongoing for assessment of the efficacy of ganciclovir to treat milder cases of congenital infection, but presently no efficacy data is available.

Unlike rubella, 90% of babies born to mothers who get primary CMV infection in pregnancy will not be infected or be asymptomatically infected; therefore therapeutic

Fig. 42.1. Congenital CMV. (See Fig. 7 in colour plate section)

termination is not recommended. Also CMV infection is asymptomatic in the vast majority of adults so it is not possible to identify significant contact with a case. Furthermore there is no effective prophylaxis or vaccination for CMV. For these reasons screening for CMV in pregnancy is not advocated.

Postnatal CMV infection is common, with about third of the babies born to mothers who are positive for CMV antibody acquiring it in the first year of life mostly via breast milk. It is essential to identify congenitally infected neonates in the first three weeks of life, as after that congenital infection can not be distinguished from postnatally acquired CMV infection (see Table 42.2).

Varicella-zoster (chickenpox)
Fortunately, as the prevalence of VZV antibody in the UK is >95% in adults, most women by the time they reach the reproductive age group have evidence of past infection.

Maternal chickenpox
Chickenpox in pregnancy may be more severe for the mother, although there is no clear-cut evidence that pregnant women are at increased risk of complications such

Table 42.2. *Diagnosis of congenital infections.*

| Infection | In utero investigations of fetus | | | Investigations in the neonate |
	Fetal blood obtained by cordocentesis	Amniotic fluid obtained by amniocentesis	Other	
Rubella[a]	IgM (can get false negative before 24 weeks)	PCR for rubella virus	PCR for rubella on choriovillus biopsy	PCR on urine, throat swab for rubella virus. Rubella IgM tests at birth.
CMV[b]	CMV PCR and CMV IgM on fetal blood (false negative IgM may occur before 24 weeks)	PCR for CMV		CMV PCR on urine. CMV PCR on 'Guthrie blood spot', which is taken at birth to screen for metabolic disorders.
Parvovirus B19[c]	Parvovirus B19 IgM and PCR		Ultrasound for monitoring of hydrops fetalis. Parvovirus B19 PCR on fetal tissue in case of miscarriage.	Parvovirus B19 IgM tests
Toxoplasma	Toxoplasma IgM and PCR	Toxoplasma PCR		Toxoplasma IgM and PCR

Notes:

[a]In utero diagnosis for rubella is rarely indicated, as risk to the fetus can be assessed on basis of gestational age.

[b]For a definitive diagnosis of congenital CMV infection, CMV should be demonstrated in a specimen taken by 3 weeks of age as after that distinction from postnatally acquired CMV can not be made. In the absence of tests in the first three weeks of life 'Guthrie blood spot' can be tested retrospectively by CMV PCR. A positive result indicates CMV viraemia at birth and confirms congenital infection, but a negative result does not rule it out as all neonates who are congenitally infected with CMV do not have CMV viraemia at birth.

[c]In utero diagnosis for parvovirus B19 infection is rarely indicated as congenital malformation does not occur.

as primary varicella pneumonia. Pregnant women with no evidence of previous chickenpox who have a significant (in the same room for 15 minutes or face to face) contact with a case of chickenpox in the infectious period (Chapter 28) should be tested for IgG antibody to VZV, and those found to be negative should be given prophylaxis with zoster immunoglobulin (ZIG) preferably within 7 days of contact but not later than 10 days after contact. Zoster immunoglobulin has a 70% protective efficacy to prevent clinical chickenpox and in the others it attenuates clinical disease. There is also some evidence that ZIG may reduce the risk of transmission of infection to the fetus (see below). Aciclovir treatment should be offered to all >=20 weeks' pregnant women who have clinical chickenpox, and should be considered on clinical grounds for those who are <20 weeks' gestation.

Fetal and neonatal infection

Chickenpox in the first 20 weeks of gestation has an overall risk of about 2% for fetal malformation as a result of *congenital infection*. Varicella-zoster virus causes infection of the developing neural tube, resulting in rudimentary limbs and scarring.

In addition, if chickenpox develops in the mother in the week before or after delivering then there is a high risk of the neonate developing chickenpox in the first 10 days of life. This is because the neonate would have been exposed in utero to maternal viraemia in the absence of protective maternal antibodies. Neonatal chickenpox infection has a high mortality rate (approximately 30%). Therefore all babies born to mothers who develop chickenpox a week before or after birth should be given prophylaxis with ZIG. Aciclovir prophylaxis may also be used where ZIG is not available.

Live attenuated varicella vaccine is now licensed for use in the UK and there is a case for identifying chickenpox-susceptible women of reproductive age and vaccinating them to prevent infection in pregnancy.

Parvovirus B19

There is no evidence that congenital parvovirus B19 infection leads to malformation, but infection in the first 20 weeks of pregnancy leads to fetal loss in about 7–10% of infected women. The most serious but fortunately rare complication is *hydrops fetalis* as a result of fetal anaemia due to infection of the fetal red cell precursors. If hydrops is detected and managed in time by in utero blood transfusion the fetus survives to term with no long-term ill effects. Pregnant women with an acute parvovirus B19 infection should be referred to an obstetrician and followed up with regular scans.

Toxoplasma gondii

Maternal primary *Toxoplasma gondii* infection is transmitted to the fetus and leads to congenital infection and malformation. The risk of severe disease in the baby is greatest if acquired in the first trimester. Infection can be transmitted throughout

pregnancy, but fetal damage is less severe in later stages. In the first trimester, transmission of infection occurs in about 25% of cases, most (75%) of which will be severely affected and develop myocarditis, hydrocephalus, mental retardation, retinochoroiditis etc. Retinochoroiditis may be unilateral and may follow a relapsing course and lead to blindness later in life if untreated.

Pregnant women with acute toxoplasmosis in pregnancy should be treated with an appropriate antibiotic (pyrimethamine + folic acid supplement) to reduce the risk of and to limit fetal damage due to toxoplasmosis. Expert opinion should be sought as pyrimethamine should only be instituted once intrauterine fetal infection is established on the basis of laboratory investigations (Table 42.2). Treatment should also be given to the infected neonate at birth.

Herpes simplex

There have been rare instances of in utero HSV infection as diagnosed by the presence of HSV lesions at birth. A fifth of the cases of neonatal herpes are acquired postnatally by direct contact with maternal skin lesions or from other close relatives and carers. The clinical disease generally tends to be milder in postnatally acquired HSV infection, and depends upon the age at infection and whether the neonate has passively transferred maternal antibody for protection.

By far the most common route (in 80% of cases) is acquisition of infection at the time of birth from the infected maternal genital lesions. *Prolonged rupture of membranes* and use of *scalp electrodes* increase the risk of transmission, so both should be avoided. The risk is greatest (30%) if the mother has *genital lesions due to primary infection at the time of delivery;* therefore caesarean section is recommended. Herpes simplex virus reactivation poses a much lower risk (3% or less) as the baby would be protected by passively transferred maternal HSV antibody.

Very often it is difficult to distinguish whether the genital herpes lesions present at the time of labour are due to primary infection or reactivation (unless a previous history of documented genital herpes is present).

Clinical manifestations in the neonate as a result of vertically acquired HSV infection at the time of birth are:

- **Localized skin or eye infection** – usually presents in the second week of life; if not treated more than a third of the babies may go on to develop complications (see below).
- **HSV encephalitis** – skin lesions are absent in about 40% of the babies. Presents in the second week of life with seizures or other non-specific symptoms. If untreated this condition has a 50% mortality rate with a 70% risk of long-term sequelae in those who survive.
- **Disseminated HSV infection** – presents generally in the first week of life and is the most severe form of neonatal herpes simplex infection. Skin lesions may only be present in 20% of cases so a high clinical index of suspicion is required to diagnose this condition. Infection disseminates to almost all organs with the involvement
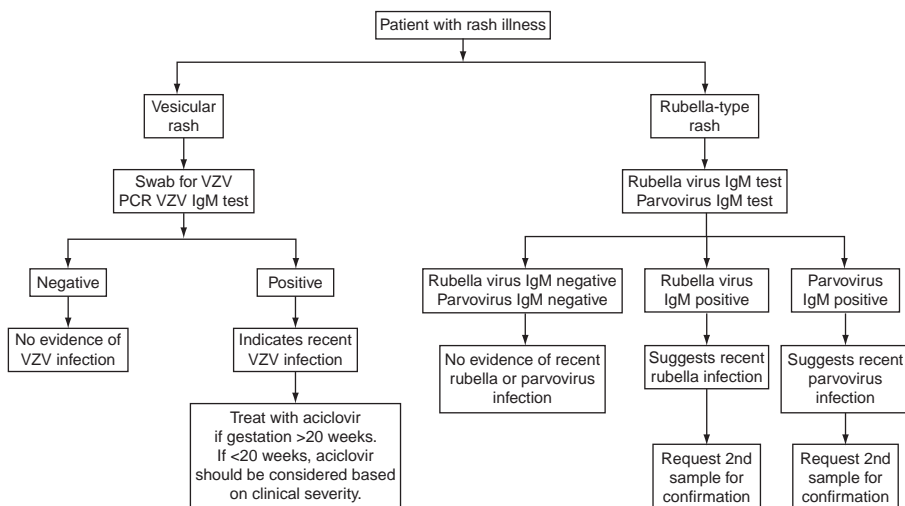
Fig. 42.2. Investigations in a pregnant woman suspected of having a viral rash.

of the CNS (in most cases), liver, kidney, heart, lungs etc. If untreated it is invariably fatal (80% mortality rate).

Management of neonatal herpes infection

Neonatal herpes simplex infection is a medical emergency and immediate specialist advice should be sought. The neonate should be treated without delay (on clinical suspicion) with intravenous aciclovir pending the results of laboratory investigations.

Management of maternal genital herpes infection

Expert advice should be sought, but some general principles that apply are given below.
- Presence of primary genital herpes *lesions* at the time of delivery is an indication for elective caesarean section.
- Use of fetal scalp electrodes should be avoided if mother has genital lesions or a past history of genital herpes infection.
- Pregnant women who present with primary genital herpes after 34 weeks of gestation should be started on aciclovir treatment, which should be continued until term.
- Those presenting before 34 weeks of gestation should be treated with oral aciclovir from 36 weeks onwards (for viral suppression).
- Screening of genital swabs for HSV is not recommended to identify asymptomatic viral shedding.
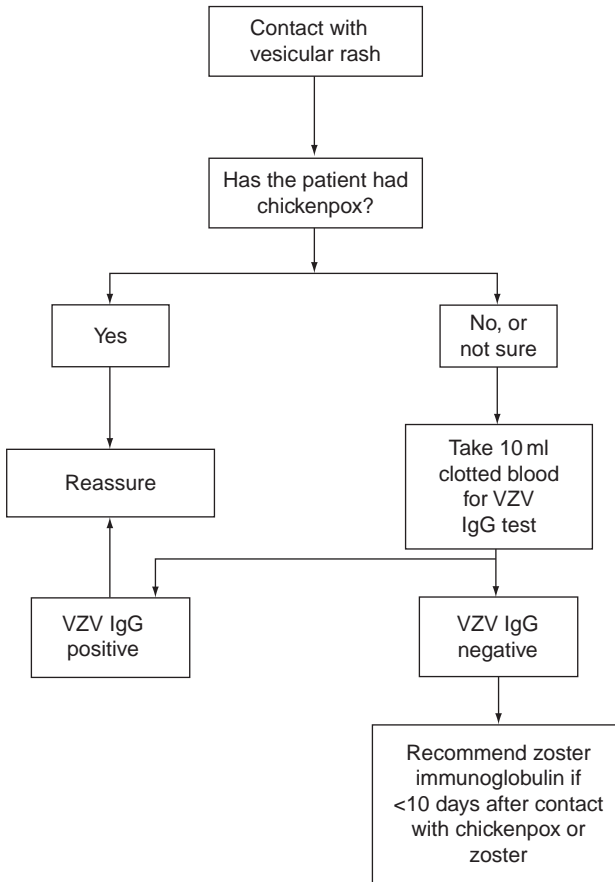
Fig. 42.3. Investigation of a pregnant woman in contact with a case of vesicular rash.

Chlamydia trachomatis

Maternal genital chlamydia infection at the time of birth classically presents as *ophthalmia neonatorum* and is discussed in Chapter 29.

Maternal and neonatal infection with *HIV, Hepatitis B, Hepatitis C and HTLV 1* are discussed in detail under the individual chapter headings and the reader is referred respectively to Chapters 7, 8, 11 and 13.

Follow up of babies suspected of vertically acquired infection

Many congenital infections are not clinically apparent at birth and others manifest late as they are acquired at the time of birth. It is therefore important to follow the new born clinically and by laboratory investigations to ensure that infection has not occurred. For bloodborne viruses, such as HIV, long-term follow up for a year or 18 months may be required. For others, such as CMV and toxoplasmosis, some of the long-term sequelae may appear only in the teenage years.
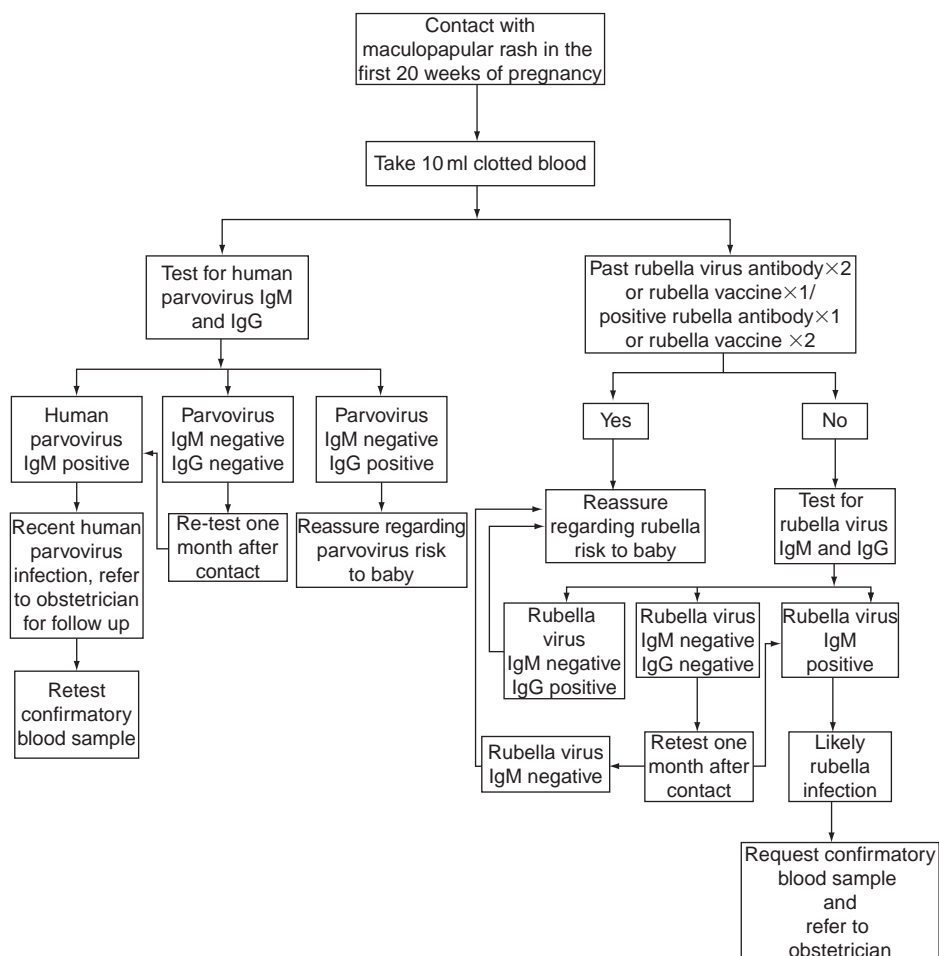
Fig. 42.4. Investigation of a pregnant women in contact with a maculopapular rash.

Laboratory diagnosis

Figure 42.2 shows the laboratory diagnosis for a pregnant women with a rash illness. Figures 42.3 and 42.4 show respectively investigation of a pregnant women in contact with a vesicular and maculopapular rash. Table 42.2 shows the investigations for an infected fetus or neonate suspected of congenital (in utero) infection.

