8.5.29 Newly discovered viruses 951

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8.5.29 Newly discovered viruses 951 Henderson–Paterson molluscum bodies. These are 35 µm in diam- eter, ovoid, eosinophilic, intracytoplasmic inclusion bodies within keratinocytes (Fig. 8.5.28.4). They stain purple with Tzanck re- agent in scrapings from the lesions. In HIV patients, histological appearances can differ. Differential diagnosis The differential diagnosis includes lepromatous leprosy, Darier's disease (keratosis follicularis), epithelial naevi, and skin tumours such as basal cell epithelioma or trichoepithelioma. Giant lesions might be confused with keratoacanthoma, common warts, or warty dyskeratoma. In the genital area, genital warts (condylomata acuminata) may look similar. In immunosuppressed people, umbilicated cutaneous lesions of disseminated Talaromyces marnef- fei infection, histoplasmosis, paracoccidioidomycosis, or crypto- coccosis can appear identical to molluscum. Treatment (See also Section 23.) Treatment might not be necessary, depending on the site and number of lesions and the age of the patient. An enormous number of local treatments are claimed to be effective, but evidence is lacking. Mechanical methods include picking out lesions on the tip of a needle or with adhesive tape, curettage, cryotherapy with liquid nitrogen, and diathermy. Topical chemicals include tre- tinoin, podofilox, cantharidin, acetic acid, phenol, salicylic acid, silver nitrate, trichloroacetic acid, lactic acid, and benzoin. Agents can be delivered to the inside of the lesion using the sharpened end of a wooden applicator stick. In children, local anaesthetic cream should be applied beforehand. Curettage might be the most effective therapeutic approach but requires skilled staff, so in many cases it might be more appropriate to wait for spontaneous resolution. In patients with HIV, molluscum usually responds dramatically to highly active antiretroviral therapy (HAART). In severe cases, 5% imiquimod cream or cidofovir (intravenously or topically) have proved effective but in immunocompetent children, 5% imiquimod cream is not recommended. Prevention In schoolchildren, spread can be prevented by avoiding swimming pools, contact sports, and shared towels, until the lesions have resolved. FURTHER READING Brown J, et al. (2006). Childhood molluscum contagiosum. Int J Dermatol, 45, 93–9. De Clercq E (2003). Clinical potential of the acyclic nucleoside phosphonates cidofovir, adefovir, and tenofovir in treatment of DNA virus and retrovirus infections. Clin Microbiol Rev, 16, 569–96. Haral A, et al. (2016). To treat molluscum contagiosum or not— curettage: an effective, well-accepted treatment modality. Paediatr

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 increasingly in international outbreak information over the last few years. How they will influence global public health remains to be seen. Emerging viruses that might be of particular global public health importance include, respiratory coronaviruses, Zika virus, and se- vere fever and thrombocytopenia syndrome virus. Other emerging viruses of importance include bocavirus, Bufavirus, PARV4, human parechovirus, Itaya, Heartland, and Bourbon virus. The human pathogenicity of other emerging viruses is less certain. Coronaviruses Severe acute respiratory syndrome (SARS) Coronaviruses (CoV) are single-stranded RNA viruses commonly associated with respiratory illness and less often with gastrointes- tinal and neurological disease in a wide variety of mammals and birds. They have high rates of mutation and recombination and a propensity to cross host species. The severe acute respiratory syn- drome (SARS) outbreak of a new human coronavirus, SARS- associated coronavirus (SARS-CoV), between November 2002 and July 2003 spread across five continents and caused over 700 human deaths. This pandemic triggered renewed interest in this area, leading to increased understanding of the origin of SARS-CoV. In the early phase of the outbreak, the infecting SARS viruses showed closer similarities to animal viruses than later on in the pandemic. Virological studies suggest that the animal viruses crossed over to humans on more than one separate occasion, so repeated similar events should be expected in the future. Bats are increasingly rec- ognized as reservoirs of emerging viruses. The discovery of species- specific, SARS-like coronaviruses in horseshoe bats with the same genome organization as human SARS coronaviruses indicates that a human SARS virus originated in one or more bat species. It is likely that an intermediate animal host is also required to allow modifica- tion of the mutating progenitor virus before transmission to humans is possible. Understanding this reservoir might help to prevent fu- ture human outbreaks of SARS-CoV. MERS-CoV Middle Eastern respiratory syndrome (MERS) has recently emerged as a novel pathogen that remains an endemic low level public health threat. First isolated from a patient who died in September 2012 in Saudi Arabia, it was similar to the SARS-CoV strain involved in the 2002–2003 epidemic and was termed the Middle East Respiratory Syndrome coronavirus (MERS-CoV). From the initial case to the end of September 2018, there have been 2260 laboratory confirmed cases in 27 countries with a mortality rate of 36%. Death is more likely in patients with

