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section 8 Infectious diseases 1076 There are no agents with proven efficacy for the treatment of pertussis-induced cough. Prognosis/outcome Pertussis in young infants is unpredictable with the potential for rapid deterioration. Complications include pneumonia, pulmonary hypertension, seizures, and encephalopathy. Pneumonia, seizures, and encephalopathy also occur in adults with pertussis. Other complications reported in adults include cough-induced urinary incontinence and syncope, herniated inter- vertebral disc, inguinal hernia, hearing loss, angina, carotid artery dissection, and death. Areas of uncertainty or controversy and future developments Modifications to current acellular vaccine immunization schedules could potentially increase protection of young infants against per- tussis. Maternal immunization during pregnancy is one such option. Because of the potential for pregnancy immunization to alter the immune response of the infant to vaccine doses received during in- fancy, it may be necessary for booster childhood dosing to begin at a younger age. The immunization of household members may provide indirect protection of young infants against exposure to B. pertussis. Much remains to be learnt about the pathogenesis of pertussis and the pathophysiology of clinical manifestations and the optimal man- agement of young children with life-threatening pertussis. Vaccines with greater efficacy against B. pertussis infection will be necessary for immunization to be able to reduce endemic disease incidence. Improved surveillance is required in both developed and developing countries. The need to extend the duration of immunization-induced pro- tection will lead to further refinement of immunization schedules and of pertussis vaccines. Multicentre randomized clinical trials are necessary to provide the evidence base for the intensive care man- agement of life-threatening pertussis. FURTHER READING Black RE, et al. (2010). Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet, 375, 1969–87. Cherry JD (2014). Adult pertussis in the pre- and post-vaccine eras: lifelong vaccine-induced immunity? Expert Rev Vaccines, 13, 1073–80. Crowcroft NS, Pebody RG (2006). Recent developments in pertussis. Lancet, 367, 1926–36. Hewlett EL, et al. (2014). Pertussis pathogenesis—what we know and what we don’t know. J Infect Dis, 209, 982–5. Mattoo S, Cherry JD (2005). Molecular pathogenesis, epidemi- ology, and clinical manifestations of respiratory infections due to Bordetella pertussis and other Bordetella subspecies. Clin Microbiol Rev, 18, 326–82. Mooi FR, Van Der Maas NA, De Melker HE (2014). Pertussis resur- gence: waning

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8.6.16 Melioidosis and glanders 1077 Genetics and pathogenesis The Burkholderia pseudomallei K96243 genome is composed of two chromosomes of 4.07 Mbp and 3.17 Mbp which show func- tional partitioning of genes. The large chromosome encodes many of the core functions associated with metabolism and growth, while the smaller chromosome carries more accessory functions associated with adaptation and survival in different environments. At least 6% of the genome is made up of puta- tive genomic islands that have probably been acquired via hori- zontal gene transfer. Findings from whole genome sequencing of B. pseudomallei are indicative of a high rate of genetic recombin- ation, and consistent with Australia as an early reservoir for the current global B. pseudomallei population with transmission to Southeast Asia, followed by onward transmission to South Asia and East Asia. Experimental studies indicate a role in virulence for lipopoly- saccharide, capsular polysaccharide (CPS), flagella, hemolysin- coregulation protein 1 (Hcp1), a type VI secretion system, and a type III secretion system (TTSS3) that shares homology with the inv/spa/prg TTSS of Salmonella typhimurium and the ipa/mxi/ spa TTSS of Shigella flexneri. Other candidate virulence factors include a siderophore for iron acquisition, and secreted proteins such as haemolysin, lipases, and proteases. Data from in vitro models and post-mortem studies indicate that B. pseudomallei is equipped for intracellular survival. The organism survives and replicates within neutrophils and monocytes, and employs mul- tiple mechanisms to escape macrophage killing and evade host immunity. Epidemiology, aetiology, and prevention The first reported case of