43 Virus infections in immunocompromised patients

There are several categories of immunocompromised patients. Different viruses cause different clinical symptoms in these patients as shown below. HIV positive/AIDS patients often have different symptoms from transplant recipients and need different treatment and prophylactic strategies.

Organ transplant recipients

See Table 43.1.

Cytomegalovirus (CMV)

Cytomegalovirus is the most important virus infection in transplant recipients. Infection acquired from the donor organ is usually most severe and can be fatal. Eighty per cent of CMV antibody negative patients who receive an organ from a CMV antibody positive donor will acquire primary CMV infection. The severity of their symptoms will depend on the amount and type of immunosuppressive treatment they are receiving. Lung and bowel transplants usually have more severe CMV disease than heart, liver or kidney recipients. Between 30% and 60% of CMV antibody positive organ recipients will experience CMV reactivation from one to three months after transplantation. Antiviral treatment for severe CMV disease is intravenous ganciclovir (or foscarnet or cidofivir if ganciclovir is contraindicated).

Herpes simplex virus (HSV)

Herpes simplex virus infection in transplant recipients is almost always a reactivation of latent infection, which occurs from a few weeks to a few months after transplantation. Symptoms can vary from a small cold sore, genital or skin lesion to extensive skin eruptions and, rarely, encephalitis. It can be treated with oral or intravenous aciclovir (depending on the severity of the symptoms).

Varicella-zoster virus (VZV)

Primary VZV infection causes chickenpox; reactivation of latent VZV infection gives rise to zoster (shingles), usually presenting in one dermatome served by a sensory nerve on one side of the body, but widespread vesicular lesions do occur in the most severe infections. Zoster is most common from 1–4 months after transplantation. Chickenpox is usually treated with intravenous aciclovir, but less severe infections and zoster can be treated with oral valaciclovir or famciclovir.

Table 43.1. *Virus infections in transplant recipients.*

Viruses	Symptoms and signs	Diagnosis and samples	Strategies to reduce risk of severe symptoms
CMV	• Pneumonitis • Fever • Malaise • ↑LFTs • ↓WBC • GI tract lesion • Retinitis	• EDTA blood for CMV PCR and quantitative CMV PCR • Clotted blood for CMV IgM in organ recipients. (CMV PCR is preferred)	• Identify CMV antibody negative organ recipients who have received organ(s) from a CMV antibody positive donor and give 3 months' oral valganciclovir prophylaxis • Monitor bone marrow recipients for CMV infection and treat infected patients with ganciclovir
HSV	• Skin lesions • Pneumonitis (especially in lung and heart-and-lung recipients) • Encephalitis	• Vesicle fluid or skin lesion swab in virus transport medium for virus culture or PCR • CSF (if encephalitis) • BAL or lung biopsy (if pneumonitis)	• Identify HSV antibody positive organ recipients at high risk of potentially fatal HSV pneumonitis (e.g. lung and heart-and-lung recipients) and give 6 weeks' oral aciclovir prophylaxis
VZV	• Chickenpox • Shingles • CNS symptoms in the absence of skin lesions	• Vesicle fluid or skin lesion swabs in virus transport medium for virus culture or PCR • CSF (if encephalitis or meningitis)	• Identify VZV antibody negative patients and warn them to avoid contact with persons with chickenpox or shingles. If they do come in contact, give zoster immunoglobulin (ZIG) or oral aciclovir prophylaxis promptly • Good infection control to prevent infection in other VZV antibody negative patients
EBV	• Vague symptoms such as fever, malaise, respiratory	• EDTA blood for EBV PCR or quantitative EBV PCR	• If severe EBV infection (especially lymphoproliferative disease or lymphoma) reduce immunosuppression

Table 43.1. (*cont.*)

Viruses	Symptoms and signs	Diagnosis and samples	Strategies to reduce risk of severe symptoms
	• Lympho-proliferative disease/lymphoma	• Clotted blood (paired samples) for EBV IgM and VCA antibody tests • EDTA blood for EBV PCR	as much as possible and consider treatment with rituximab
Adenoviruses	• Pneumonia • Diarrhoea and vomiting	• Nose and throat swabs in virus transport medium for culture and PCR • Nasopharyngeal aspirate (NPA) for immunofluorescence (IF) or PCR • EDTA blood for PCR • Stools for PCR	• Good infection control to prevent infection in other patients • Treat with cidofovir if clinically indicated
Parainfluenza viruses	• Pneumonia	• Nose and throat swabs in virus transport medium for culture and PCR • NPA for IF or PCR	• Good infection control to prevent infection in other patients
Polyoma viruses	• CNS symptoms	• CSF for PCR	• None
Papilloma viruses	• Skin warts • Genital warts	• Clinical diagnosis, but lesion biopsy for PCR may be done if unsure of diagnosis	• None
Toxoplasma gondii	• Fever • Pneumonia • Encephalitis • Myocarditis	• Clotted blood for *T. gondii* IgM in organ recipients • EDTA blood or CSF for *T. gondii* PCR	• Identify *T. gondii* antibody negative liver, heart and heart-lung organ recipients who receive organs from *T. gondii* antibody positive donor and give 6 weeks' co-trimoxazole or pyrimethamine after transplantation

Epstein–Barr virus (EBV)

Epstein–Barr virus causes glandular fever in immunocompetent persons, but not in transplant recipients, who usually have vague symptoms (fever, headache). About 60% of organ transplant recipients will have reactivation of EBV latent infection in the first few years after transplantation (most in the first year). The most important symptoms associated with EBV infection are post-transplant lymphoproliferative disease (PTLD) or lymphoma, which occur in 2–5% of UK organ recipients (there is a higher percentage in the USA because higher levels of immunosuppression are given there). There is no specific antiviral drug recommended for treating EBV but the use of humanized monoclonal antibody (rituximab) directed against the CD20 epitope of infected B cells has some success in treating PTLD. Lowering the doses of immunosuppressive drugs should always be attempted in patients with PTLD or lymphoma. Primary EBV infection is rare in transplant recipients, is more common in children and is usually acquired with the donor organ.

Adenoviruses

Adenoviruses can cause respiratory, eye or gut infections in organ transplant recipients. They are usually not life threatening, but are more severe and frequent in children. Excretion of the virus can be prolonged, and patients may need regular monitoring after infection to check their infectivity and prevent spread to other vulnerable patients. The most severe infections can be treated with cidofovir.

Polyoma viruses

Polyoma viruses cause haemorrhagic cystitis and CNS symptoms in organ transplant recipients (especially renal transplant recipients). See Chapter 19.

Papilloma viruses

Papilloma viruses cause wart lesions in transplant recipients. Transplant patients can have extensive lesions.

Toxoplasma gondii

Toxoplasma gondii infection can be acquired from organ donors. Sixty per cent of heart, 20% of liver and <1% of kidney *Toxoplasma gondii* antibody negative transplant patients acquire primary infection from antibody positive organ donors. Infection can be life threatening, but sulphadiazine and pyrimethamine treatment is available. For those at risk of donor-acquired infection, cotrimoxazole or pyrimethamine prophylactic treatment can prevent symptomatic infection. Between 1–2% of patients experience symptomatic *Toxoplasma gondii* reactivation after transplantation.

Bone marrow transplant patients

Cytomegalovirus (CMV)

Cytomegalovirus is the most important virus infection in bone marrow transplant recipients. Donor-acquired and CMV reactivation infections can both cause severe or

fatal infections in the first few months after transplantation. Antiviral treatment for severe CMV disease is intravenous ganciclovir (or foscarnet or cidofivir if ganciclovir is contraindicated). Patients who are CMV antibody positive or who receive bone marrow from CMV antibody positive donors will need monitoring regularly by CMV DNA polymerase chain reaction (PCR) to check for CMV infection. If infection is detected, pre-emptive treatment with ganciclovir is indicated.

Herpes simplex virus (HSV)
Herpes simplex virus infection in bone marrow transplant recipients is almost always a reactivation of latent infection, which occurs from a few weeks to a few months after transplantation. Since patients are often very immunosuppressed, especially in the first few months after transplantation, lesions can be extensive. It can be treated with oral or intravenous aciclovir (depending on the severity of the symptoms).

Varicella-zoster virus (VZV)
Primary VZV infection (chickenpox) is rare, but reactivation of latent VZV infection (zoster or shingles), usually presenting in one dermatome served by a sensory nerve on one side of the body, is more common. Widespread vesicular lesions in more than one dermatome occur in the most severe infections. Zoster is most common from 1–4 months after transplantation. Chickenpox is usually treated with intravenous aciclovir, but less severe infections and zoster can be treated with oral valaciclovir or famciclovir.

Epstein–Barr virus (EBV)
Epstein–Barr virus causes vague symptoms (fever, headache) in bone marrow transplant recipients. There is no antiviral drug recommended for treating EBV.

Adenoviruses
Adenoviruses can cause respiratory, eye or gut infections in bone marrow transplant recipients. They can be life threatening, and are more severe and frequent in children. The most severe infections can be treated with cidofivir.

Parainfluenza and respiratory syncytial viruses (RSV)
Parainfluenza viruses types 1–4 and RSV can cause severe respiratory infections in bone marrow transplant recipients. These viruses can spread easily in bone marrow transplant units, and careful infection control precautions are necessary in order to limit their transmission to other vulnerable patients. Treatment with aerosolized ribavirin can be given to patients with severe infections.

Polyoma viruses
Polyoma viruses cause central nervous system symptoms in bone marrow transplant recipients.

Papilloma viruses
Papilloma viruses cause wart lesions in bone marrow transplant recipients.

Toxoplasma gondii

Toxoplasma gondii infection in bone marrow transplant recipients is usually reactivation of latent infection. Infection can be life threatening, but sulphadiazine and pyrimethamine treatment is available.

HIV antibody positive/AIDS patients

See Table 43.2.

Cytomegalovirus (CMV)

Cytomegalovirus is the most important virus infection in HIV antibody positive/AIDS patients. Symptoms in HIV antibody positive patients are different to those in transplant recipients, due to the different nature of the immunosuppression in these patients. Transplant patients are given immunosuppressive drugs to eliminate the T-cell response related to organ rejection. HIV antibody positive/AIDS patients have a far more extensive T-cell immunosuppression. Most infections result from reactivation of latent infection. Antiviral treatment for severe CMV disease is intravenous ganciclovir (or foscarnet or cidofivir if ganciclovir is contraindicated). Intra-ocular ganciclovir can be used to treat CMV retinitis.

Herpes simplex virus (HSV)

Herpes simplex virus infection in HIV positive patients is almost always a reactivation of latent infection, which occurs when white blood cell levels fall, and can be one of the earliest signs that a patient is developing AIDS. It can be treated with oral or intravenous aciclovir, valaciclovir, famciclovir or foscarnet (depending on the severity of the symptoms).

Varicella-zoster virus (VZV)

Zoster is the most frequent VZV infection in HIV antibody positive/AIDS patients. It usually presents when white cell counts fall and before patients develop AIDS. Patients can have several episodes of zoster. Severe VZV infections are treated with intravenous aciclovir, but less severe infections can be treated with oral valaciclovir or famciclovir.

Epstein–Barr virus (EBV)

Epstein–Barr virus causes vague symptoms (fever, headache) in HIV antibody positive/AIDS patients, but is also associated with hairy leukoplakia, which presents with lesions on the tongue. Primary EBV infection is rare, because 95% of persons have had EBV infection by late teenage.

Polyoma viruses

Polyoma viruses cause lesions in the brain (progressive multifocal leukoencephalopathy).

Table 43.2. *Virus infections in HIV antibody positive/AIDS patients.*

Viruses	Symptoms and signs	Diagnosis and samples	Strategies to reduce risk of severe symptoms
CMV	• Fever • Malaise • GI tract lesion • Retinitis • Encephalitis	• EDTA blood for CMV PCR and quantitative CMV PCR	• Oral valganciclovir prophylaxis to prevent CMV retinitis for those with advanced HIV infection and low white cell blood counts
HSV	• Skin lesions • Genital herpes • Pneumonitis • Encephalitis	• Vesicle fluid or skin lesion swab in virus transport medium for virus culture or PCR • CSF (if encephalitis) • Bronchoalveolar lavage (BAL) or lung biopsy (if pneumonitis)	• Some severely immunocompromised patients with frequent recurrent HSV infections require continuous oral aciclovir prophylaxis
VZV	• Chickenpox • Shingles • CNS symptoms in the absence of skin lesions	• Vesicle fluid or skin lesion swabs in virus transport medium for virus culture or PCR • CSF (if encephalitis or meningitis)	• Identify VZV antibody negative patients and warn them to avoid contact with persons with chickenpox or shingles. If they do come in contact, give zoster immunoglobulin (ZIG) or oral aciclovir prophylaxis promptly • Good infection control to prevent infection in other VZV antibody negative patients

Organism	Symptoms	Diagnosis	Prophylaxis/Treatment
EBV	• Vague symptoms such as fever, malaise, respiratory • Hairy leukoplakia on the tongue	• EDTA blood for EBV PCR or quantitative EBV PCR	• None
Polyoma viruses	• CNS symptoms	• CSF for PCR	• None
Papilloma viruses	• Genital warts • Skin warts	• Clinical diagnosis, lesion biopsy for PCR if unsure	• Vaccines are available (see Chapter 19)
Toxoplasma gondii	• Encephalitis • Fever • Retinitis • Myocarditis	• CSF and EDTA blood for *Toxoplasma gondii* PCR	• Co-trimoxazole or pyrimethamine prophylaxis for very immunosuppressed patients

Papilloma viruses

Patients with AIDS develop difficult-to-treat and extensive wart lesions as a result of infection with papilloma viruses. They are also more prone to develop malignancies related to the oncogenic papilloma viruses (genotypes 16, 18).

Toxoplasma gondii

Toxoplasma gondii infection in HIV antibody positive/AIDS patients is usually a reactivation of latent infection. The most likely symptoms are fever, malaise, retinitis and space-occupying lesions in the brain, which need to be differentiated from lymphoma. Infection can be life threatening, but sulphadiazine and pyrimethamine is available for treatment and continuous prophylaxis in those severely immunosuppressed patients at risk of reactivation.

44   Viral malignancies

Cell growth, differentiation and death are controlled by genes. Mechanisms are needed for both stimulating and suppressing growth. Breakdown in the mechanism for control of cell growth leads to uncontrolled growth and malignancy. There are many ways in which cells may lose this genetic control, viral infections being one of those. Not all viruses are oncogenic (e.g. able to induce cancer). It is mainly, though not exclusively, the DNA viruses that have this potential. Human T-cell leukaemia virus types 1 and 2, and hepatitis C virus are examples of RNA viruses that are able to induce malignancy.

How do viruses cause cancer?

There are several mechanisms by which this may occur.

Some viruses, such as HTLV 1, possess a *viral oncogene* or *v-onc* gene. Integration of viral genome into the infected cell enables the v-onc gene to be activated. Products of this activated v-onc gene are able to transform the cell by affecting the function of cellular products normally responsible for cell growth. It is believed that v-onc genes have been acquired by viruses through capturing cellular gene material during the process of evolution.

Oncogenes are not unique to viruses, they also form part of the normal cellular genetic material. *Cellular oncogenes* are different in their structure to v-onc and are referred to as *c-onc* to differentiate them from viral oncogenes. The c-onc products are required for normal cell activities.

Mutation in the c-onc gene is an important mechanism for cell transformation. This mutation can be triggered by viral integration next to the c-onc gene (*insertional mutation*) or exposure to radiation, chemicals and other toxins and explains the role of these agents in the pathogenesis of human cancer.

Products of viral genes may bind to *cell-suppressor proteins* such as *p53* (a nuclear protein). These proteins are important in restricting cell growth during the normal repair mechanism, therefore inhibition of these proteins by viruses leads to unchecked cell proliferation and cancer.

Besides these direct mechanisms other indirect mechanisms such as viral *immuno-suppression* (e.g. by HIV) make the host susceptible to malignancies because of the inability of normal immune mechanisms to keep in check the proliferation of 'abnormal' cells.