increasing age and with other comorbidities. The viral origin of MERS-CoV is still unclear but, like SARS, it is thought to have originally infected bats. Unlike SARS, however, at some point in the distant past MERS-CoV spread to dromedy camels that are currently thought to be the main reservoir. Camels have been found with virus identical to human strains across the Arabian Peninsula. New human coronaviruses Two new human coronaviruses have been discovered since the SARS epidemic.: HCoV-NL63 and HCoV-HK. HCoV-NL63 was first identified in a child with bronchiolitis in the Netherlands. Studies published in 2004 and 2005 found 8 to 9% of children aged under 5 years with known respiratory illness were positive for HCoV-NL63 by polymerase chain reaction (PCR), while tests for common re- spiratory viruses were negative. Longitudinal studies showed that seroconversion usually occurred by the age of 3.5 years. Significant sequence heterogeneity exists and it is likely, therefore, that there are two closely related genotypic subgroups. In 2005, another human coronavirus was discovered, HCoV- HKU1. It was first described in Hong Kong in a 71-year-old man with pneumonia who had recently returned from China. It has since been reported in patients in Australia and the United States of America. Common clinical findings in young children included rhinorrhoea, cough, fever, and abnormal breath sounds on auscul- tation. The possibility of central nervous system infection and hepa- titis (in a liver transplant recipient) was suggested in two separate patients in one study. Genomic and phylogenetic analysis suggests that this virus is most closely related to the mouse hepatitis virus, a coronavirus studied since the 1930s. Both HCoV-HKU1 and HCoV-NL63 have a worldwide distribu- tion and are associated with a low mortality which suggests they are not viruses that have only recently infected humans rather they have only recently been identified. They join the two previously identified coronoviruses HCoVOC43 and HCoV229E in causing respiratory tract infection. New human polyomaviruses: KI, WU, and
Merkel cell polyomavirus The double-stranded DNA human polyomaviruses, JC virus and BK virus, are ubiquitous worldwide and are pathogenic in immuno- compromised hosts. In 2007, two new human polyomaviruses were described, KI virus and WU virus. They share a phylogenetic rela- tionship and together may form a new subclass. They have been iso- lated primarily from respiratory secretions. KI was discovered after molecular screening of respiratory samples. WU was first detected by high-throughput sequencing of respiratory secretions from a patient with an acute respiratory disease of unknown aetiology. Analysis of two more cohorts in different continents revealed that most patients positive for WU were aged under 3 years, and that all infected adults were immunocompromised. The clinical spectrum of the disease included upper and lower respiratory tract infection, bronchiolitis, croup, and, rarely, gastroenteritis. However, the role of these viruses as respiratory pathogens has since been questioned after further studies detected them both in asymptomatic children and those concurrently infected with other respiratory viruses. Studies to establish the role of WU and KI in immunocomprom- ised adults have been inconclusive. The relatively high seropreva- lence of these viruses in healthy blood donors suggest that a benign primary infection with these viruses occurs in childhood, followed by a period of latency and subsequent reactivation in the context of immunosuppression. In 2008, another novel polyomavirus termed ‘Merkel cell polyomavirus’ was found to be integrated within the cellular genome of cells of the rare skin cancer Merkel cell carcinoma which primarily occurs in elderly and immunosuppressed people. This is consistent with the oncogenic potential of other polyomaviruses. Merkel cell