melioidosis occurred in a 40-year-old morphine addict in Rangoon (Yangon), Myanmar in 1911. The incidence of recognized cases is highest in north-east Thailand and northern Australia, but melioidosis is also known to occur in nu- merous countries across South and East Asia, in Central America, Ecuador, and Brazil, and in several countries in Africa. The route of infection is most commonly via skin inoculation or bacterial contamination of wounds, but other routes include ingestion, in- halation, and aspiration including near drowning. Activities of daily living associated with disease acquisition include exposure to soil or water, an open wound, eating food contaminated with soil or dust, drinking untreated water, and outdoor exposure to rain. Melioidosis incidence peaks between the fourth and sixth decades; children represent one-sixth of infected individuals in north-east Thailand. Diabetes mellitus, excess alcohol consump- tion, smoking, steroid intake, chronic renal failure, and chronic lung disease are independent risk factors. One or more risk fac- tors are present in approximately 80% of affected adults but only 30% of children (most commonly penetrating injury). Most cases in Thailand occur in rice farmers who work without protective footwear. Avoidance of contact with the environment in which B. pseudomallei exists is likely to prove an effective preventive measure, but such strategies are not in place across rural Asia. Clinical features, differential diagnosis, and criteria for diagnosis The period between B. pseudomallei exposure and onset of clin- ical manifestations is difficult to define since most patients do not report a specific inoculation event. An incubation period of 1 to 21 days (mean 9 days) was determined for 25% of cases in Australia with a specific inoculation event, but this may not be representa- tive for cases overall. The longest recorded incubation period is 29 years. Time from onset of disease to clinical presentation is also variable; in north-east Thailand, approximately one-third of pa- tients have symptoms for less than 7 days, one-half for 7 to 28 days, and the remainder have symptoms for more than 28 days. Manifestations range from a fulminant sepsis and rapid death to a chronic illness characterized by fever, weight loss, and wasting. The most frequent clinical picture is a septicaemic illness, often associ- ated with bacterial dissemination to distant sites such that concomi- tant pneumonia (Fig. 8.6.16.1) and hepatic and splenic abscesses are common. Pneumonia occurs in around 50% of patients. Infection can also occur in bone, joints, skin (superficial pustules and cuta- neous abscesses, Fig. 8.6.16.2), soft tissue (pyomyositis), testis, and prostate. A specific syndrome of meningoencephalitis with brain stem involvement and risk of respiratory arrest, flaccid paraparesis, or peripheral motor weakness occurs in 4% of cases in northern Australia. Central nervous system infections occur in around 1.5% of melioidosis patients in Thailand (Fig. 8.6.16.3), although menin- goencephalitis is not recognized in this setting. Involvement of the vascular tree is recognized but unusual. Acute parotitis accounts for one-third of childhood cases in Thailand but is unusual in adult- hood. The number of sites involved is variable and possible combin- ations include positive blood cultures but no other focus, positive blood cultures and one or more distant foci, and negative blood cul- tures with one or more foci. Classification of patients into different categories based on these observations has been suggested, but it may be more accurate to consider disease as a continuum. A high index of suspicion is required in order to diagnose melioidosis in the nonendemic setting. Clinicians should con- sider the possibility in patients with a fever who have one or more of the following: (1) residency at any time in an endemic region or a relevant travel history; (2) an occupation or other pursuits that may have resulted in contact with soil or water containing B. pseudomallei (including military personnel who are on exer- cise or active service); and (3) the presence of risk factors such as diabetes mellitus or renal disease. The variability in clinical features is such that it is often impossible on clinical grounds to differentiate between melioidosis and other acute and chronic bacterial infections, including tuberculosis. Confirmation of the diagnosis relies on good practices for

specimen collection, la- boratory culture, and identification of B. pseudomallei. Clinical investigation and confirmation of diagnosis Early discussion with the clinical microbiology laboratory is im- portant during investigation of suspected cases. This will raise