Table 44.1. *Examples of viral malignancies.*

Malignancy	Associated DNA virus	Associated RNA virus	Co-factors
Hepatocellular carcinoma	Hepatitis B virus	Hepatitis C virus	Other co-infections, ingestion of aflatoxins, cirrhosis
Cervical cancer	Human papilloma viruses types 16, 18, 31, 33		Smoking
Adult T-cell leukaemia		HTLV 1	
Burkitt's lymphoma	Epstein–Barr virus		Malaria
Nasopharyngeal carcinoma			Nitrosamines Genetics
Post-transplant lymphoproliferative disease			Immunosuppression
Hodgkin's and B-cell lymphomas			
Kaposi's sarcoma	Human herpes virus 8		Immunosuppression

Human malignancies and their viral causes

Often it is difficult to associate a viral aetiology directly to human malignancy because of the long latent period between infection and development of cancer. Infections are common but cancers are rare, and the development of cancer also involves a complex interplay between the virus and the host and may require other co-factors so that not all who are infected necessarily develop the disease. Even though viruses are the direct cause of the following malignancies, other co-factors may be required for the development of some if not all of the cancers listed below. Therefore the important co-factors and their roles are also outlined. See Tables 44.1 and 44.2.

Adult T-cell leukaemia/lymphoma (ATL)

This is an aggressive form of adult leukaemia/lymphoma associated with HTLV 1 (Chapter 13). It is limited to southern Japan and its epidemiology is linked to the prevalence of HTLV 1 in Japan. Most at risk for ATL are those who acquire infection at birth from infected mothers. HTLV 1 mediates the lymphocyte transformation through the activation a v-onc gene subsequent to integration of pro-viral DNA into the cellular DNA.

Burkitt's lymphoma (BL)

This is geographically limited to specific parts of Africa and is a lymphoma of childhood. The commonest presenting site is the angle of the jaw or the orbit

Table 44.2. *Viruses as cause of human cancers.*

Virus	Cancer
Epstein–Barr virus (EBV)	Burkitt's lymphoma, nasopharyngeal carcinoma, post-transplant lymphoproliferative disease, Hodgkin's and B-cell lymphomas.
Hepatitis B virus (HBV)	Hepatocellular carcinoma (HCC)
Hepatitis C virus (HCV)	Hepatocellular carcinoma (HCC)
HTLV 1	Adult T-cell leukaemia (ATL)
Human herpes virus 8 (HHV 8)	Kaposi's sarcoma
Human papilloma virus (HPV)	Cervical, squamous cell, penile and vulval cancers

of the eye. If untreated it is invariably fatal. Epstein–Barr virus (EBV) is present in 95% of Burkitt's lymphomas. All cases of African BL are associated with EBV, but some sporadic cases may not be. There is a strong association with malarial infection (which may act as a co-factor) as African BL is limited to the malaria hyper-endemic belt in Africa. The mechanism of oncogenesis is considered to be through activation of a cellular oncogene (c-myc) as a result of integration of viral DNA in close proximity to the gene.

Cervical cancer

There is overwhelming aetiological evidence implicating human papilloma viruses (HPV) as the cause of cervical cancer, the virus being detected in virtually all cases of cervical cancer. About 70% of all cervical malignancies are associated with papilloma virus types 16 and 18, and the others are associated with higher types 31, 33 and 35 etc. Collectively these are referred to as high-risk papilloma viruses.

The two envelope proteins E6 and E7 of papillomaviruses are consistently expressed in the cancer cells. E6 has binding properties for the nuclear p53 protein responsible for regulating cell growth; destruction or inhibition of p53 leads to unchecked proliferation and cancer. Not all patients infected with high-risk HPV types develop cancer and it is likely that other co-factors such as smoking are important.

The recent introduction of a papilloma virus vaccine (against HPV types 16 and 18) targeted at pre-pubertal girls is expected to reduce (but not eliminate – as the vaccine does not cover all the high-risk types) the incidence of cervical cancer considerably for future generations.

Hepatocellular carcinoma (HCC)

This is associated with both *hepatitis B (HBV)* and *hepatitis C (HCV)* infection. There is a very strong clinical and epidemiological link between HBV and HCV chronic infection and HCC. In countries of South East Asia and Africa with a high prevalence of hepatitis B virus (HBV), HCC is the most common malignancy in males.

The mechanism by which HBV induces the cancer may be twofold: HBV is a double-stranded DNA virus and capable of integrating in the cellular genome, and

integrated HBV viral DNA can be demonstrated in most cases of HCC. Such insertions have been shown to deregulate the cellular control functions possibly by activating one or more c-onc genes responsible for cell growth.

Chronic HBV and HCV infection lead to cirrhosis of the liver, due to repeated cycles of cell damage and repair. Hepatocellular carcinoma invariably follows cirrhosis in patients with chronic HBV and HCV infection, therefore may simply be a result of cell overgrowth during the repair cycles. This mechanism is most likely for *HCV*, which is an RNA virus and does not integrate. This also explains the development of liver cancer post alcoholic and other cirrhosis.

In Africa, contamination of the staple diet of groundnuts by the fungus aspergillus, which produce aflatoxins (chemicals), and its consumption is an important co-factor for development of HCC.

Hepatitis B virus-associated HCC is another of the vaccine-preventable malignancies (see cervical cancer above).

Kaposi's sarcoma

This is an endothelial cell carcinoma, which used to be seen only in elderly African men before the arrival of AIDS. It is a common cancer in patients with full blown AIDS. It is directly associated with human herpes virus 8 (HHV 8), and HHV 8 sequences can be demonstrated in the tumour. Human herpes virus 8 most likely transforms the cells through insertional mutations in the cellular oncogenes.

Nasopharyngeal carcinoma

This is another EBV-associated cancer, and the virus can always be demonstrated in the cancer cells. It is found most commonly in southern China and Africa. Unlike Burkitt's lymphoma, which is a malignancy of childhood, nasopharyngeal carcinoma occurs in adults. Several co-factors have been identified such as consumption of nitrosamines in a salt-cured fish diet, the inhalation of recreational drugs (snuff) and a genetic predisposition of certain HLA types. These co-factors vary depending upon the part of the world the cancer is seen in.

Post-transplant lymphoproliferative disease (PTLD)

This is an aggressive form of lymphoma seen only in immunosuppressed patients, and has a high mortality rate. Epstein–Barr virus infection in immunosuppressed patients leads to unchecked proliferation of the infected B-cells and subsequently to lymphoma. The initial B-cell proliferation is polyclonal; transformation of one or more B-cell clones leads to development of lymphoma. It is the most common malignancy seen post bone marrow and solid organ transplantation (hence the name) and EBV naive patients who receive an organ from an EBV positive donor (R−/D+) are the most at risk. The incidence of PTLD varies from centre to centre according to the organ transplanted and immunosuppression regime in use, but is reported to be between 2–10% (lower in the UK than in the USA because of lower immunosuppressive regimes).

AIDS patients, due to the immunosuppression induced by HIV, are also at risk of PTLD mostly due to reactivation of EBV infection.

In addition to the standard treatment for lymphoma, rituximab (a monoclonal antibody against CD20) should also be used.

Hodgkin's lymphoma, B-cell lymphoma and hairy cell leukoplakia
Some but *not* all forms of these malignancies are associated with EBV infection.

Squamous cell, penile and vulval cancers
Some squamous cell carcinomas are due to the high-risk HPV types, and there is strong evidence now linking genital HPV infection with penile and vulval cancers.

Control of viral malignancies

Serendipitously, the associated viral malignancies will be controlled at the same time as control of the primary viral infections through:
- public health campaigns on avoidance of infection, e.g. avoidance of HTLV 1 infected mothers breast feeding in high-risk populations to prevent vertical transmission of infection
- use of viral vaccines such as those against hepatitis B and human papilloma viruses
- where possible, immune restoration in the immunosuppressed so the native immune system is able to check tumour cell proliferation (e.g. reducing immunosuppressive drugs in transplant recipients).

45   Travel-related infections

There has been an explosion in international travel during the past two decades. Travel in the past was the domain of the rich, but due to the availability of cheap air travel and 'package holidays' it has come within the grasp of most people in the developed world. People are travelling far, and to parts of the world that were previously inaccessible to them. The desire to visit far-flung 'exotic' locations is insatiable. With this travel comes the danger of being exposed to infections outside one's routine experience. There is also a tendency to throw caution to the wind, not to take the usual precautions and to expose one's self to risks. One of the aims of a holiday, after all, is to relax and try new experiences; it is not surprising therefore that many travellers become ill with infections while on holiday or bring them back. Below are some common (and some not so common) clinical illnesses due to infections that are seen in returning travellers in the UK (See Table 45.1). The reader should consult the individual virus chapters for details of individual infections.

Gastroenteritis

Diarrhoea is by far the most common complaint in travellers. Most of the infections are due to bacteria. Noroviruses are important viral pathogens, especially in those who indulge in eating raw shellfish such as oysters and prawns. Impressive outbreaks of *norovirus gastroenteritis* have occurred in hotels and cruise ships where a large number of people are confined in an enclosed space, and there are many horror stories of ruined holidays because of this.

Pyrexia of unknown origin (PUO)

A febrile illness in returning travellers requires the elucidation of an accurate travel history and activities while on holiday, as often there are clues as to the diagnosis. Malaria and typhoid should be considered first and need to be ruled out. *Dengue virus infection* may present as a non-specific febrile illness, but the most dangerous are the *hemorrhagic fevers* (Chapter 2). The Advisory Committee on Dangerous Pathogens (ACDP) has provided guidelines for risk assessment. Specialist advice should be sought in case of suspected infection. Detailed discussion is outside the scope of this chapter and the reader should refer to the following:

Advisory Committee on Dangerous Pathogens (1996) *Management and Control of Viral Haemorrhagic Fevers.* London: The Stationary Office, pp. 1–65.

Table 45.1. *Viral infections associated with travel outside the UK.*

	Virus	Clinical presentation	Transmission routes
Viruses endemic in the UK and also imported by returning travellers from endemic countries	Hepatitis A	Hepatitis	Consumption of contaminated food or water
	Hepatitis B	Hepatitis	Medical intervention, unprotected sexual intercourse
	HIV	Suspected acute HIV (seroconversion) illness	Medical intervention, unprotected sexual intercourse
	Norovirus	Diarrhoea and vomiting	Consumption of contaminated food or contact with a case
Viruses non-endemic in UK and imported by returning travellers from endemic countries	Hepatitis E	Hepatitis	Consumption of contaminated food or water
	Dengue and other arboviruses	See Chapter 2	See Chapter 2
	Viral haemorrhagic fevers (VHF)	See Chapter 2	See Chapter 2
	Rabies	History of a dog or animal bite	A dog or animal bite

Respiratory infections

The most likely cause of these will be the common respiratory viruses prevalent at the time of travel. *Avian influenza (H5N1)* should be excluded if the traveller has returned from an endemic area or there is history of contact with infected birds. It is well worth remembering that the SARS outbreak was a result of infected travellers carrying the virus with them while incubating the infection, with fever and respiratory illness manifesting in a place different to where the infection was acquired.

Hepatitis

Hepatitis A and E are the most common causes of hepatitis in returning travellers from countries where these infections are endemic (mostly developing and under developed

countries of the world). The infections are spread by the faecal–oral route through contaminated food and water. While in endemic countries it is therefore advisable to avoid eating salads and other uncooked food, and to drink only bottled water. There is effective vaccination for hepatitis A, and all travellers to endemic countries should be immunized prior to travel. *Hepatitis B (HBV)* should be considered in the differential diagnosis in the case of at-risk sexual activities, especially while travelling to countries with high HBV prevalence.

Rabies

A dog bite or animal bite or lick on an open wound in countries where rabies is still endemic is a medical emergency, and post-exposure vaccine and immunoglobulin prophylaxis should be given immediately as rabies is invariably fatal.

Infections associated with medical tourism

The term 'medical tourism' is used for people who travel abroad with the express purpose of receiving medical treatment. Patients with chronic renal failure who are on haemodialysis have to receive their regular dialysis from a local unit. The most significant risk is that of acquiring bloodborne viruses such as *hepatitis B, C* and *HIV* especially in countries with a high prevalence of infection and where control of infection standards are not as high as in the UK. Transmission of HBV and HCV infection occurs in many haemodialysis units abroad. Transfusion of blood or blood products in countries where there is no universal screening programme of blood donors for bloodborne viruses also carries a high risk of infection.

Miscellaneous infections

Infections in the returning traveller are not limited to those mentioned above, and the differential diagnosis will depend upon the presenting clinical features and epidemiological history. The clinician must not be misled by the history of travel and forget to think of common infections such as EBV, CMV or parvovirus B19 infections. Sexual history, if relevant, should be taken to rule out sexually transmitted infections.

Section 4 – Diagnostic techniques

46   Sending specimens to the laboratory

Sending the correct specimens

It is important to establish which are the best specimens to send to the laboratory. Chapters in this book suggest which specimens are suitable for the diagnosis of different virus infections and clinical syndromes, but the reader is also advised to check with the local laboratory's user manual as not all assays are offered by all laboratories. It is important to consider when in the patient's clinical course specimens should be sent. There are a few simple rules of thumb.

- Virus antibody is usually not present in serum reliably until about 10 days after the onset of symptoms.
- For those viruses where specific IgM is not tested for, an acute sample taken as soon as possible after the onset of symptoms and a second specimen taken 10 days after the onset of symptoms allows for the detection of a specific antibody rise.
- Viruses causing maculopapular rashes (e.g. measles virus) usually produce specific IgM antibody within a few days of the onset of the rash.
- When diagnosing acute hepatitis, HBs Ag will be present at the onset of symptoms of HBV infection, but HAV IgM is not detectable until at least 5 days after the onset of symptoms.
- In general, if you are sending specimens for virus culture, send them in virus transport medium. Do not send dry swabs for virus investigations – they will almost always be discarded.
- In general, EDTA blood specimens are preferred for molecular diagnosis – but as with all test requests, check your local guidelines relating to which specimens to send when.

Filling in the specimen request form correctly

It is important to fill in the specimen request form with as much detail as possible.

- Always provide at least three patient identifiers from the list below. Failure to do so (or providing different information on the specimen container and the request form) will result in the specimen being discarded or not being tested.
  first and last names
  date of birth
  NHS number (in the UK)
  hospital number
  address.

Fig. 46.1. Specimen request form.

- Always provide full details of the healthcare professional to whom the result should be sent. It is useful to provide a telephone number, especially for telephoning urgent or abnormal results. This is particularly important if it is likely that the result will need to be phoned (e.g. specimens from needle-stick injury, donors or a pregnant woman in contact with chickenpox).
- Specimen type.
- Tests requested.
- Date and time the specimen was taken.
- Clinical information – include relevant epidemiology and date of onset of symptoms. This is the most important information because it allows the laboratory doctor to request the most appropriate tests and to interpret the laboratory findings. Failure to provide this hampers the provision of an individual service.
- Have previous specimens been sent? This is important for paired serological investigations.

Packaging specimens correctly

Ensure that specimens are in leak-proof containers. Hospital specimens should be sent in plastic marsupial bags, which allow the request form to be kept separate from the specimen. Postal and air freight regulations and those relating to dangerous organisms must be followed at all times.

Notifying the laboratory that urgent/important specimens are being sent

It is useful to telephone the duty virologist or microbiologist if urgent or important specimens are to be sent to the laboratory. This will ensure that specimens are processed correctly, the required tests are done and the results are telephoned promptly. Tests can often be done urgently if the clinical outcome is likely to be affected by the result.

Ideal specimen request form

A typical request form is shown in Fig. 46.1.

47 Serological techniques

Very often it is difficult to make a clinical diagnosis of a specific viral infection, as many viruses have clinically similar presentation (e.g. hepatitis viruses, Chapter 38) and the same virus can have many different clinical presentations (e.g. enteroviruses, Chapter 5). It is therefore essential to seek specific laboratory diagnosis to enable correct management of the patient. This may be important from an epidemiological perspective as well. It has been shown that even experienced clinicians are not able to clinically diagnose cases of rubella or measles correctly. A specific diagnosis of a viral rash is important, not only to the clinical management of the patient, but essential for control of infection, outbreak control and the public health perspective of continuing to ensure the efficacy of vaccination programmes.