8.5.29 Newly discovered viruses 953 polyomavirus has also been isolated in respiratory samples from symptomatic adult and paediatric patients though its precise role as a pathogen in this

context is still yet to be confirmed. New human Parvoviruses: Bocavirus, Bufavirus, Human parvovirus 4 (PARV4) Parvoviruses are a family of small nonenveloped, linear single- stranded DNA viruses. They are divided into two subfamilies depending on their ability to cause infection in vertebrates. Identified in 1975, parvovirus B19 was previously thought to be the only parvovirus known to be pathogenic in humans as the cause of fifth disease in children (Chapter 8.5.20). However, since 2005 fur- ther genera and species of Parvovirus have been identified and asso- ciated with disease in humans. Human bocavirus Human bocavirus (HBoV) was first described in September 2005 following isolation by random PCR in pooled respiratory samples from hospitalized children in Sweden. HBoV is closely related to ca- nine minute virus and bovine parvovirus. Although Koch's postulates have not yet been fulfilled, supportive molecular evidence demonstrated this virus in respiratory sam- ples from children with lower respiratory tract disease who tested negative for common respiratory viruses. It has been found most commonly in children aged under 3 years, particularly in preterm infants with mild to severe respiratory symptoms. Although a study conducted in the Netherlands showed no difference between the detection of HBoV in children with or without lower respiratory tract infection in paediatric intensive care, higher levels of HBoV were seen in the symptomatic patients compared to asymptomatic controls. This may reflect differences in viral load of acute infection versus asymptomatic shedding. A more recent study of patients hos- pitalized with acute lower respiratory tract infection in Argentina in 2010 found a bimodal age distribution of HBoV (<1 year and

> 30 years) with a significantly higher rate of coinfection (predomin- antly with respiratory syncytial virus) found in children compared to adults. Severe cases are rare although life threatening infections with HBoV1 have been reported. Related viruses HBoV2, HBoV3, and HBoV4 have more recently been identified in faecal samples of children in several countries including the United Kingdom, Pakistan, and Thailand. An asso- ciation with acute gastroenteritis has been described: in one study, HBoV2 was the third most prevalent virus seen in children with acute gastroenteritis after rotavirus and astrovirus. Of these newer viruses HBoV2 is the most commonly isolated species. Further studies are needed to determine the site of replication and potential association with clinical disease. The conditions that have been associated with bocavirus infection are gastroenteritis and flaccid paralysis. Bufavirus Metagenomic analysis of faecal samples from children with acute diarrhoea in Burkina Faso identified a highly divergent parvovirus that was named Bufavirus. Analysis of samples revealed it was pre- sent in 4% of samples. Sequencing of the coding region demon- strated less than 31% similarity with known parvoviruses: it was therefore declared a new genus with at least two species. Similar studies in Tunisia have demonstrated the presence of at least one of the genotypes in 1.6% of samples. Analysis of stool from patients of all ages with gastroenteritis in Finland revealed 1.1% had PCR de- tectable Bufavirus. Unlike the initial studies all the positive samples in the Finish study were from adults. This virus has been shown to be circulating in northern Europe as well as Africa and its causative role in gastroenteritis remains unclear. Human Parvovirus 4 (PARV4) In 2005 a novel DNA virus was identified in a high risk patient with symptoms in keeping with an

> HIV seroconversion illness. The virus was identified via a sequence independant PCR amplification method. This virus was termed Human Parvovirus 4 (PARV4) and subsequent studies have demonstrated its presence in a large number of intravenous drug users that are also HIV positive. Investigation of patients with HIV acquired by other routes does not demonstrate PARV4 infection. Studies on blood donors and pooled blood prod- ucts has demonstrated the presence of PARV4 which is biologically plausible as parvoviruses are resistant to viral inactivation methods used on plasma derived products. Unlike other parvoviruses, PARV4 has been shown to be a blood borne virus; studies in haemophiliacs who received blood products in the 1970s and 1980s have a high rate of PARV4 compared to their sibling controls that did not have haemophilia, or receive blood products, all of whom were seronega- tive. Autopsy samples on HIV positive patients from the Congo and Nigeria have a genetically distinct PARV4 from that which is seen in European patients, which suggests different transmission networks. Vesivirus Single-stranded RNA vesiviruses of the Calciviridae family are common marine microorganisms, but are also known to infect land mammals. They cause a broad spectrum of disease in animals including vesicular rash, encephalitis, haemorrhagic disease, spon- taneous abortion, and hepatitis. Their effect on humans is not well established, but a recent seroprevalence study has shown that 12% of successful blood donors tested had evidence of past exposure to vesivirus. This was significantly higher (29%) in patients with hepa- titis of unknown, but suspected, infectious cause, and even higher (47%) in patients with hepatitis of unknown cause associated with blood transfusion or dialysis. Vesivirus viraemia was also shown to be present in some of those tested. Picornaviridae New parechoviruses: Human parechovirus and Ljungan virus Human parechovirus and Ljungan virus are the two species of the genus parechovirus of the family Picornaviridae. Human parechoviruses are single-stranded RNA viruses which differ from other family members in having only three, rather than four, capsid proteins, and in exerting atypical cytopathic effects. HPeV- 1 and HPeV-2 were previously designated enterovirus 22 and 23, but were reclassified in 1999. By 2015 16 human parechovirus genotypes had been described.