section 8 Infectious diseases 1078 awareness for the presence of a significant pathogen in a mixed culture. In addition, B. pseudomallei is classified as a hazard group 3 biological agent and safe handling requires use of a containment level 3 laboratory. Samples of blood, urine, throat swab, and re- spiratory secretions should be obtained for culture from all pa- tients, together with pus and wound swabs where relevant. All sample types should be taken where possible since site of culture positivity may not necessarily relate to clinical focus of infection (as an extreme example, it is possible for a throat swab to be positive (a) (b) Fig. 8.6.16.1 Chest radiographs of two patients with melioidosis. (a) Left upper lobe involvement with abscess formation. (b) Diffuse pulmonary involvement with marked radiological changes in the right lung field. (a) (b) Fig. 8.6.16.2 Skin and soft tissue involvement in two patients with melioidosis. Skin pustules (a) and subcutaneous abscess (b) occurring as secondary foci of infection associated with disseminated infection. Fig. 8.6.16.3 CT brain scan of a patient presenting with fever, headache, confusion, and hemiparesis. The image shows a ring-enhancing lesion with surrounding oedema in the right frontoparietal lobe, pus from which grew B. pseudomallei.

8.6.16 Melioidosis and glanders 1079 in a patient with a splenic abscess in the absence of features of re- spiratory infection). B. pseudomallei colonization is extremely rare and isolation of even a single colony from a low-quality sample can clinch the diagnosis. Bacterial detection and identification using the polymerase chain reaction on clinical specimens is described but is not available in routine microbiology laboratories, and is re- ported to be less sensitive than culture. Negative microbiological cultures do not rule out melioidosis since patients who have been commenced on effective antimicro- bial agents may be culture-negative. Serodiagnostic tests should be considered for the investigation of persons with suspected meli- oidosis who are culture-negative, but should be interpreted with caution. A rising antibody titre to B. pseudomallei in paired serum samples taken 2 weeks or more apart in an individual who does not normally reside in an area where melioidosis is endemic is highly supportive of the diagnosis of melioidosis in the presence of clin- ical features of disease. This ideal is often difficult to achieve since the potential exposure event may have occurred months or years before presentation and may not be remembered. In such cases, a single high antibody titre at presentation is indicative of exposure. Serodiagnostic tests in people who have resided in areas where melioidosis is endemic have very limited value since background seropositivity in the healthy population is high and the detection of antibodies to B. pseudomallei has a low diagnostic accuracy for active melioidosis. A small number of patients with culture-proven melioidosis do not mount a detectable antibody response, and a negative serological result does not rule out exposure or active in- fection. The most commonly used serodiagnostic method is the in- direct haemagglutination assay (IHA). Cut-off points ranging from an IHA titre of 1:20 to 1:80 have been used to indicate exposure. In patients with melioidosis, laboratory tests should be em- ployed to detect acute renal failure, abnormal liver function tests, and anaemia, all of which are well recognized during severe meli- oidosis. Arterial blood gases should be taken in patients with lung involvement and/or any evidence of respiratory impairment. Serum C-reactive protein levels do not give an accurate reflection of dis- ease severity. Chest radiographs should be obtained in all patients. Features are highly variable and include focal, multifocal, or lobar consolidation, localized patchy alveolar infiltrate, diffuse interstitial shadowing