Antibodies are produced as a host response to viral infection. Immunoglobin A is produced at the local site of infection and provides local immunity, for example in the gut or respiratory tract. The generalized humoral immune response is mounted by B lymphocytes and the first antibody to appear is of the IgM class, which can be detected as early as a couple of days after an acute infection. Some of the B lymphocyte clones then switch over to producing IgG antibody, which appears from 7–15 days after onset of infection. Both classes of antibodies continue to rise in response to the infection, peaking at about 6 weeks post infection. Viral specific IgM then declines and is normally undetectable by about 3 months after infection. *IgG antibody persists for life* and is responsible for *providing lifelong immunity* to the particular virus. Figure 47.1 shows the sequence of serological response after viral infection.

Acute or recent infection can therefore be diagnosed by:
- demonstrating the presence of virus specific IgM (IgG may or may not be present)
- showing a rise in antibody titre between an acute and convalescent specimen, *or*
- a high antibody titre in a convalescent specimen.

Past infection or immunity is diagnosed by:
- demonstration of virus specific IgG alone (and absence of IgM).

Serology is used widely to diagnose viral infections as many of the viruses cannot be easily cultured. 'Serology' means the study of serum and can be used to detect both antibody and antigen (e.g. hepatitis B surface antigen). Several techniques have been developed, but the fundamental principles are similar for all.
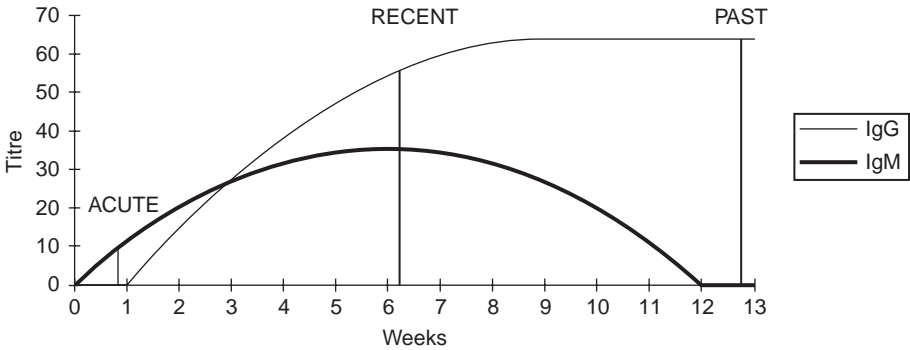
Fig. 47.1. Figurative representation of serological response to viral infection.

Principle of serological techniques

Assays may be *qualitative* (e.g. give only a yes or no answer) or be *quantitative* (e.g. measure the antibody level).

As a rule, assays that utilize the presence of IgM or IgG to make a diagnosis are usually qualitative, as presence or absence of these antibodies is sufficient to make a diagnosis.

On the other hand if diagnosis relies on detection of a rising or a high antibody titre, then the assay needs to measure the level of antibody response (quantitative). *Antibody 'titre'* is expressed as the inverse of the highest serum dilution at which the antibody is detected. For example, influenza A antibody titre of 128 means that antibody to influenza A was detected until a 1 in 128 serum dilution, but not in higher dilutions.

Many of the quantitative assays have been developed by exploiting the functional properties of antibody response (e.g. complement fixation, haemagglutination, neutralization tests). Table 47.1 shows diagnostic uses of the serological techniques.

Techniques

All serological techniques that detect antibody are based on the principle of adding specific viral antigen(s) to patient serum. If virus-specific antibody is present in the serum then it will bind to the antigen to form an antigen/antibody complex. An indicator system (depending on the technique) is then used to detect whether such a complex has been formed. These techniques can be reversed to detect the presence instead of viral antigen, such as hepatitis B surface antigen, in the patient's serum.

Enzyme-linked immunosorbent assays (EIA or ELISA)

These are the most widely used serological assays in routine diagnostic laboratories. There are several variations on the technique but essential steps are shown in Fig. 47.2 a to d.

Table 47.1. *Diagnostic uses of the serological techniques.*

Test	Example of use
Complement fixation test (CFT)	Respiratory viruses – measures total antibody, is quantitative; to diagnose recent infection acute and convalescent serum samples are required to show rise in titre.
Enzyme-linked immunosorbent assays (EIA or ELISA)	IgG/IgM antibody – rubella, measles, mumps, HIV, hepatitis A etc.
	Antigen – hepatitis B surface antigen in serum samples, norovirus and rotavirus antigen in faeces.
Immunofluorescence (IF)	IgG/IgM antibody – EBV, VZV.
	Antigen – RSV, influenza and other respiratory viruses in respiratory secretions.
Latex and gel particle agglutination	Antibody – rubella, toxoplasma.
	Antigen – rotavirus, norovirus.
Western blot (WB) and line assays (LIA)	Used to confirm HIV and HCV-screen positive specimens.
IgG avidity assays	To confirm recent CMV, rubella and toxoplasma infections.
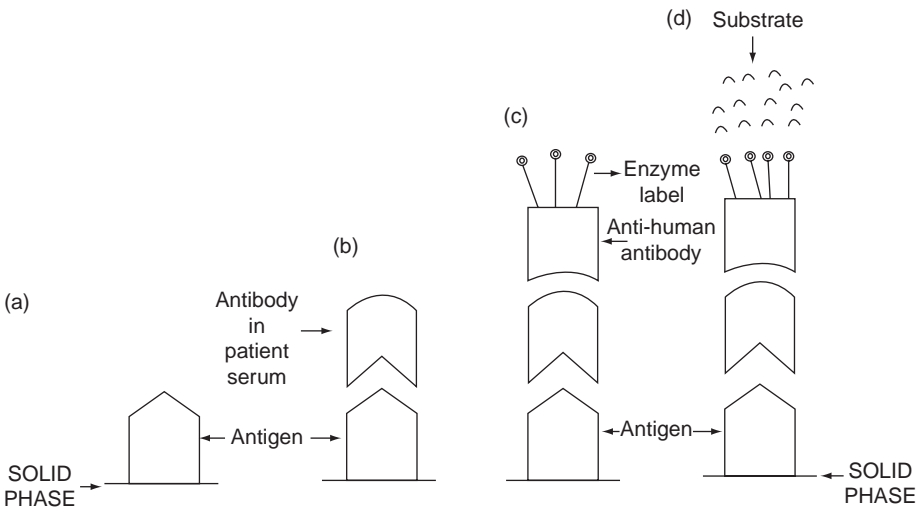
Fig. 47.2. a–d Figurative representation of enzyme-linked immunosorbent assay (EIA).

(a) Antigen is attached to the base of a plastic microtitre well (solid phase).
(b) Patient's serum is added to this microtitre well. If specific antibody is present in the serum it will attach to the antigen on the solid phase. Excess serum is washed off.
(c) Anti-human antibody coupled to an enzyme is added to bind to this antibody/antigen complex. Excess enzyme is washed off.
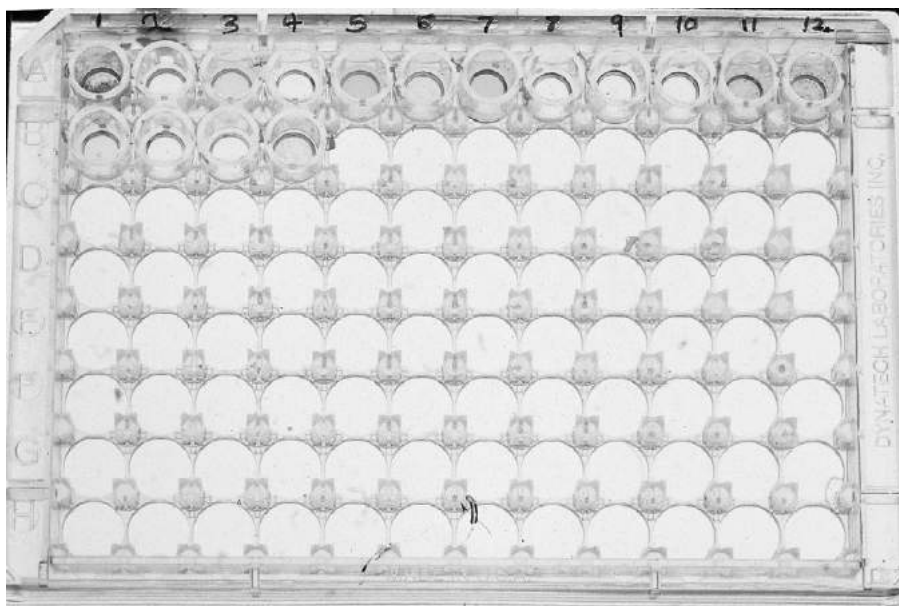
Fig. 47.3. Enzyme-linked immunosorbent assay (EIA) plate. (See Fig. 8 in colour plate section)

(d) A substrate for the enzyme is added, a colour change indicates a positive reaction due to the action (on the substrate) of the enzyme which has been bound to the antigen/antibody complex.

The colour change in the EIA can be detected by eye or measured in a spectrophotometer, and the intensity of the colour can indicate how much antibody is present in the serum. Figure 47.3 shows positive (coloured) and negative (colourless) reactions in the EIA test.

The EIA can be constructed to detect either IgG or IgM depending upon whether the anti-human antibody is directed to the IgM or IgG class. Positive and negative controls are added to the assay runs to ensure the quality of the assay system. Most of the EIAs in use have a very high sensitivity and specificity (>95%), some even approaching 100%.

The assay can also be done in reverse to *detect viral antigens* simply by coating the solid phase by antibody (mono- or polyclonal) specific for the antigen to be tested.

Advantages of EIAs are:
- they are rapid – most can be done within 2–3 hours
- they can be easily automated
- they are objective – the reaction can be read by spectrophotometer.

Immunofluorescence tests (IF or IFT)

These assays use the same principle as EIA, and like EIA they can be constructed to detect either viral antibody or antigen in the patient specimen. However, instead of the enzyme/substrate detector system of EIA, fluorescein-labelled anti-human
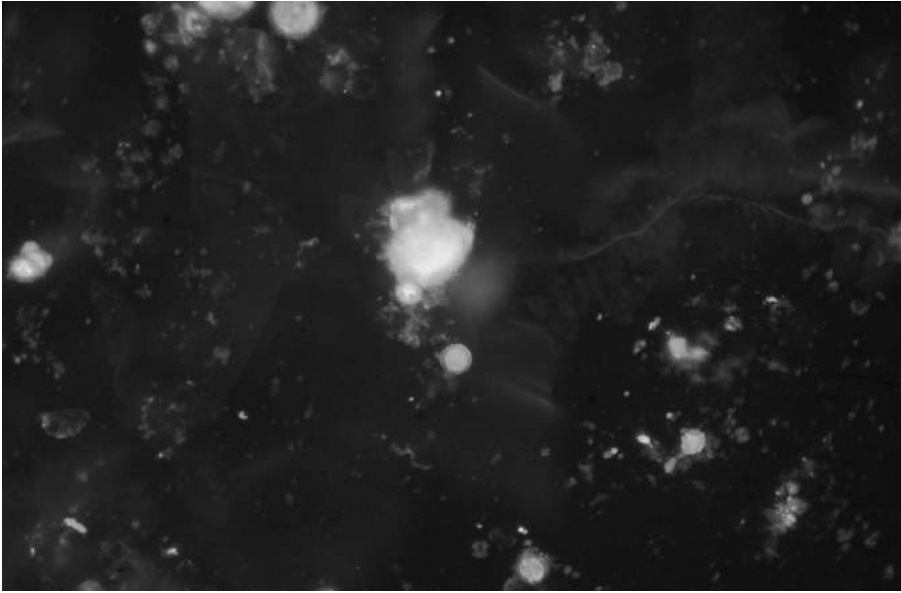
Fig. 47.4. Varicella-zoster virus immunofluorescence. (See Fig. 9 in colour plate section)

antibody is used to detect a positive reaction, which appears as apple-green fluorescence under a light microscope. Figure 47.4 shows a positive VZV IF reaction.

To look for *viral antigen*, cells from the patient's secretions (e.g. nasopharyngeal aspirate) are fixed to a spot on the glass slide and fluorescein-labelled monoclonal antibody against the virus (RSV, influenza A etc.) is added. A mixture of these monoclonal antibodies can be added at the same time to detect a panel of viruses (e.g. respiratory viruses, all at one go).

Immunofluorescence tests are also *rapid* serological tests, but the *disadvantage* is that they require subjective interpretation and are therefore labour intensive to carry out and are dependent upon operator expertise.

Latex agglutination (LA) and gelatin particle agglutination test (GPAT)
Here the antigen or antibody is adsorbed on an inanimate particle (latex or gelatin) and a positive reaction is indicated by agglutination of the particles.

Complement fixation test (CFT)
This test is based on the principle that when an antigen/antibody complex is formed it will 'fix' (bind) complement, so free complement is not available to lyse sensitized red cells that are added as indicator.

Complement fixation tests have been extensively used in the past to aid clinical diagnosis; however, because of their complexity and relative insensitiveness they are now being replaced by newer tests such as EIA.

Haemagglutination (HA) and haemagglutination inhibition tests (HAI)

These tests detect antibodies to viruses (rubella, influenza) that possess a haemagglutinin antigen. These are also relatively insensitive and can give non-specific reactions, and have mostly been replaced by more sensitive and specific techniques.

Neutralization tests (NT)

Virus-specific neutralizing antibodies, if present in the serum, will neutralize the virus so it is not able to grow in culture. This is a very specific but labour-intensive and technically demanding technique, and is being replaced by more modern techniques.

Western blot (WB) or line immunoassays (LIA)

Specific viral proteins are transferred on blotting paper either from a gel (western blot) or produced by recombination or peptide synthesis (line immunoassays). Further steps are similar to those of EIA (see above). The viral antigen band on the blotting paper develops colour if specific antibody to that particular antigen is present in the serum.

The *advantage* of these techniques is that the assays are able to distinguish antibody directed against specific virus proteins and are therefore *very specific*.

Antibody avidity assays

The host antibody response matures over several weeks post acute infection. Therefore, antibody detected >3 months after acute infection binds strongly (high avidity) to antigen(s) used in laboratory assays; as a corollary the antibody in the first 3 months has weak binding (low avidity) and can be easily dissociated from the antigen/antibody complexes.

This is used as a principle in tests devised to measure IgG avidity. These tests are *helpful in distinguishing* primary infections from reinfections or reactivations, as in the latter IgG is of high avidity.

Use of non-serum samples for antibody tests

Enzyme-linked immunosorbent assay antibody tests have been adapted for use on *urine* (HIV) or *salivary samples* (HIV, Hepatitis B and C, measles, mumps and rubella). This is of great advantage in those who are needle phobic or difficult to bleed, such as intravenous drug users (IVDUs) or neonates/small children. A special kit is required to collect the salivary sample for antibody testing.

Automation in serology

All the steps in the EIA lend themselves to automation, and several systems are now available on the market. This has enabled the laboratories to process thousands of specimens very quickly and improve turnaround times for results. The latest generation of automated machines are called 'random access', as the specimens do not have to be

batched and an urgent specimen can be put on the machine at any time without disrupting the other assays already on it. Results can be obtained in under an hour.

Many of this automated serology equipment in use in the virology laboratory is common to clinical chemistry and immunology, therefore the technology is further driving the way that specialist laboratories work. Many hospitals now have 'blood sciences laboratories' where automated machines are linked with specimen tracks that act as assembly lines to load the specimens on to the machines.

Most laboratories also have interfaces linking their machines to a laboratory computer system; linking of the laboratory computer system to a hospital-based IT system allows the clinician to access these results as soon as they are ready. This also has the advantage that if barcodes are used for specimen recognition, samples are not registered to the wrong patients accidentally.

Future of serology

- Despite the availability of rapid molecular diagnosis (Chapter 49) serology remains an important tool for the diagnosis of acute and chronic viral infections.
- It is of particular value in assessing the immune status of patients, either as a result of natural infection or post-immunization.
- Serological screening of blood for bloodborne viruses is mandatory in many countries around the world.
- It is a very important public health tool for epidemiological studies to provide prevalence of infection data.