954 section 8 Infectious diseases HPeV infections are common, with at least 95% of the adult popu- lation positive for HPeV-specific antibodies. Most infections are thought to predominantly affect neonates and young children and, although the clinical spectrum of disease differs between the viruses, it has been compared to infection with enterovirus. Earlier studies of HPeV-1 suggested infection resulted in more gastrointestinal and re- spiratory illness which was often severe, and was occasionally found as a copathogen with other respiratory viruses such as respiratory syncytial virus. The role of HPeV-1 as a respiratory pathogen has since been challenged and often infections are asymptomatic. HPeV- 3 has been shown to present as a sepsis-like syndrome predominantly affecting neonates. Cerebrospinal fluid (CSF) from central nervous system infection with HPeV-3 has a noninflammatory profile; how- ever, virus has been amplified from the CSF, nasopharyngeal swabs, and rectal swabs. The range of neurological infection is poorly de- fined because of the

benign CSF appearance. Children with HPeV-3 positive CSF specimens in the United States of America showed a predominance of male infants presenting with sepsis-like syndromes in a late summer/autumn distribution in odd numbered years. This seasonal distribution was not reflected in a similar survey in the United Kingdom, in which patients presented in the spring in even-numbered years, and were almost always infants less than 3 months of age. The combination of prominent abdominal distension with erythematous rash has been seen in infants with confirmed HPeV in- fection during an outbreak of HPeV3 infection in New South Wales; such signs are postulated to be important clues to the diagnosis in the absence of raised C-reactive protein or lymphocyte count. More recently described HPeV-8 (Brazil, 2009) and HPeV-10 (Sri Lanka, 2010) were both found in stool specimens of children with acute gastroenteritis. It is also likely that further novel human parechoviruses will be discovered and their contribution as human pathogens investigated. Another parechovirus, Ljungan virus, has recently been postu- lated as a major aetiological agent in sudden infant death syndrome. Ljungan virus mainly affects rodents and is known to be associated with perinatal rodent death both in the wild and in laboratory mice. Interestingly, a strong epidemiological link between small rodent numbers and human intrauterine fetal death has been described in Sweden. In addition, Ljungan virus has been detected in brain, heart, and lung tissue in cases of sudden infant death syndrome. Whether true causation can be proven is yet to be established. Small rodent models for type 1 diabetes mellitus have shown high rates of Ljungan virus infection leading to the investigation of its role in the pathogenesis of diabetes mellitus. Swedish patients with diabetes mellitus have also been found to have an increased prevalence of antibodies to Ljungan virus; however, Ljungan virus RNA has not been detected in patients with diabetes. Investigations into this as- sociation are ongoing. Human cardiovirus Saffold virus Investigation of an 8-month old girl with pyrexia of unknown origin, led to the discovery in 2007 of a novel cardiovirus of the family Picornaviradae, named Saffold virus. Several strains of Saffold virus have since been described and have been detected in faecal and respiratory specimens of children worldwide, from a patient with aseptic meningitis and from children with non-polio acute flaccid paralysis, though causality has not yet been proven. Interestingly, Saffold virus is grouped with Theiler’s murine encephalomyelitis virus, which is known to cause a multiple sclerosis-like syndrome in mice. Although this might be the first human cardiovirus, a specific clinical association is yet to be found. Emerging and Novel human flaviviruses Usutu virus Usutu virus, named after a river in Swaziland, was first isolated from mosquitoes in South Africa in 1959. It is a mosquito-borne flavivirus of the Japanese encephalitis group and was isolated once from a man with fever and rash. Although a virus of tropical or subtropical Africa, the epidemiology might be changing, as demonstrated by its isolation from several bird species during a die-off in Austria in 2001. This reflects the pattern of the emergence of West Nile virus in the United States of America in 1999, which first affected birds and subsequently humans. Neuroinvasive infection secondary to Usutu virus was reported for the first time worldwide in 2009 when Usutu virus was detected by RT-PCR in CSF and serum samples in two im- munocompromised patients in Italy who had both received blood transfusions. Clinical symptoms in both patients included fever (>39.5°C), headache, and neurological disease. Since then there have been a total of 17 cases of neuroinvasive disease reported in Europe. The extent of the human pathogenic potential of Usutu virus remains to be seen, but there is concern that it might follow a re- current theme of flavivirus emergence in previously cooler climates following climate change. Surveillance systems already in place in areas of endemic West Nile virus could be adapted to detect more cases of Usutu virus if surveillance in wild birds and vectors indi- cated a need. Alkurma virus Alkhurma virus, a re-emerging tick-borne flavivirus, is related to Kysanur Forest disease and shares