(consistent with blood-borne spread of infection), pleural effusion, and upper lobe involvement which may include cavitation. The radiographic pattern may be indistinguishable from tuberculosis. The development of empyema and/or lung abscess(es) is well recognized, and repeat chest radiographs are indicated for patients with respiratory involvement. Abdominal ultrasound examination or computed tomography (CT) scan should be performed to ex- clude the presence of abscesses in liver and spleen. Clinical evidence of prostatic involvement requires appropriate imaging (transrectal ultrasonography or CT scan). The need for other imaging should be guided by clinical features and organ involvement. Management, prognosis, and outcome Appropriate antimicrobial agents should be started immediately on suspicion of the diagnosis of melioidosis. Recommendations are given in Box 8.6.16.1. Treatment is divided into intravenous and oral phases. Initial parenteral therapy is given for 10 to 14 days or until clinical response is seen (whichever is the longer). Ceftazidime or a carbapenem antibiotic is the treatment of choice. Ceftazidime is used as first-line therapy in Thailand, with a switch to a carbapenem antibiotic in the event of treatment failure on ceftazidime. Parenteral treatment at the Royal Darwin Hospital, Australia, consists of ceftazidime or meropenem plus granulo- cyte colony stimulating factor (G-CSF) if the patient has septic shock. The routine addition of trimethoprim/sulfamethoxazole (TMP-SMX) to ceftazidime or meropenem during the initial in- tensive therapy phase has been discontinued, although this drug is still used in some centres for patients with neurological or prostatic melioidosis in view of its excellent penetration. Intravenous amoxicillin/clavulanate is second-line therapy but is associated with higher rates of treatment failure and there are few indica- tions for this agent if first-line agents are available. Oral treatment is given for 12 to 20 weeks or longer if clinically indicated and consists of TMP-SMX. The routine addition of doxycycline to oral regimens has ceased following the outcome of a randomized controlled trial conducted in Thailand, which found equivalence between TMP-SMX alone and TMP-SMX plus doxycycline. First- line oral treatment for pregnant women and children is amoxi- cillin/clavulanate; this is also an alternative for adults who cannot tolerate TMP-SMX. Collections of pus should be drained wherever feasible. Patients with severe melioidosis associated with septic shock, respiratory failure, acute renal failure, and other manifestations of a severe septic illness require intensive care management, Box 8.6.16.1 Antimicrobial therapy for melioidosis Initial parenteral therapy • Ceftazidime 50 mg/kg per dose (up to 2 g) every 6 h, or meropenem 25 mg/kg per dose (up to 1 g) every 8 h. • Intravenous amoxicillin/clavulanate can be used as a second-line agent and is associated with equivalent mortality but a higher rate of treatment failure compared with ceftazidime. Dosage 20/5 mg/kg every 4 h. • Duration of parenteral therapy: a minimum of 10 days or until clear clinical improvement (whichever is the longer). Extend therapy to 4–8 weeks for deep-seated infection such as septic arthritis, osteomyelitis and central nervous system infection. Oral eradication therapy Adults • Trimethoprim/sulfamethoxazole using a weight-based dosing schedule: 2 × 160/800 mg (960 mg) tablets every 12 h if more than 60 kg, 3 × 80/400 (480 mg) tablets every 12 h if 40–60 kg, and 1 × 160/800 mg (960 mg) OR 2 × 80/400 (480 mg) tablets every 12 h if less than 40 kg. Children ≤8 years and pregnant women • Amoxicillin/clavulanate 20/5 mg/kg orally every 8 h. • For adult patients less than 60 kg, a dose of 1000/250 mg three times daily is suggested. In regions where amoxicillin/clavulanate is only avail- able in fixed 2:1 combinations, use 500/250 mg three times daily with additional amoxicillin (500 mg three times daily). For patients more than 60 kg, use a maximum dose of 1500/375 mg three times daily. • Duration of oral therapy: 12–20 weeks.

 although many cases occur in geographical regions where such resources are scarce. Fever clearance is often slow (median fever clearance time of around