Conclusion

The technically demanding serological assays of the past have largely been replaced with rapid diagnostic techniques in serology. Automation of EIA has further revolutionized the way that the laboratories operate, and a result can be given for patient management to the clinician within hours of the specimen arriving in the laboratory.

Despite the popularity of molecular diagnostic techniques for viral diagnosis, serological techniques will continue to form an important part of the laboratory's armoury for some time to come.

48 Virus detection

Detection of viruses in a patient's secretions or tissue provides direct evidence of current or ongoing infection (Table 48.1). This can be by:
- virus culture (also referred to as cell or tissue culture)
- electron microscopy – visualization of whole virus particles
- detection of viral antigens
- detection of viral genome (RNA or DNA) by molecular techniques.

This chapter will discuss the first three techniques; molecular diagnosis is discussed in Chapter 49.

Virus or cell culture

Viruses, like bacteria, can be cultured in the laboratory. However, viruses are fastidious intracellular organisms and therefore living cells are required to grow viruses in the laboratory. Many cell lines have been developed to support the growth of different viruses. A single type of cell line is not adequate, as specific viruses need specific receptors on the cell surface to which they attach to gain entry into the cell and to initiate replication. The presence of specific cell receptors on the cell surface determines which viruses will be able to infect them, and this is called 'viral cell tropism'. For this reason many cell lines have to be maintained in a diagnostic laboratory. Another problem in the laboratory is to maintain these living cells in culture long enough to allow sufficient virus growth.

A suspension of cells in *growth medium* (consists of a buffer plus calf serum to provide protein and amino acids, and antibiotics to prevent bacterial overgrowth) is put in glass or plastic tubes/flasks, the cells attach to the sides of the container and grow until they become confluent. The patient's *specimen is then added* and *cells incubated at 37 °C* to allow the virus to grow (33 °C for respiratory viruses). The tubes are examined daily to look for evidence of *virus growth*, which may take from a *day to weeks*. If virus is present then it kills off the cells; depending upon the cell line and the virus growing in it this gives a typical appearance in the cell sheet and is referred to as *cytopathic effect* (CPE). An experienced virologist can make a provisional diagnosis on the basis of CPE but confirmation is required, and this can be by electron microscopy, immunofluorescence, neutralization etc. of the growth medium to see if the suspected virus is present in it.

Table 48.1. *Virus detection methods and their specimen types and clinical indication for use.*

Specimen type	Clinical infection	Techniques and the viruses they detect		
		Cell culture	Antigen detection	Molecular techniques
Throat swab[a,b]	Respiratory infection	Influenza A/B, parainfluenza viruses, RSV, rhinoviruses, adenoviruses	Not available	Respiratory viruses as for culture plus metapneumovirus, bocavirus, respiratory coronaviruses.
Nasopharyngeal aspirate or bronchoalveolar lavage	Respiratory infection	As above	Influenza A/B, parainfluenza viruses, RSV	As above, on throat swab.
Cerebro-spinal fluid	Meningitis, encephalitis	Enteroviruses, mumps virus – for *meningitis only*	Not available	HSV 1 and 2 viruses, enteroviruses, mumps virus, and others as clinically suspected.
Faeces[b]	Viral gastroenteritis	Not available. Electron microscope (EM) examination can be used instead for diagnosis of all viral causes.	Rotavirus, norovirus	*Available in only limited centres –* norovirus, enteric adenoviruses 40/41, rotavirus.
Blood (serum)	Hepatitis B, C, parvovirus B19	Not available	Not available	HBV, HCV and parvovirus B19.
Blood (EDTA)	HIV, HTLV 1, CMV, EBV, BK virus	Not available	Not available	HIV, HTLV 1, CMV, EBV, BK virus.
Urine	CMV, BK and JC virus, measles, mumps, chlamydia	Culture for CMV, mumps and measles viruses only	Not available	CMV, BK and JC virus, measles virus, mumps virus, chlamydia.

Vesicle fluid/lesion swab	Herpes, chickenpox, shingles	Herpes simplex virus 1 and 2, varicella-zoster virus	Herpes simplex virus 1 and 2, varicella-zoster virus	Herpes simplex virus 1 and 2, varicella-zoster virus.
Genital swabs	Cervicitis, vaginal or urethral discharge or lesions	Herpes simplex virus 1 and 2, chlamydia	For chlamydia only	Herpes simplex virus 1 and 2, chlamydia.
Eye infections – conjunctival/corneal swab as indicated	Conjunctivitis or keratitis	Enteroviruses, adenoviruses, herpes simplex virus, varicella-zoster virus	Possible, but not preferred	Enteroviruses, adenoviruses, herpes simplex virus, varicella-zoster virus, chlamydia.
Tissue biopsies	As indicated	Depending upon suspected virus	Possible, but not preferred	Depending upon suspected virus.

Notes:

[a]Although viruses such as CMV and HSV can be grown in cell culture or detected by molecular techniques throat swab is not the recommended specimen type for their diagnosis.

[b]Throat swabs and faeces are useful specimens to culture or test by PCR for enteroviruses to provide indirect evidence of their implication in meningitis, especially if CSF is not available or the patient presents late, as enteroviruses are shed in the faeces for prolonged periods (results have to be interpreted with caution though for this very reason).

Fig. 48.1a Uninfected Graham 293 cells. (See Fig. 10 in colour plate section)

Cell lines can be *from human or non-human sources* and can be broadly divided into the following.

- *Continuous* – these are immortalized cell lines derived mostly from tumour cells or cells that have been transformed in the laboratory. They can be maintained in indefinite growth cycles in the laboratory. Examples are HeLa (human cervical cancer cell line), hep2 and Graham 293 cells (transformed human epithelial cell line). Figure 48.1a shows the uninfected Graham 293 cells and Fig. 48.1b shows adenovirus cytopathic effect in this cell line.

- *Primary or semi-continuous* – as the name implies they can be maintained for only one or a limited number of growth cycles. They are more sensitive to infection by viruses, and fastidious viruses like VZV, CMV, and influenza virus will only grow in them. Examples are MRC5 (human lung fibroblast cell line), PMK (primary monkey kidney cell line).

Cell culture, although a very sensitive and specific technique, is labour intensive and requires considerable technical expertise. Results may take up to a few weeks and the specimens need to be transported quickly and under correct conditions to the laboratory to maintain the viability of the infecting virus. Many viruses, such as the hepatitis viruses, papilloma viruses, parvovirus B19, rotavirus and norovirus, cannot be grown in cell culture and others, such as EBV and HIV, need special cells and therefore are not suitable for culture in a routine diagnostic laboratory.

Electron microscopy

Viruses are below the resolution of light microscopy and therefore require an electron microscope for visualization. A limiting factor of electron microscopy (EM) is that
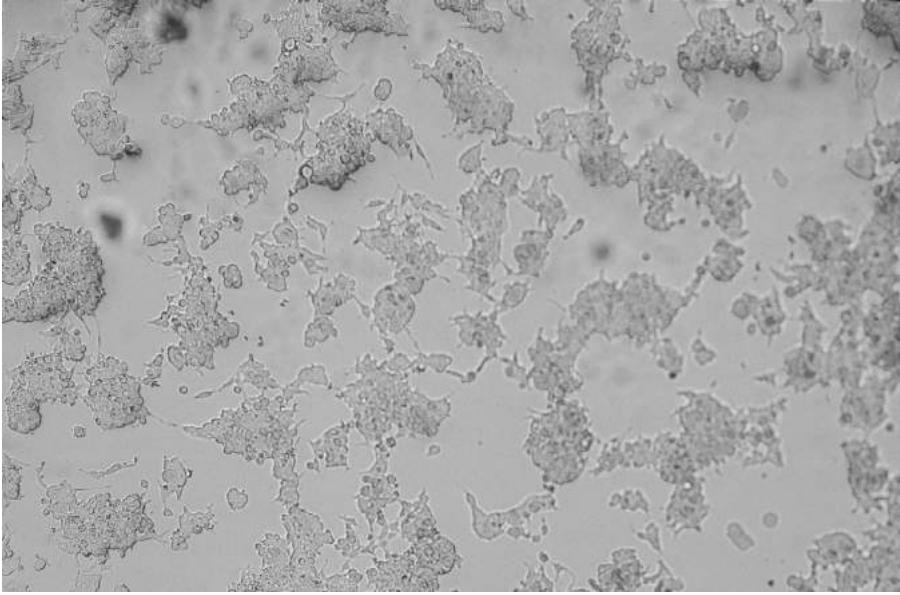
Fig. 48.1b Graham 293 cells showing adenovirus cytopathic effect. (See Fig. 11 in colour plate section)

viruses belonging to the same family can not be distinguished from each other as they will have the same *morphology (size, shape and surface characteristics)*. Therefore EM can not be used to make the differential diagnosis of a herpes simplex or chickenpox lesion, as both will contain a 'herpes' virus with exactly the same morphology (Fig. 48.2). On the other hand EM is a useful tool in making a differential diagnosis of viral gastroenteritis, as rotavirus, norovirus and enteric adenoviruses all belong to a different family and can be distinguished from each other on the basis of their morphology. It is a 'catch all' technique and many viruses (rotavirus, norovirus) were discovered by EM.

Electron microscopy was first used in the 1950s to distinguish the vesicular rash of smallpox from that of chickenpox; each is caused by a morphologically distinct virus. Figures 41.4 and 48.2 show electron micrographs of smallpox virus and varicella-zoster (a herpes group) virus respectively. During the 1980s and 1990s it was the only available tool to diagnose the viral gastroenteritis viruses (rotavirus, norovirus, calici-virus, enteric adenoviruses 40/41). However, due to the availability of rapid sensitive and specific antigen detection and molecular tests for these viruses, EM has largely become redundant for diagnosis of viral gastroenteritis.

Electron microscopy is expensive, technically demanding, requires specialist training and is relatively insensitive (requires a minimum of one million viral particles per ml or gram of specimen), and its use has therefore largely been limited to research institutions.
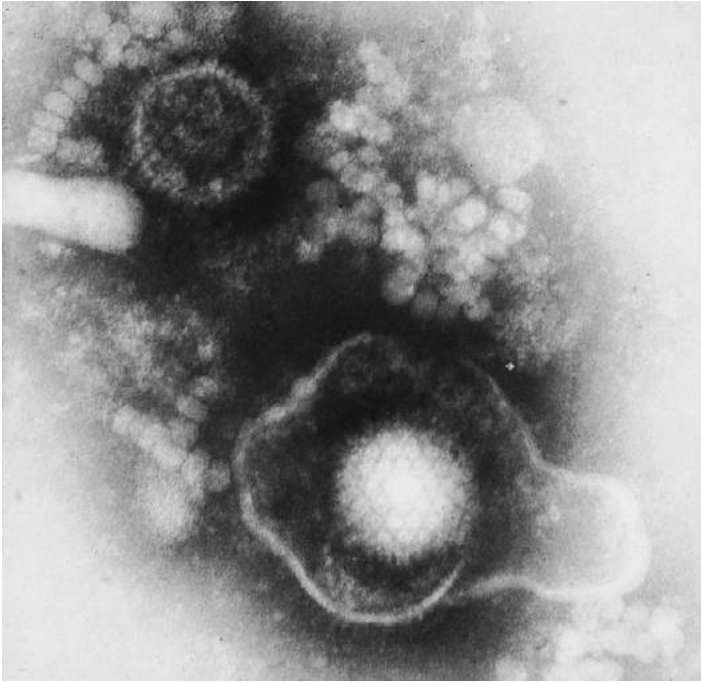
Fig. 48.2. Herpes virus.

Antigen detection

Detection of viral antigen in a patient specimen is sufficient to provide evidence of viral presence. Various techniques such as:
- enzyme linked immunosorbent assay (EIA or ELISA)
- immunofluorescence tests (IF or IFT)
- latex agglutination (LA) tests

are in wide use and have already been described in Chapter 47.

Viral genome detection (RNA or DNA) by molecular techniques

The techniques provide sensitive, specific and rapid evidence of viral presence. The polymerase chain reaction (PCR) is the most widely used technique. Collectively they are referred to as nucleic acid amplification techniques (NAATs). These are discussed in detail in Chapter 49.

49   Molecular techniques

Molecular techniques are those that use the principles of molecular biology to detect viral genomes (RNA or DNA). The use of these techniques has been commonplace in virology and has led to the discovery of new viruses, the study of viral resistance, designing of new antiviral drugs and vaccines.

Many are in use in routine diagnostic laboratories to aid viral diagnosis. Those that are in current and common use are described.

DNA or RNA hybridization

A complementary RNA or DNA probe is used to bind to the DNA or RNA viral genome. The DNA–RNA hybrid can then be detected using a labelled monoclonal antibody. This technique can be used on tissue samples, in which case it is called *in situ hybridization*, or the viral genome can first be transferred on to a blotting paper *(dot blot hybridization)*.

To obtain a positive reaction, high numbers of copies of viral DNA or RNA are required; therefore the technique is relatively insensitive and has been largely superseded by *nucleic acid amplification techniques (NAATs)*.

Polymerase chain reaction (PCR)

This was the first NAAT to be described. It is a technique by which a single copy of DNA or RNA can be amplified more than a million times. To detect RNA viruses, RNA has to be first transcribed to complementary DNA by means of an enzyme called reverse transcriptase; this type of PCR is referred to as *reverse transcription PCR (RT PCR)*.

Polymerase chain reaction uses a bacterial enzyme, *taq polymerase*, to initiate DNA amplification. The first steps in the process though are extraction and denaturation of the DNA or RNA followed by amplification. These steps involve complex chemical reactions, and heating and cooling of the sample mix in a thermocycler. Each heating and cooling cycle takes only a few minutes to complete, and doubles the number of DNA copies. Greater than a million copies of the genome can be produced in about 40 such cycles, which take only 2–3 hours to complete.

The amplified DNA product or *amplicons* can be detected by use of specific probes labelled with a chemiluminescent or fluorescent dye.

Table 49.1. *Nucleic acid amplification techniques and their application.*

NAAT technique	DNA	RNA	Diagnostic application
Polymerase chain reaction (PCR)	Yes	Yes	Most popular of NAATs. Used to detect a wide range of viruses in different clinical specimens.
Transcription mediated amplification (TMA)	No	Yes	Messenger RNA of chlamydia.
Nucleic acid sequence based amplification (NASBA)	No	Yes	HIV, HCV.
Strand displacement assay (SDA)	Yes	No	Chlamydia.

Many variations of the PCR technique are in use.

- **Nested PCR** – this type of PCR uses two separate amplification steps, so in theory can generate twice the amount of amplicons as compared to traditional PCR.
- **Multiplex PCR** – can detect several different viral genomes in a single reaction mixture. This allows detection of several viruses at the same time by a single test. Useful for testing specimens from patients in whom a suspected infection may be caused by different unrelated viruses, e.g. respiratory viruses.
- **Real-time PCR** – here the amplification and detection steps of PCR occur simultaneously (rather than sequentially). Therefore, the time taken to get a result is much shortened.
- **Quantitative PCR** – comparison of the amount of DNA or RNA present in the patient sample to a set of known positive standards included in the PCR assay is used to determine the virus quantity or *viral load* in the patient specimen.

Subsequent to the discovery of PCR, many other NAATs have been described, which differ in their methodology to achieve amplification of the viral genome; some are limited to only DNA or only RNA amplification. These are described in Table 49.1.

Nucleic acid sequencing

Complete virus genomes of several viruses have been sequenced and identified. This allows typing and comparison of viral isolates for epidemiological purposes, and to establish the infection transmission chain. The most important clinical application, though, is for resistance testing to identify if the infecting virus may have any mutations that may confer resistance to the antiviral drug(s) in use. This is crucial in the management of HIV infection (see Chapter 11 HIV and AIDS).

Technical consideration for molecular assays

Molecular assays need a great deal of technical expertise and expensive equipment. The NAATs are exquisitely sensitive but this renders them prone to cross-contamination;

therefore great care has to be taken that there is no carry over of positive material and 'clean' steps of the assay have to be physically separated from infected material.