clinical features with dengue fever. It was first described in a butcher in Saudi Arabia in the 1990s, and over the next 10 years, had a case fatality rate of around 25%. In 2009, 4 further sporadic cases were described in Jeddah in the post-Hajj period and all might be linked to the slaughtering/processing of sheep. In 2010 two discrete cases were reported in travellers returning to Italy from Egypt, neither of whom had links to the slaughtering of sheep. Both patients had recalled visiting the same camel market and one recalled a tick bite. These cases have highlighted the need to fur- ther understand the epidemiology of this re-emerging disease. Zika virus This RNA arbovius was first isolated from a Rhesus monkey in the Zika forest in Uganda in 1947 and until recently only caused spor- adic cases. It is a single-stranded RNA virus related to Dengue and Chikungunya virus. Entomological and epidemiological studies undertaken in Africa and Asia have demonstrated ongoing viro- logical activity since its initial isolation in these regions. Infections are often asymptomatic. When symptoms occur they are generally mild and consist of fever, maculopapular rash, arthralgia, myalgis, and nonpurulent conjunctivitis. Symptoms develop three to twelve days after being bitten by an infected Ades mosquito. Early in clinical

8.5.29 Newly discovered viruses 955 infection it is not possible to distinguish between infections with Zika, Dengue, or Chikungunya. (See Chapter 8.5.14.) In 2007 the largest documented outbreak occurred in French Polynesia on the island of Yap when 11% of the population were in- fected and more severe neurological features, such as Guillian–Barré syndrome, were seen. This outbreak was noticeable not only for its size but also because it documented transmission outside the trad- itional endemic areas of Africa and Asia. Outbreaks in Polynesia have continued since then. In 2014–2015, following an outbreak, there was noted to be an increase in fetal central nervous system malformations. Viraemic travellers have introduced Zika to countries outside its previously known range. Zika virus infection was first reported in South America in 2015 further establishing it as an emerging infectious disease. In 2015 in Brazil, the number of cases of micro- cephaly increased 20-fold. This increase occurred less than a year after the emergence of Zika virus infection in the region. Zika virus RNA has been found in the amniotic fluid of pregnancies with microcephalus and in the blood and tissue samples of micro- cephalic neonates. Along with microcephaly, other abnormalities have been described and it is now recognized that there is a distinct congenital Zika syndrome. Zika virus has emerged beyond its geographical range and has the potential for causing outbreaks wherever the Ades mosquito is found. Its clinical features and mode of transmission is similar both to dengue and chickunguna viruses, both of which are global public health concerns. Zika has the potential to follow the same course although with the possible potential for neurological and teratogenic complications. This highlights the need for ef- fective mosquito control and for vaccine development. Novel human Bunyaviruses The genus Phleobovirus in the family Bunyaviridae consists of more than 70 antigenically different viruses divided into complexes depending on their route of spread either by sand flies, mosquitoes, or as more recently reported, by ticks. Garissa and Ngari Genetic reassortment of segmented RNA viruses such as influenza is well known to have an important role in the emergence of vir- uses with new disease potential and host range. There is less gen- etic information on bunyaviruses, but there is increasing evidence that this mechanism could account for their evolution and increase their potential to cause disease in humans. Bunyaviruss have a trisegmented negative sense RNA genome. Evidence supports gen- etic reassortment as the driving force in bunyavirus evolution, as novel reassortment viruses continue to be identified. The first association of Ngari virus with human haemorrhagic fever was discovered during an extensive investigation of a large outbreak in Kenya, Tanzania, and Somalia in 1997 to 1998. A pre- viously unidentified member of the