9 days), and without evidence of clinical deterioration is not normally sufficient to indicate a change in therapy. Sputum and draining abscess cultures may remain posi- tive for several weeks in a patient who is otherwise responding to treatment. The benefit of other interventions for critically ill septic patients such as goal-directed therapy, intensive glycaemic control, and activated protein C has not been evaluated in pa- tients with melioidosis. A randomized placebo-controlled trial of G-CSF for severe melioidosis conducted in Thailand failed to show an outcome benefit. Several features can be used to predict risk of death. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score is an independent predictor of death from melioidosis. Time to blood culture positivity has prognostic significance, with a mor- tality rate of 74% for those with a positive culture within 24 h compared with 41% in those with a positive culture after 24 h. In patients who have a positive blood culture, counts of less than one colony-forming unit (CFU)/ml blood have been reported to be as- sociated with a mortality of 42%, compared with a mortality of 96% in those with counts of more than 100 CFU/ml. B. pseudomallei count in urine is also associated with mortality. Patients with meli- oidosis whose urine culture was negative for B. pseudomallei had the lowest death rate (39%). Mortality was 58% in those with posi- tive spun urine pellet only, 61% in those with between 103 CFU/ml and 105 CFU/ml B. pseudomallei in neat urine, and 71% in those with ≥105 CFU/ml B. pseudomallei in neat urine. Sputum culture positive for B. pseudomallei in patients with culture-confirmed melioidosis is associated with a higher mortality (72%) compared with that for melioidosis patients with sputum culture-negative for B. pseudomallei (42%). Recurrent melioidosis is not uncommon (6% in the first year and 13% over 10 years). Three-quarters of recurrent cases are due to relapse caused by a strain that has persisted within the host following the pri- mary episode, and the remainder represent reinfection by a different strain. One-quarter of patients with recurrence die as a direct result. The risk of nosocomial infection between patients or transmis- sion to family or other contacts has not been the subject of specific study. Several case reports have been published. Melioidosis in two infants in northern Australia was related to breastfeeding by mothers with mastitis caused by B. pseudomallei, and the wife of a Vietnam veteran with chronic prostatitis caused by B. pseudo-mallei developed an antibody response to the organism in the ab- sence of clinical manifestations of melioidosis. Person-to-person transmission occurred between two siblings with cystic fibrosis and may have occurred between a diabetic brother and sister living in north-east Thailand, and a case of nosocomial infection from a suspected environmental source has been reported from an endemic area. Likely developments in the near future The overall incidence of melioidosis is likely to rise among wealthier nations within Asia as the number of susceptible elderly people increases. The number of reported cases worldwide is also likely to increase alongside the dissemination of diagnostic la- boratories. Probably the most important strategy required to reduce mortality from melioidosis in rural Asia is early recogni- tion and timely administration of antimicrobial drugs together with adequate fluid resuscitation. Further studies are required to define safe and affordable interventions that improve outcome where intensive care facilities are unavailable, such as protocols to optimize fluid management and glycaemic control in a general ward setting. Overview of glanders Burkholderia mallei, the cause of glanders, appears to have evolved through genomic downsizing from a single clone of B. pseudomallei. Historically, this pathogen was an important cause of morbidity and mortality in horses worldwide and was occasionally transmitted to humans or other animals. In horses, donkeys, and mules it causes nodules and ulcerations in the upper respiratory tract and lungs. The cutaneous form is known as ‘farcy’. The mallein skin test is a sensitive and specific clinical test for equine glanders. No naturally acquired case has been reported in the United States of America or the United Kingdom since 1938, but it is thought to still occur in the Middle East, Africa, and Asia. Outbreaks of equine glanders reported in Bahrain since

2010 and in Lebanon since 2011 may be linked to importation of horses from elsewhere in the region, including Syria. Clinical manifest- ations of glanders in humans resemble those of melioidosis. The untreated case fatality rate is 95%. The approach to investigation, diagnosis, and management is as for melioidosis. The organism requires handling in a containment level 3 laboratory; important differentiating bacterial features between B. mallei and B. pseu- domallei are that the former is nonmotile and susceptible to gen- tamicin. In vitro susceptibility is otherwise similar to that for B. pseudomallei, and glanders should respond to the regimens used to treat melioidosis. FURTHER READING Cheng AC, et al. (2008). Consensus guidelines for dosing of amoxicillin- clavulanate in melioidosis. Am J Trop Med Hyg, 78, 208–9. Chetchotisakd P, et al. (2014). Trimethoprim-sulphamethoxazole versus trimethoprim-sulphamethoxazole plus doxycycline as oral eradicative treatment for melioidosis (MERTH): a multicentre, double-blind, non-inferiority, randomised controlled trial. Lancet, 383, 807–14. Chierakul W, et al. (2005). Two randomized controlled trials of ceftazidime alone versus ceftazidime in combination with trimethoprim-sulfamethoxazole for the treatment of severe melioid- osis. Clin Infect Dis, 41, 1105–13. Currie BJ, et al. (2010). The epidemiology and clinical spectrum of melioidosis: 540 cases from the 20-year Darwin prospective study. PLoS Negl Trop Dis, 4, e900. Wiersinga WJ, et al. (2018). Melioidosis. Nature Disease Primers Reviews, 4, 17107.

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