Future of molecular assays

As in serology, many steps in the NAATs have now been automated, and it is possible to do the complete assay (extraction, amplification and detection) using automated equipment. This has made the assays a lot more user friendly and less technically demanding. As this automated equipment is completely closed, cross-contamination is less of an issue. Real-time PCR allows a result turnaround of a few hours, and multiplex PCR allows several viruses to be looked for at the same time in a single test. The sensitivity and specificity of NAATs, along with the advances described, have made NAATs the diagnostic assay of choice in routine diagnostic laboratories to replace other less sensitive methods of virus detection.

Section 5 – Patient management

50 Antiviral drugs

The most successful antiviral agent to date, aciclovir, was a serendipitous discovery. It was manufactured as an anticancer drug but was found to have good in vitro activity against herpes simplex virus, and after clinical trials it was licensed for use in the 1980s. Subsequently, the antivirals have been designed and manufactured with specific viral targets in mind that will inhibit viral replication.

One disadvantage of the antivirals that act by DNA polymerase inhibition is that they affect the cellular DNA replication at the same time, and therefore can cause cytotoxic side effects such as nausea, vomiting, bone marrow suppression etc. For this reason they are not licensed to be used in pregnancy (except in life threatening situations or in HIV cases where risk to the fetus is outweighed by the benefit of treatment) because of risk of fetal teratogenesis. These side effects are limited in certain drugs, such as aciclovir, because the drug is preferentially activated in virus-infected cells and has little or no side effects on normal uninfected cells (see below). Table 50.1 gives examples of antiviral drugs targeted to different steps in the viral life cycle.

Human immunodeficiency virus (HIV)

See below under antiretrovirals.

Herpes viruses

Drugs: aciclovir, valaciclovir, penciclovir/famciclovir, ganciclovir, foscarnet, cidofavir, rituximab.

Aciclovir
Mechanism of action
Aciclovir (acicloguanosine) is an acyclic analogue of the purine nucleoside guanine and is inert until phosphorylated to aciclovir triphosphate. Fortunately, as the first step in phosphorylation to aciclovir monophosphate is initiated specifically by a viral enzyme called thymidine kinase (TK), the drug only gets activated in virally infected cells (further phosphorylation to its triphosphate form is aided by cellular enzymes) and therefore there are very few side effects as relatively little active drug is formed in the uninfected cells. Furthermore, the drug reaches a higher concentration in infected as compared to uninfected cells. This specific action of the drug gives it its safety

Table 50.1. *Examples of antiviral drugs targeted to different replication steps in the viral life cycle.*

Stage	Drug	Target	Agent
Viral attachment/ adsorption	Enfurvitide	HIVgp120/CD4 cell receptor	HIV 1
Viral uncoating/ penetration	Amantadine	Matrix protein	Influenza A virus
Viral nucleic acid synthesis	Zidovudine	Reverse transcripatase	HIV
	Aciclovir/ Penciclovir	Viral DNA polymerase	HSV and VZV
	Ganciclovir	Viral DNA polymerase	CMV
	Adefovir	Viral DNA polymerase	HBV
	Ribavirin	mRNA	RSV/HCV
Virus release/ budding	Indinavir	Protease inhibitor	HIV
	Oseltamivir/ Zanamivir	Neuraminadase (NA)	Influenza A/B viruses
Miscellaneous	Interferon alpha	Immune modulator	HBV/HCV
	Rituximab	CD20 molecule B-cell	EBV
	Palivizumab	Monoclonal antibody	RSV
	Maraviroc	Anti-CCR5 monoclonal antibody	HIV

profile and narrow spectrum for treatment (herpes simplex virus and varicella-zoster virus) as these are the only two herpes viruses that possess the TK enzyme required to change the drug to its active form.

Aciclovir triphosphate inhibits viral replication in two ways.

- Aciclovir triphosphate competes with guanosine triphosphate to be incorporated in the DNA chain. Incorporation leads to DNA 'chain termination' as further nucleosides cannot be attached to allow the DNA chain to complete.
- It directly inhibits the viral DNA polymerase enzyme that is responsible for initiation of viral DNA synthesis. It is able to inhibit cellular DNA polymerase as well, but to a much lesser degree, hence it has little effect on cellular DNA synthesis.

Resistance
Clinical resistance is uncommon and may be due to a variety of viral factors.

- Viral TK mutants
  The loss of viral TK enzyme (TK mutants) will result in the inability of the virus to activate aciclovir to its active form, and hence treatment failure. Fortunately such strains are generally not virulent and therefore do not cause clinically significant infection.
  Altered viral TK gene so that the viral TK enzyme is not able to effectively start the phosphorylation step.

- Mutations in the viral DNA polymerase (DNA polymerase mutants), so that it does not preferentially take up aciclovir triphosphate for incorporation in the DNA chain. Such HSV mutants are a clinical problem, especially in severely immunocompromised patients (e.g. those with AIDS) where recurrent or persistent infection may occur.

Valaciclovir

This is a pro-drug of aciclovir – it is aciclovir with an attached valine ester. This results in greater absorption through the gut, and about 70% of the drug is absorbed when taken orally as compared to 20% of aciclovir. In the body valaciclovir is hydrolysed (the valine ester is removed) to aciclovir and therefore has exactly the same mechanism of action and resistance profile as aciclovir. The advantage is that oral valaciclovir does not have to be given as frequently as aciclovir.

Penciclovir and famciclovir

Famciclovir is the pro-drug of and is converted to penciclovir in the body. Penciclovir is very similar to aciclovir in structure and mechanism of action, and is active against HSV and VZV once it is phosphorylated to its triphosphate form.

Ganciclovir and valganciclovir

Mechanism of action

Ganciclovir is an anti-CMV drug, and is a nucleoside analogue derived from aciclovir. It does not need the viral TK enzyme for activation to its triphosphate form. Instead it is activated by a virally encoded enzyme (encoded by the UL97 gene of CMV). Ganciclovir triphosphate inhibits the CMV viral DNA polymerase.

Unfortunately, as cellular enzymes can activate it equally, it does have serious cytotoxic side effects. It is therefore limited to treatment of life- and sight-threatening CMV infections.

Ganciclovir is poorly absorbed when given orally (<10%); however, valganciclovir (the valyl ester of ganciclovir) is used orally as it is much better absorbed (40%). Once absorbed it is converted to ganciclovir in the body by removal of the valine moiety.

Resistance

This develops rarely and is due to mutations in the UL97 gene of CMV, so the drug cannot be activated. Resistance may also occur due to mutations in the DNA polymerase enzyme to make it resistant to the drug action.

Cidofovir

Is a nucleotide analogue. It is activated by cellular enzymes. However, the drug preferentially acts upon the viral rather than cellular DNA polymerase. As with aciclovir (see above) it inhibits DNA synthesis by acting as a 'chain terminator'. As the drug is activated in uninfected cells it has cytotoxic side effects. It is also nephrotoxic and should be administered with probenecid to prevent renal damage.

It is active against CMV and some other DNA viruses, such as adenovirus, BK virus and smallpox virus.

Foscarnet

Inhibits viral DNA synthesis but is a different class of drug. It is a pyrophosphate analogue so does not need phosphorylation to an active form. It is active against all herpes viruses, including CMV.

Rituximab

This is a monoclonal antibody directed against CD20 of B-cells. As EBV infects the B-cells, rituximab has been used in treatment of post-transplant lymphoproliferative disease (PTLD) caused by EBV (Chapter 44).

Respiratory viruses

Drugs: ribavirin, amantadine, oseltamivir, zanamivir, palivizumab.

Ribavirin

This is a nucleoside analogue of guanosine, and is phosphorylated intracellularly to its active form. Its active triphosphate form interferes with protein synthesis by acting upon mRNA and therefore it is active against a range of RNA and DNA viruses. However, in clinical use its role is limited to treatment of RSV and HCV infections, although it has also been used to treat other RNA viruses such as parainfluenza, measles and Lassa fever viruses.

Amantadine

This was the first anti-influenza agent to be licensed for use. It acts specifically on the matrix protein of influenza A virus to prevent uncoating of this protein from the viral RNA therefore preventing the RNA replication. Resistance develops readily and because amantadine has dopaminergic side effects, such as restlessness, agitation, insomnia, confusion etc., it has not found wide acceptance either among clinicians or patients as an anti-influenza agent.

Oseltamivir and zanamivir

Both are 'designer' anti-influenza drugs. They inhibit the neuraminidase (NA) enzyme of influenza viruses. After replication, the virus particles bud out of the cell and NA breaks the sialic acid bond between the virus and the cell surface to allow the release of the virus particles from the cell surface to initiate further infection cycles. Inhibition of NA results in infectious viral particles not being released.

These drugs act against both influenza A and B viruses and have relatively few side effects. Resistance develops due to point mutations in the NA enzyme of the virus, so it becomes resistant to the action of the drug. Recent reports from Norway suggest a high prevalence of oseltamivir-resistant influenza A strains in that country. Resistance prevalence is much lower in other Western European countries.

Palivizumab

Is a humanized monoclonal antibody against respiratory syncitial virus (RSV). It is used in the prophylaxis of RSV infection in children at risk of severe life-threatening RSV infection.

Hepatitis viruses

Drugs: interferon alpha, adefovir, entecavir, ribavirin.

Interferon alpha and PEG interferon alpha

This was the first drug to be used for treatment of chronic hepatitis B and C infections. It is an immune modulator and acts through various immune-mediated pathways; the initial expectation that it will therefore be effective against a large range of virus infections has not been borne out in clinical terms. Interferons are solely used for treatment of chronic HBV and HCV infection. For HCV it is most effective as a combination treatment with ribavirin. Pegylated (or PEG) interferon alpha is produced by attaching a polyethylene glycol (PEG) molecule to interferon alpha and has a longer half-life.

Lamivudine

Is a nucleoside analogue reverse transcriptase inhibitor (RT) and was first manufactured as an anti-HIV agent (see Table 50.2). As HBV also has a reverse transcriptase step in its replication it is now used as a first line anti-HBV agent. However, resistance develops very rapidly due to point mutations in the viral RT, and adding or switching over to second line agents may be required.

Adefovir, entecavir and tenofovir

These are newer nucleoside analogue agents used to treat HBV infection. Adefovir acts on the reverse transcriptase enzyme.

Tenofovir is an anti-HIV agent and is also effective against HBV, therefore it is the drug of choice for treating patients who are co-infected. Entecavir is the newest nucleoside analogue.

Antiretrovirals

Zidovudine (or AZT) was the first drug to be used in the treatment for *HIV.* Since then, several drugs have become available targeting different replication steps in the viral cycle and are shown in Table 50.3. None of the drugs eradicate the virus, and the aim of the therapy is to keep viral replication suppressed. Drug resistance is a major issue because of mutations in the viral gene under drug selective pressure, therefore the drugs are used in combination popularly referred to as *highly active antiretroviral therapy (or HAART)*.

Triple therapy using at least two different classes of drugs (see Table 50.3) is the norm, with two NRTIs forming the backbone of treatment combined with one NNRTI

Table 50.2. *Antiviral drugs for use with herpes viruses, respiratory viruses and hepatitis viruses.*

Virus type	Drug	Preparations	Indication for use	Toxicity
Herpes group viruses *Herpes simplex virus type (HSV) 1 and 2* and *varicella-zoster virus (VZV)* (chickenpox and shingles)	Aciclovir	Topical Oral Intravenous Eye ointment	Treatment and prophylaxis of HSV and VZV infections. Intravenous preparation should be used to treat HSV encephalitis and HSV and VZV infections in the immunosuppressed. Topical preparations are available over the counter and should be used for treatment of localized HSV skin lesions only in immunocompetent patients.	Very little, good safety profile (see mechanism of action above). Sometimes renal toxicity, as drug is excreted through the kidneys. Dose may need adjustment in renal failure.
	Valaciclovir and famciclovir	Oral	Indications are same as for aciclovir except where intravenous aciclovir is indicated.	Same as aciclovir.
Cytomegalovirus (CMV)	Ganciclovir	Intravenous, given as infusion	Life- or sight-threatening CMV infection in the immuno-compromised.	Leucopaenia, especially neutropaenia, is the most serious side effect, white blood cell count should be monitored while on treatment.
	Valganciclovir	Oral	Prophylaxis and maintenance therapy for CMV infection in the immunocompromised.	As ganciclovir.
	Cidofovir	Intravenous, given as infusion	Ganciclovir-resistant CMV infection, BK and adenovirus infections in the immunocompromised.	Renal toxicity, bone marrow suppression.

	Drug	Route	Indication	Side effects
	Foscarnet	Intravenous, given as infusion	Ganciclovir-resistant CMV infection.	Renal toxicity.
Epstein–Barr virus (EBV)	Rituximab	Intravenous, given as infusion	Post-transplant lymphoproliferative disease (PTLD) due to EBV.	Infusion-related side effects.
Respiratory viruses				
Respiratory syncitial virus (RSV)	Ribavirin	Particle aerosol for RSV infection Oral for HCV (see below)	Severe RSV infection in neonates and in immunocompromised adults.	Anaemia.
	Palivizumab	Intramuscular	Prophylaxis of RSV in children at risk of severe RSV infection.	
Influenza A	Amantadine	Oral	No longer recommended for treatment and prophylaxis for influenza A.	Restlessness, agitation, confusion.
Influenza A and B	Oseltamivir	Oral	Treatment and post-exposure prophylaxis (of high-risk individuals) for influenza A and B.	Gastrointestinal (GI) symptoms.
	Zanamivir	Inhalation of powder	As above.	Bronchospasm and respiratory impairment may occur rarely.
Hepatitis viruses				
Hepatitis B virus (HBV)	Interferon alpha	Intramuscular	Treatment of chronic HBV infection.	Chills, rigors, fever, fatigue – 'flu like symptoms'.
	Lamivudine	Oral	Chronic HBV infection.	Bone marrow suppression.
	Adefovir	Oral	Chronic HBV infection, alone or in combination with lamivudine.	GI symptoms, rash.

Table 50.2. (*cont.*)

Virus type	Drug	Preparations	Indication for use	Toxicity
	Tenofovir	Oral	HBV and HIV co-infected patients.	
	Entecavir	Oral	Chronic HBV infection.	GI symptoms, raised serum amylase and lipase.
Hepatitis C virus (HCV)	Ribavirin	Oral	HCV infection, in combination with PEG alpha interferon.	Anaemia.
	Interferon alpha	Intramuscular	HCV infection, in combination with oral ribavirin.	Chills, rigors, fever, fatigue – 'flu like symptoms'.
Miscellaneous				
Adenovirus	Cidofovir	Intravenous, given as infusion	Clinical adenovirus disease in immunocompromised patients.	As above.
BK virus	Cidofovir	Intravenous, given as infusion	Clinical BK virus disease in immunocompromised patients.	As above.

Table 50.3. *Antiretroviral drugs in common use.*

Drug class	Mechanism of action	Drugs in the class	Drug resistance	Drug side effects
Nucleoside reverse transcriptase inhibitors (NRTIs) or nucleoside analogues (NAs). *This class of drug inhibits (thereby stopping viral replication) the HIV reverse transcriptase (RT) enzyme, which facilitates the transcription of HIV RNA to DNA as the first step in the viral replication cycle.*	Phosphorylated first to their triphosphate compounds by cellular enzymes. Inhibit HIV RT by binding to the substrate binding site. Also act as DNA chain terminators.	Abacavir Didanosine (DDI) Lamivudine (3TC) Stavudine (D4T) Zalcitabine (DDC) Zidovudine (AZT)	Several point mutations in the RT gene are required to confer resistance. Resistance to one drug does not necessarily mean resistance to all drugs within the class.	Lactic acidosis and mitochondrial toxicity.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs) (not effective against HIV 2) *Inhibit the RT of HIV 1 (see above)*	Inhibit the RT (HIV 1 only) but by acting on a site different than NRTIs above.	Efavirenz Nevirapine	Point mutations in the RT gene confer resistance. Cross-resistance between the drugs in the class is very high, e.g. resistance to one will confer resistance to others in the class.	Rashes, abnormal LFTs. Affect cytochrome p450 function.
Protease inhibitors (PIs). *Are active at very low concentration, work in synergy with NRTIs.*	Act on HIV protease enzyme and prevent production of functional viral protein so that the virus particle is not able to mature.	Indinavir Nelfinavir Saquinavir Ritonavir Amprenavir	Single point mutations in the protease gene confer resistance to more than one PI (cross-resistance).	Abnormality of fat and sugar metabolism leading to lypodystrophy and diabetes.