orthobunyavirus genus (family Bunyaviridae) was found in two cases. The virus was initially named Garissa virus, but subsequent genetic analysis showed that it was not a separate orthobunyavirus but had arisen by genetic segment reassortment between two known orthobunyaviruses, Bunyamwera virus and Ngari virus. Further sequence analysis of multiple orthobunyaviruses revealed that Ngari virus is a reassort ment Bunyamwera virus. Itaya Orthobunyaviruses have a global distribution and novel viruses have been identified in South America that have also arisen fol- lowing genomic reassortment. Itaya virus was identified in Peru in 2015 by investigating samples from patients with febrile illnesses in 1999 and 2006. The clinical syndrome is similar to that seen with dengue virus. Genomic analysis showed that it had arisen from reassortment between Caraparu virus, a known orthobynyavirus, and an unidentified group C orthobunyavirus. Severe fever and thrombocytopenia syndrome virus Severe fever and thrombocytopenia syndrome virus (SFTSV) was the first pathogenic tick-borne phlebovirus identified. In 2009, in rural provinces in China, an outbreak of severe fever and thrombocytopenia syndrome (SFTS) was noted. Investigations were undertaken to determine if this outbreak was due to infec- tion with the bacterium Anaplasma phagoocytophilum. In view of this, enhanced surveillance of similar clinical syndromes was undertaken in selected provinces in China. Investigations led to the identification of SFTSV, a novel phlebovirus associated with a clin- ical syndrome whose major features are fever, thrombocytopenia, gastrointestinal symptoms, leucopoenia, and an unusually high case fatality rate. Epidemiological studies showed that the virus was isolated from the blood of 171 patients out of 241 hospitalized patients who ful- filled the clinical criteria for SFTS; no viral DNA was isolated form healthy matched controls. Seroprevalance studies have been under- taken in Chinese provinces where fatalities have occurred and prevalence ranges from 0.84% to 6.37% which may indicate asymp- tomatic or mild infection can occur. When investigating the patients' homes, mosquitoes and ticks were commonly found. SFTSV DNA has not been found in mosquitoes but is repeatedly reported from Haemaphysalis longicoruis ticks. Studies in animals have shown in- fection in a variety of small and large mammals with goats and cattle having the highest seroprevalance rates. Ribavarin can inhibit viral replication in vitro but does not affect mortality rates in vivo; treatment for this infection remains only supportive. Following initial reports in China, cases were reported in both Japan and South Korea. 70% of patients have been farmers and out- breaks show seasonal variation being most common between spring to early autumn when ticks, thought to be the vector, are prevalent. However, aerosolized disease has been postulated which highlights the need for infection control precautions in novel infections. SFTS remains a serious condition with an average case fatality rate of 12% for SFTSV infection. Heartland virus Heartland virus is an arthropod-borne Bunyavirus and the second reported that is transmitted by ticks. In 2009 two unrelated farmers from Missouri were admitted with a febrile illness following tick bites. Both men lived on farms and recalled removing embedded ticks in the days prior to their admission. Both men presented with fever, fatigue, headache, nausea, and non-bloody diarrhoea, with one patient also reporting a dry cough and myalgia,

 but neither had a rash. Initial blood results on both patients demon- strated leucopoenia, thrombocytopenia, mild hyponatraemia, and elevated hepatic aminotransferases. Both recovered and had problems with short term memory in the following weeks but had no long term sequalae. Since 2009, seven additional cases have been reported from the United States and two of them have been fatal. Amblyomma amer- icanum, also known as the lone star tick, is implicated as the vector as Heartland virus has been repeatedly isolated this species. The full vertebral host populations remain to be fully identified but it is known to include