Table 50.3. (*cont.*)

Drug class	Mechanism of action	Drugs in the class	Drug resistance	Drug side effects
				Affect cytochrome p450 function.
Fusion inhibitors (FIs) *Prevent the fusion of virus to the receptors on cell surface and hence prevent viral entry into the cell and cell infection.*	Blocks attachment of viral gp41 to CD4 molecule cell receptor therefore preventing viral entry into the cell.	Enfurvitide		
	Blocks the CCR5 co-receptor and hence viral entry into the cells.	Maraviroc	Those viruses that do not require the CCR5 co-receptor to gain cell entry will be resistant.	

or PI. The route of administration is *oral* for all the antiretroviral drugs, and to reduce the pill burden, zidovudine and lamivudine have been combined (combivir) to give the backbone of two NRTIs. Indication for treatment and follow up are given in Chapter 11.

Useful websites

Further details of drug routes and dosage are available from the British National Drug Formulary (www.bnf.org) or the Electronic Medicines Compendium (www.emc. medicines.org.uk). Or refer to the manufacturer's data sheet.

51 Viral vaccines

The first vaccination known to humankind was against a viral infection, when Jenner, in 1796, injected material from a lesion of cowpox into an eight-year-old boy to protect him from smallpox. The culmination of this first step was in 1980 with the declaration that smallpox was the first human infection to be eradicated from the world.

Subsequently, many viral vaccines have been developed and there have been successful public health campaigns to reduce the burden of infection. The World Health Organization (WHO) has an ongoing expanded programme of immunizations (EPI) targeting the worldwide elimination of both polio and measles. Polio is now considered to be non-endemic in all but four countries of the world.

Vaccines against hepatitis B and papilloma viruses can arguably be considered as the first vaccines that protect against cancers (hepatocellular and cervical carcinomas respectively).

Viral vaccines can be divided according to whether they are *attenuated* or *killed*.

Attenuated vaccines

Attenuation of virus implies the loss of pathogenicity, but for successful vaccination the immunogenicity has to be maintained. The first example was the smallpox vaccination, which used a related non-pathogenic virus, the cowpox virus.

Attenuation is achieved by selective pressure on the virus during repeated passages in cell culture. The whole process has to be quality controlled strictly to ensure that extraneous viruses have not been introduced and that there is no wild type pathogenic virus in the vaccine.

The advantage of live vaccines is that the virus replicates and causes a subclinical infection after vaccination, and therefore produces a good immunogenic response in the host. On the other hand there are *concerns about the vaccine strains reverting to wild type virus*, and this is certainly true for live polio vaccine; the polio 3 vaccine strain is particularly liable to revert to wild type and to cause clinical disease. Many live vaccines may cause a mild infection mimicking the wild virus infection. For example, 5% of patients who receive varicella-zoster vaccine develop a localized vesicular rash around the site of vaccination.

Live vaccines are *contraindicated* for use in immunosuppressed patients, as more serious disease may develop in them. They are also contraindicated in pregnancy because of the theoretical risk of transmission to the fetus, even though there is no evidence that rubella vaccine (unlike the wild virus) is capable of causing congenital

infection when it has been inadvertently given in pregnancy. All except live polio vaccine can be given to contacts (e.g. family members) of immunosuppressed and pregnant patients, as there is no evidence of horizontal transmission.

Killed or inactivated virus vaccines

Table 51.1 shows a list of attenuated and killed vaccines in current use.

Viruses can be killed with chemicals such as formalin or B-propiolactone. These killed virus vaccines can then be injected to induce an immune response with the advantage that they are incapable of causing disease. Inactivated vaccines can be *whole virus vaccines* (polio) or be *sub-unit* (i.e. only use particular viral *proteins or epitopes*) to induce an antibody response capable of neutralizing the virus. Examples are influenza and hepatitis B vaccines.

Even for killed vaccines the viruses have to be first grown in cell cultures. Molecular techniques are now being used to invent new processes to manufacture vaccines:

- *Recombinant vaccines.* Part of the viral genome is transfected in yeast or bacterial cells so that when they multiply they also produce the viral protein encoded by the transfected viral gene. Hepatitis B vaccine is produced like this.
- *DNA vaccines.* This is the latest genre of vaccines being evaluated. Pure viral DNA when injected into cells can use cellular protein translating systems to produce viral proteins that are capable of inducing an immune response. Thus, in effect, viral DNA acts as an attenuated virus vaccine but is incapable of causing disease by itself. There are no DNA vaccines in current use, but the research is promising.
- *Synthetic peptide vaccines.* The immunogenic virus proteins (antigens or epitopes) can be manufactured artificially in the laboratory and then injected to induce immune response. This is a promising technology as it will allow large amounts of vaccine to be produced relatively cheaply.

The *presentation of vaccine to the immune system* is as important as the vaccine itself. To enhance the immune response *adjuvants*, such as aluminium hydroxide, are used to present the killed vaccines to the immune system.

Passive immunization

There is usually a time lag between active vaccination and the development of host immunity, as the host immune system needs time to mount a protective response. Immunoglobulins against specific viruses provide a ready made source of antibody and can be injected to provide instant protection. Passive immunization is used solely or in combination with vaccines to provide protection against a range of infections (see Table 51.2).

Vaccination programmes

Different countries have their own vaccination programmes depending upon the prevalence of infection, its public health importance nationally, perceived cost

Table 51.1. *List of current viral vaccines in use in the UK and their type (live attenuated or killed).*

	Vaccine	Route of administration	Comment
Live attenuated vaccines			Contraindicated in immunocompromised and in pregnant patients.
	Measles	im	Measles, mumps and rubella are given as a triple vaccine combination (MMR).
	Mumps	im	See above.
	Rubella	im	See above.
	Polio	oral	Has been superseded in the developed world by inactivated polio vaccine because of the risk of vaccine-associated poliomyelitis.
	Varicella-zoster	im	A localized vesicular rash may occur on the site of the lesion.
	Yellow fever	im	Restricted for use in endemic countries and travellers to those countries.
	Smallpox	—	—
Killed or inactivated vaccines			Relatively very safe vaccines. Safe in immunocompromised patients, but may be less effective in them due to poor host response. Contraindicated in those who are allergic to non-viral carrier material in the vaccine.
	Influenza A and B	im	As the source virus is grown in eggs it is contraindicated in those with severe egg allergy.
	Hepatitis A and B	im	—
	Polio	im	Has replaced oral polio vaccine in many countries.
	Papilloma virus (HPV)	im	Provides protection against the high-risk HPV 16 and 18.
	Rabies	im	
	Japanese encephalitis (JE)	im	Available on named-patient basis.

Table 51.2. *Recommended post-exposure immunization schedules in the UK.*

	Indication	Vaccination	Immunoglobulin
Hepatitis A	Contacts of acute hepatitis A. Vaccine and immunoglobulin can be given at the same time on different sites.	As soon as possible but no later than 2 weeks after contact	Normal immunoglobulin as a stat im injection, given as soon as possible but no later than 2 weeks after contact.
Hepatitis B	At-risk contacts of hepatitis B patients or infected material. Vaccine and immunoglobulin can be given at the same time on different sites.	Immediately, give the accelerated dose schedule e.g. 0, 1 and 2 months	Hepatitis B specific immunoglobulin as an im stat injection given as soon as possible for those who are known non-responders to vaccine, sexual contacts of acute hepatitis B, and to babies born to hepatitis B positive mothers who are negative for anti-HBe marker.
Varicella-zoster	Those that are non-immune with at-risk exposure and if pregnant or immunocompromised.	Not indicated	Specific varicella-zoster immunoglobulin given as an im injection as soon as possible but within 10 days of exposure.
Measles	Contact of measles	Within a week of exposure	Normal immunoglobulin for pregnant patients in whom vaccine is contraindicated.
Rabies	Animal bite in countries where rabies is known to occur. Specialist advice should be sought immediately regarding the level of risk.	0, 3, 7, 14 and 30 days. Vaccine should be started as soon as possible after exposure, but should not be withheld whatever the delay.	For high-risk exposure. As much as possible should be injected locally at the site and the rest given im. Should be given as soon as possible after exposure.

Table 51.3. *Viral vaccines recommended for pre-exposure prophylaxis in the UK.*

	Vaccine	Comment
Childhood vaccinations		
All children as part of universal childhood vaccination programme	Measles/ mumps/ rubella (MMR)	Single vaccines are no longer available in the UK.
All children as part of universal childhood vaccination programme	Inactivated polio (IPV)	All vaccination is with IPV, live oral vaccine is no longer in use in the UK. Given at the same time and with other childhood vaccinations such as diphtheria/pertussis and tetanus (DPT).
Selective vaccination group	Papilloma virus	Pre-pubertal girls, 11–12 years.
Selective vaccination group	Hepatitis B	For babies born to hepatitis B positive mothers. First dose should be given immediately after birth. In addition, hepatitis B specific immunoglobulin should be given if mother is negative for anti-HBe marker.
Vaccination for those at occupational risk		
Sewage workers, food handlers	Hepatitis A	Protects long term, probably for life.
Healthcare workers and those who are likely to be exposed to blood or blood contaminated material during the course of their work.	Hepatitis B	Accelerated schedule of 0, 1, 2 months can be used if required.
Susceptible healthcare workers (HCWs)	MMR	Screen HCWs to identify those who need to be immunized.
Healthcare workers and those that work in emergency services	Influenza A and B	Annual immunization.
Susceptible healthcare workers	Varicella-zoster	Screen HCWs to identify those who need to be immunized.
Vets and others in contact with animals in quarantine facilities, laboratory workers working with rabies virus	Rabies	Routine laboratory tests are not recommended to check if immunity has developed. Regular boosters may be required depending on risk.
Travel vaccines		
Those without evidence of past infection and travelling to endemic countries	Hepatitis A	Protects long term, probably for life. Single vaccine containing both hepatitis A and B virus is

Table 51.3. (*cont.*)

	Vaccine	Comment
		available and can be given as 3-dose schedule as for hepatitis B.
Travel to endemic countries and likely to engage in at risk behaviour	Hepatitis B	Accelerated schedule of 0, 1, 2 months can be used if required.
Travelling to endemic countries only if in remote areas where immediate healthcare not available	Rabies	Booster doses in case of significant exposure should still be given to those who may have received pre-exposure vaccination.
Travel to endemic countries	Japanese encephalitis (JE)	Available on named-patient basis.
Travel to endemic countries	Yellow fever	Vaccination is mandatory for entry and exit out of endemic countries.
Vaccinations for at-risk groups		
Susceptible contacts of patients with acute hepatitis A, IVDUs and men who have sex with men (MSM), those with chronic hepatitis B and C infection.	Hepatitis A	Protects long term, probably for life. Single vaccine containing both hepatitis A and B virus is available and can be given as 3-dose schedule as for hepatitis B.
Susceptible contacts of patients with hepatitis B, those whose lifestyle puts them at risk of infection, chronic hepatitis C infection	Hepatitis B	Accelerated schedule of 0, 1, 2 months can be used if required.
>65 years of age, immunocompromised, those with chronic debilitating illnesses, those with underlying heart and respiratory diseases	Influenza A and B	Annual vaccination.
Susceptible women of reproductive age group	Rubella	All women are screened for immunity to rubella at first antenatal visit and those that are not immune are offered vaccination with MMR immediately after delivery.
Those likely to come in contact with the virus in case of a bioterrorism attack	Smallpox	Subsequent to the threat of bioterrorism, key healthcare workers have been immunized.

effectiveness and public acceptability. For example, varicella-zoster vaccine is included in the childhood vaccination schedule in the USA and Japan but in the UK it is targeted for those at occupational risk only (healthcare workers). Similarly there are universal vaccination programmes against hepatitis B in some and not in other countries. Certain vaccinations are also mandated by the WHO (e.g. yellow fever vaccination for travellers into and out of endemic countries). The World Health Organization also has an expanded programme for immunization (EPI) whereby it provides advice and support for immunization programmes for eradication of infections with high childhood morbidity and mortality. Polio and measles are both included in the EPI.

Table 51.3 lists the viral vaccines and the current recommendations for their use. Further information can be found under the chapters on individual viruses. Readers should check the latest guidelines for vaccination schedules (www.bnf.org).

Post-exposure prophylaxis

There are many reasons why individuals may remain unprotected even against common infections. In such cases post-exposure immunization can be offered. This is mostly in the way of providing ready-made passive immunity through use of immunoglobulins. However, if the infection has a long incubation period (e.g. hepatitis B) or the vaccines provoke an effective and quick immune response (e.g. hepatitis A, measles) then active vaccination with or without passive immunization is equally effective.

Public health aspects of immunization

Universal childhood vaccination programmes are aimed at eradicating the endemic infections, and this can only be done by breaking the chain of transmission. For infections that are spread by the respiratory route (e.g. measles and rubella) a herd immunity of >90% is required; therefore high vaccination rates need to be achieved. Because of adverse publicity around the MMR vaccine, the vaccine uptake rates fell dramatically in the UK during the 1990s resulting in resurgence of measles.

Useful websites

Detailed guidance and immunization schedules are available at the following websites:
- www.dh.gov.uk/en/Policyandguidance/Healthandsocialcaretopics/Greenbook/index. htm
- www.hpa.org.uk

52 Infection control

Infection control is a significant part of a clinical virologist's work. It is an important public health tool in the preventative measures to stop the spread of viral infections. To do this we must first understand how viruses spread and gain entry to infect susceptible hosts. Viruses may gain entry through mucous membranes or directly through blood. Skin, although a good barrier to infection, may also allow viral entry especially in the presence of breaks in the skin surface. Infections may then be localized to the site of entry or spread via the blood stream (*viraemia*) to distant sites and cause systemic infection. The route by which viruses enter the host to establish infection is dictated very much by viral cell tropism.

Viruses and their route of entry and spread

Respiratory route

There are a large number of viruses besides the *respiratory viruses* that enter the host via the respiratory route. Primary infection is established in the respiratory tract epithelium, and virus is also shed from the respiratory tract. Infection may remain localized to the respiratory tract or spread to other sites through viraemia and cause systemic infection (e.g. chickenpox, smallpox, measles, mumps, rubella and parvovirus B19 infections).

The infection is spread via *small droplets*, which are released in the environment while sneezing, coughing etc. These droplets containing the infectious virus may either *be inhaled* or be inoculated into respiratory mucous membrane via *contaminated hands or fomites* such as handkerchiefs.

Gastrointestinal or faecal–oral route

Viruses that replicate in the gut are shed in the faeces, and enter the host via ingestion of contaminated food and water. Faecal contamination of the environment may aid the spread, and this is probably an important factor in the explosive spread of norovirus infections.

Bloodborne

Blood is an important potential source of infection for viruses that have a *viraemic phase*. This may be *chronic* as in the *bloodborne viruses* or *transitory* during the acute viraemic phase of infection with others. This is the most significant route of spread for the bloodborne viruses. Virus is spread via blood and blood-contaminated secretions

either by direct entry to the bloodstream or enters the bloodstream via exposure to mucus membranes and abraded skin.

Genital tract

Direct exposure of genital tract mucosa or abraded skin to infected secretions is required to allow the virus to gain entry and establish infection.

Vertical route of infection

Infection is spread from the mother to the baby, either in utero or at the time of delivery (perinatal) or in the neonatal (postnatal) period. Virus may gain entry either directly through the bloodstream or through exposure of the mucous membrane. See Chapter 42 for further details.

Vectorborne

Mosquitoes, ticks and animals are important vectors of transmission of infection for alpha, flavi and arenaviruses, arbo and other bunya viruses and rabies. This may be through bites or exposure to contaminated secretions, such as urine from infected rodents.

Control of infection

In the community

Viruses in the community are ubiquitous in nature, therefore it is difficult if not impossible to impose control of infection measures. Efforts in the community for controlling virus infections should be directed at:

- public education – for avoidance of infection, including vector control and measures to protect from bites (mosquitoes, ticks, fleas etc.) for vectorborne infections such as arboviruses
- screening programmes – for identifying infected patients with a view to treat and to prevent transmission
- vaccination.

In hospitals

The aim of infection control in hospitals is to avoid the nosocomial spread of infection. Certain groups of patients, such as the immunosuppressed, pregnant, neonates and elderly, are more vulnerable than others and may require special attention. See Table 52.1.

Universal precautions

Most patients are admitted to hospital for reasons other than infection, but may have an incidental infection. Many viral infections are asymptomatic so it is not possible to identify everyone who is suffering from an infection. *Universal precautions* assume that all patients may be potentially infected, and therefore works on the principle of applying certain basic rules of hygiene and infection prevention for all healthcare related tasks.

Table 52.1. *Measures to prevent transmission of some common viral infections in hospitals.*

Virus	At-risk patients	Route of spread				Control measures
		Respiratory	Faecal–oral	Bloodborne	Other	
Adenovirus	Immunocompromised	+++	+++ for enteric types 40/41		Direct inoculation into eye causes adenovirus conjunctivitis.	As indicated respiratory or enteric precautions. Single-use eye equipment to prevent outbreaks of conjunctivitis.
Cytomegalovirus (CMV)	Pregnant, neonates, immunocompromised			+ Blood transfusion, transplanted organs	Mucous membrane exposure to infected saliva and urine.	Normal precautions. CMV negative blood and blood products to neonates and immunosuppressed patients.
Enteroviruses	Neonates		+++			Enteric precautions.
Hepatitis A and E			+++			Enteric precautions.
Hepatitis B (HBV) and hepatitis C (HCV)	Chronic renal failure patients on haemodialysis			+++		Universal precautions. HBV immunoglobulin and vaccine for post-exposure prophylaxis. In haemodialysis units, regular screening for HBV and HCV with isolation of infected should be

Table 52.1. (*cont.*)

Virus	At-risk patients	Route of spread				Control measures
		Respiratory	Faecal–oral	Bloodborne	Other	
						practised. Screening of blood and organ/tissue donors.
HIV and HTLV				+++		Universal precautions. In haemodialysis units, regular screening for HIV and isolation of infected patients should be practised. Screening of blood and organ/tissue donors.
Influenza	Elderly, those with underlying heart conditions, immunocompromised	+++				Respiratory precautions. Special FFP 2 face masks should be worn for avian influenza, post-exposure prophylaxis with oseltamivir.
Measles	Immunocompromised All non-immune	+++				Respiratory precautions, measles vaccine for immunocompetent immunocompromised and immunoglobin for pregnant and

				immunocompromised patients as post-exposure prophylaxis.
Mumps	Young adults	++	Droplet spread from infected saliva, contaminated fomites.	Universal.
Norovirus		+++	Environmental contamination. +++	Enteric precautions, environmental cleaning, cohort nursing of patients. Wards have to be closed to new admissions to break the chain of transmission.
Parainfluenza viruses	Immunocompromised	+++		Respiratory precautions.
Parvovirus B19	Pregnant, immunocompromised, patients with haemolytic anaemia	+++		Respiratory precautions.
Respiratory syncitial virus (RSV)	Neonates, immunocompromised	+++		Respiratory precautions, cohort nursing of infected babies.
Rotavirus		+++		Enteric precautions.
Rubella	Pregnant	+++		Respiratory precautions.
Varicella–zoster virus (VZV) – chickenpox and shingles	Pregnant, immunocompromised	+++	Virus is also shed from the infected vesicles.	Respiratory precautions, VZV immunoglobulin for post-exposure prophylaxis.

- Hand washing or use of alcohol gel before and after examining patients.
- Wearing of gloves and other protection, such as plastic aprons and eye masks (as indicated), when dealing with blood and other body secretions.

Respiratory precautions
- Patients should be isolated in single rooms (ideally in a negative pressure room) wherever practicable.
- Gloves and other appropriate protection (eye protection) should be worn during respiratory procedures, such as taking of naso-pharyngeal aspirates. Face masks (FFP 2) should be worn in addition if a highly pathogenic respiratory virus, such as Avian influenza or SARS CoV, infection is suspected.

Enteric precautions
- Strict hand washing.
- Patients with infective diarrhoea and/or vomiting should be isolated in single rooms wherever practicable, or cohort nursed in isolated bays or wards.

Precautions for highly dangerous pathogens
Patients suspected of viral haemorrhagic fevers (VHF), smallpox, rabies, avian influenza or SARS require special isolation facilities. Patients with viral haemorrhagic fever should be admitted only to designated centres (see Chapter 2) as a special room and equipment is required to isolate these patients. Avian influenza and SARS should be managed as other respiratory pathogens, but FFP 2 face masks should be worn in addition. Smallpox has been eradicated worldwide, but special isolation facilities have been identified in the UK in case of a bioterrorist attack.

Use of post-exposure prophylaxis
Post-exposure prophylaxis is an important part of controlling the spread of infection in hospitals. This could be in the form of antiviral drugs (as for influenza and HIV), or vaccine (as for measles) or immunoglobulin (as for varicella-zoster). Details of post-exposure prophylaxis are given under individual virus or relevant clinical syndromes chapters.

Outbreaks

Outbreaks of infection occur in both community and hospital settings. An outbreak is defined as the occurrence of two or more cases of the same infection associated in time and place. Outbreaks may arise from a common source (*point source outbreaks*) or be due to *person-to-person spread*. Point source outbreaks by nature are explosive (several persons are infected in a short space of time) and are usually food- or waterborne. Certain outbreaks that spread from person to person may also spread rapidly because of high infectivity (e.g. norovirus).

Outbreak investigation

This requires establishing the link between cases, preferably by molecular epidemiology to demonstrate either a common source or a person-to-person spread. Careful questioning of the infected patient will often point to the potential source and mode of spread of infection. Once these facts are established then measures can be put in place to control the outbreak.

Control of outbreaks

Measures that are put in place to control an outbreak will depend upon the infecting agent, its source and suspected route of transmission. These consist of:

- Isolation of infected cases.
- Prophylaxis by vaccination, immunoglobulins or antiviral drugs as indicated.
- Surveillance (and isolation) of new cases by:
  - careful follow up of those (for clinical signs of infection) who have been exposed and may be incubating the disease
  - laboratory screening tests on those exposed to identify those who may develop asymptomatic infection.

Outbreak committee

Management of outbreak control requires good team working between the laboratory, clinician and public health specialist.

An outbreak committee should be instituted at the outset to investigate and manage the outbreak and should include:

- control of infection doctor (usually a microbiologist or virologist)
- control of infection nurse
- public health specialist (doctor or nurse); in the UK this person is usually the consultant in communicable disease control (CCDC) or their representative
- clinician looking after the cases
- others, such as nurse managers, laboratory staff and various experts, should be co-opted to the committee as required.

Notifiable infections

In the UK it is mandatory to report cases of following the viral infections to the consultant in communicable disease control (CCDC) who is the designated 'proper officer' in public health.

- All cases of acute hepatitis
  - Hepatitis A
  - Hepatitis B
  - Hepatitis C
- Measles
- Mumps
- Rubella
- Viral haemorrhagic fevers
- Smallpox
- Rabies

53 Occupational health

Introduction

There are several health-related aspects of being employed as a healthcare professional that affect the health and wellbeing of staff, carers and patients. All health provider organizations have an occupational health department, or have arrangements with another provider to provide this function. Listed below are some aspects of the service that should be provided in relation to virus infections.

Pre-employment health check

All employees should have a pre-employment health check before their employment contract is confirmed. There are several issues that need to be addressed; the best example of a virological issue is ensuring that those health professionals in direct physical contact with patients do not pose a risk of transmitting bloodborne virus infections (hepatitis B, hepatitis C and HIV) to patients. These details are included in the latest UK Department of Health advice: *Health Clearance for Tuberculosis, Hepatitis B, Hepatitis C and HIV: New Healthcare Workers* published in March 2007.

- Hepatitis B – Health professionals who have a high HBV DNA viral load are at risk of transmitting the infection to patients if they are performing exposure-prone procedures (See note below).
- Current regulations in the UK state that healthcare workers should not perform exposure-prone procedures if they have HBs Ag and either HBe antigen or an HBV DNA viral load of $>10^3$ genome equivalents per ml of blood.
- Hepatitis C – Newly employed healthcare workers performing exposure-prone procedures should be tested for HCV antibody before starting to perform this work in the UK. Those who are HCV antibody positive should be tested for HCV RNA, and healthcare workers who are HCV RNA positive should not perform exposure-prone procedures.
- HIV – Newly employed healthcare workers who will be performing exposure-prone procedures should be tested for HIV antibody before commencing this work and those who are HIV positive should not be allowed to perform exposure-prone procedures.
- Existing staff performing exposure-prone procedures employed before this guidance was issued in March 2007 – there is no statutory requirement for them to be tested for HCV and HIV antibody, unless they have risk factors for infection or they believe they may be infected.

Note: Exposure-prone procedures are those invasive procedures where there is a risk that injury to the healthcare worker may result in the exposure of the patient's open tissues to the blood of the healthcare worker. These include procedures where the healthcare worker's gloved hands may be in contact with sharp instruments, needle tips or sharp tissues (e.g. spicules of bone and teeth) inside a patient's open body cavity, wound or confined anatomical space where the hands or fingertips may not be completely visible at all times.

Vaccination

There are vaccines that can be given to healthcare professionals to protect them against the risk of occupationally acquired virus infections.

- Hepatitis B – All healthcare staff in contact with patients or specimens are recommended to be vaccinated, followed by a check for immunity (blood sample to test for anti-HBs).
- Varicella-zoster virus – It is recommended by the Chief Medical Officer for England (CMO/2003/8) that all VZV non-immune healthcare workers are vaccinated to protect them against chickenpox.
- Influenza – All healthcare staff are recommended to have an annual influenza vaccination. This is to prevent staff acquiring infection from patients or in the community, but most importantly to reduce the risk of staff transmitting influenza to patients, many of whom will be particularly susceptible to severe infection.
- Measles – Non-immune healthcare staff are recommended to have MMR vaccination. Measles is a serious infection, and can be fatal in immunocompromised patients.
- Mumps – Non-immune healthcare staff are recommended to have MMR vaccination.
- Rubella – Non-immune healthcare staff are recommended to have MMR vaccination. This is particularly important for those staff caring for pregnant women.
- Poliomyelitis – Non-immune healthcare staff are recommended to be vaccinated.

It is important that staff who are pregnant, or who are actively trying to become pregnant, advise occupational health staff of this; many of these vaccines contain live attenuated viruses, which could theoretically pose a risk to the unborn fetus.

There are other bacteriological vaccine-preventable diseases for which vaccines and health checks are advised. They include:

- Tuberculosis
- Diphtheria
- Meningococci
- Tetanus.

Needle-stick injuries

Needle-stick and other sharps injuries, as well as contamination of mucosa, are an occupational hazard for healthcare staff. The greatest concern about the risk of infection from these incidents centres around the three bloodborne viruses (HBV, HCV and HIV). Since there is a vaccine for HBV, prophylactic antiviral regimes for HIV,

and effective antiviral treatment regimes for HCV, prompt and active management of these incidents are essential in order to provide maximum protection for staff.

If a member of staff has a needle-stick or other sharps injury or mucosal contamination with blood or blood-stained body fluids, they should seek urgent medical attention, preferably through the relevant occupational health department. If that department is closed, the advice of a local medical member of staff should be sought. The most important aspects to be considered urgently are as follows.

- Patient risk factors – does the patient whose blood or blood-stained body fluid has contaminated the member of staff have any risk factors for bloodborne viruses (e.g. intravenous drug use, men who have sex with men, born in sub-Saharan Africa etc.)?
- What was the nature of the incident – was it a deep intramuscular injection with an open bore needle, or a slight scratch from a probe?
- Has the staff member been vaccinated against HBV?
- When did the incident happen?

Where the source patient is known and able to give consent, permission should be sought from the patient to test a 10 ml clotted blood sample for HBs Ag, HIV antibody and HCV antibody (HCV RNA if the patient is immunosuppressed). If the patient is not competent to give consent, urgent discussions should be held with the patient's consultant. There should be procedures in place to test the patient's blood sample urgently and the result should be telephoned promptly to the relevant person as agreed in the incident management plan. These test results should be available within a few hours of arriving in the testing laboratory. In the vast majority of cases, the patient tests negative and no action is required. When the patient tests positive, the following actions are required:

- Hepatitis B virus – If the member of staff has not received HBV vaccine and is not already infected, an accelerated HBV vaccination schedule is recommended as well as hepatitis B immunoglobulin. If the staff member has been vaccinated, has not achieved a satisfactory anti-HBs level ($>$100 mIU/ml), has not received the full course, or was vaccinated several years previously, a booster dose of HBV vaccine is recommended. There is a chart that details all the relevant options in the UK publication *Immunisation against infectious disease – 'The Green Book'* (type 'The Green Book' into Google to get the latest version).
- Human immunodeficiency virus (HIV) – Urgent post-exposure prophylaxis (PEP) with three anti-HIV drugs is recommended. If there is a risk of HIV infection from the incident and a delay in getting the source patient's blood sample tested, the staff member should be offered PEP, which can be reviewed once the results are known.
- Hepatitis C virus – There are no vaccines or prophylactic antiviral regimes for protecting staff against HCV infection. If the source patient is HCV RNA positive, test the healthcare worker's clotted blood at 6 weeks post exposure (for HCV RNA), at 12 weeks (HCV RNA and antibody) and 24 weeks (HCV antibody) post exposure. Any positive test result must be confirmed by testing a second blood sample. If the healthcare worker has confirmed HCV infection (HCV RNA positive), prompt treatment with ribavirin and pegylated interferon alpha should be considered after seeking specialist advice.

Outbreak control

Healthcare workers are frequently in contact with patients with infectious diseases. Airborne and faecal–orally transmitted infections can transmit readily to them. Some of these pose particular risks to other patients, especially if they are immunosuppressed. Some problem infections and their management are listed below.

- Varicella-zoster virus – Chickenpox can be fatal in immunocompromised patients and can cause congenital abnormalities in babies if the mother is infected in the first 20 weeks of pregnancy. Any healthcare worker with chickenpox or zoster must not work with immunocompromised or pregnant patients. If a healthcare worker is in contact with chickenpox or zoster in the healthcare setting and they are unsure if they have had chickenpox before or they are unaware of their VZV antibody status, their blood should be tested for VZV IgG to establish their immune status to VZV. Infection control procedures differ in different healthcare facilities, but in most a healthcare worker looking after immunocompromised or pregnant patients would be removed from patient contact from days 8–21 from the date of contact (remember that by the time a person develops chickenpox, they have been infectious for 2 days). Zoster-immune globulin (ZIG) is available in the UK for providing prophylaxis against severe VZV infection for non-immune immunocompromised and pregnant persons in contact with VZV. It is not available for staff. Aciclovir can also provide prophylaxis and may be recommended in some circumstances.
- Hepatitis A – This is transmitted by the faecal–oral route. Non-immune healthcare workers exposed to infection in this way should receive HAV vaccine or human normal immunoglobulin within 14 days of exposure.
- Influenza – Healthcare workers should receive annual vaccination for influenza. For those not vaccinated, if they are in contact with a case of influenza, prophylactic oseltamivir should be offered.
- Measles – This is one of the most infectious viral diseases and can cause severe or fatal infection in immunocompromised patients. Any healthcare worker who is suspected of having measles should be removed from patient contact immediately. Prophylactic human normal immunoglobulin is recommended for non-immune immunocompromised patients. Healthcare staff in contact with measles should have their immune status established (have they had two doses of measles vaccine, have they had natural measles?). Non-immune staff should be offered MMR vaccine (normal immunoglobin if pregnant) and warned to stay away from work during the incubation period or if they suspect they may be in the early stages of measles.

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Note: page numbers in *italics* refer to figures and tables.