white-tail deer, raccoons, moose, and coyotes. The wildlife distribution includes central and eastern United States. Lujo virus Lujo virus is a novel, genetically distinct, highly pathogenic arena virus associated with haemorrhagic fever with an exceptionally high case fatality rate of 80%. It was first isolated in South Africa in 2008 during a nosocomial outbreak of five cases following the transfer of the index case from Zambia. The technique of unbiased pyrosequencing used during the investigation of this outbreak might be useful in identifying other novel pathogens in the future. Mimivirus With a diameter of 600 nm and with a dsDNA genome of 1.2 Mb, mimivirus is the largest virus so far discovered. It was initially thought to be a Gram-positive coccoid bacterium and is visible with the light microscope. The virus species Acanthamoeba polyphaga mimivirus is within a family of its own, the Mimiviridae. Phylogenetic analysis has shown its relationship to other large DNA viruses including the Iridoviridae and Poxviridae, though its precise position in the phylogenetic tree remains under debate. Discovered during the investigation of respiratory pathogens using an amoeba coculture system, it might have originated in marine environments. Although it replicates within amoebae, it has yet to be shown to multiply ef- fectively in mammalian cells. Mimivirus might have a role in re- spiratory disease. A pneumonic illness can be produced in mice and a laboratory technician occupationally exposed to high con- centrations of mimivirus antigens developed a subacute, spontan- eously resolving pneumonia with seroconversion to mimivirus. The prevalence of antibodies to mimivirus was 9.66% in 376 Canadian patients with community acquired pneumonia compared to 2.3% of healthy controls. Two studies of pneumonia in intensive care units have shown seroconversion to the virus in more patients with ventilator-associated pneumonia than in controls. Seropositivity to mimivirus in ventilated patients in a prospective matched cohort study was associated with longer duration of ventilation and longer intensive care unit stay. There was no mortality difference between seropositive patients and matched seronegative controls. Mimivirus antibodies have been found to be more prevalent in populations admitted from nursing homes and in those rehospitalized after dis- charge. These seroprevalence studies must be interpreted cautiously because of possible cross-reactivity with other pathogens. More recent studies using real-time PCR have also been inconclusive. Although mimivirus DNA was recovered from a bronchoalveolar lavage of a patient with relapsing pneumonia in the absence of other causative pathogens, a prevalence study of 69 ventilated patients in an intensive care setting found no evidence of mimivirus infection using real-time PCR. A study of paired serological and DNA detec- tion in lower respiratory sampeles may be useful in investigating the role of mimivirus in respiratory disease. Titi Monkey adenovirus An outbreak of fulminant pneumonia affected 34% of New World monkeys housed in a closed colony in the United States. The Virochip microarray was used to identify the causative agent, a novel adenovirus—the Titi Monkey adenovirus. An exposed worker subsequently developed an acute respiratory tract infec- tion lasting 4 weeks and seroconverted to Titi Monkey adeno- virus.
A critically ill family member of this person also developed symptoms and tested positive serologically, suggesting poten- tial for primate–human and human–human transmission of this novel agent. Bourbon virus Bourbon virus is a novel virus that has been isolated twice from clinical cases. A member of the Thogotovirus genus of the orthomyxoviridae family it joins six distinct viruses, two of which (Thogoto and Dhori) are known to cause disease in humans. The initial case was reported in a previously well male patient in his fifties who lived in Bourbon County in Kansas, United States. He became unwell several days after sustaining tick bites while working on his house. His initial symptoms were nausea, weakness, and diar- rhoea and progressed to multiorgan failure and death in 11 days. Throughout his illness a diffuse maculopapular rash on his chest, abdomen, and back was noted along with persistent periodic fevers. His initial laboratory findings

were leucopoenia, thrombocyto- penia, and elevated liver transaminases. Both traditional culture and electron microscopy combined with newer genetic techniques were used to identify this novel virus which shares greater than 70% overall average nucleotide sequence identity with Dhori virus. Unlike other Thogotovirus infections, no neurological symptoms were reported and unlike other orthomyxoviriae, infections no re- spiratory symptoms were noted. The precise role of Bourbon virus in his illness is unknown but the high-level virus noted in his blood samples suggests it contributed. The precise route of infection is unknown but the infection occurring in late spring following an embedded tick supports a tick-borne route of infection. A second case has been reported again in the United States from the state of Oklahoma; this patient made a complete recovery. FURTHER READING Abed Y, et al. (2006). Human parechovirus types 1, 2 and 3 infections in Canada. Emerg Infect Dis, 12, 969–75. Allander T, et al. (2005). Cloning of a human parvovirus by molecular screening of respiratory tract samples. Proc Natl Acad Sci U S A, 102, 12891–6.

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