

# Important Unusual Infections in Australia: a Critical Care Perspective

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## ABSTRACT

**Objective:** *To review a number of the important unusual infections in Australia that can lead to critical illness.*

**Data sources:** *Articles, reports and published reviews on Japanese encephalitis, murine typhus, Australian spotted fever, Australian bat lyssavirus, leptospirosis, Capnocytophaga canimorsus, Chromobacterium violaceum, Edwardsiella tarda and Vibriosis. Emphasis was placed on articles, reports and published reviews published between 1990-2001.*

**Summary of review:** *Japanese encephalitis has recently emerged in Australia, with reported outbreaks in the Torres Strait and north Queensland. Murine typhus needs to be included in the differential diagnosis of a patient with fever, headache and rash, especially if there has been possible exposure to rats and/or their droppings. If the symptoms follow exposure to ticks, or following a known tick bite, then Australian spotted fever needs to be considered. Australian bat lyssavirus can cause a fatal rabies-like disease in humans exposed to infection by bites or scratches from bats. Leptospirosis should be suspected in any patient with an appropriate history of exposure (especially occupational) and a history of myalgia, arthralgia, fever, malaise and/or chest X-ray shadowing. Capnocytophaga should be specifically sought in any patient with fever and/or septicaemia following a dog bite, especially if immunocompromised. Along with melioidosis, Chromobacteriosis should be considered in the differential diagnosis of a rapidly progressing septic illness with skin lesions and/or multiple visceral abscesses in a patient exposed to soil or muddy water. Edwardsiella ought to be considered as the causative agent of a soft tissue infection, septic arthritis or septicaemia in a recreational fisher or swimmer, especially if following a marine puncture wound. If the exposure is related to salty or brackish water, then Vibriosis needs to be considered. Vibriosis should also be suspected in a patient with septicaemia and a history of recent ingestion of raw or under-cooked seafood, especially oysters.*

**Conclusions:** *Critical care physicians need to remain alert to unusual infectious agents as many can lead to significant morbidity and are associated with a high mortality rate. (Critical Care and Resuscitation 2001; 3: 262-272)*

**Key words:** *Japanese encephalitis, murine typhus, Australian spotted fever, Australian bat lyssavirus, leptospirosis, Capnocytophaga canimorsus, Chromobacterium violaceum, Edwardsiella tarda, Vibriosis*

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An unusual infection may be defined as one that is uncommon with features that are curious and exotic. This presentation will focus on a number of the important unusual infections that have been reported in Australasian literature in the last five years that may present in a critically ill patient.

## Classification

The individual organisms discussed are categorised according to their important vectors and routes of transmission. For example,

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<i>Arthropod borne:</i>	Japanese encephalitis, murine typhus, Australian spotted fever
<i>Vertebrate borne:</i>	Australian bat lyssavirus, Leptospirosis, <i>Capnocytophaga canimorsus</i>
<i>Soil borne:</i>	<i>Chromobacterium violaceum</i>
<i>Marine borne:</i>	<i>Edwardsiella tarda</i> , non-cholera vibrio species

### Arthropod borne infections

#### *Japanese encephalitis*

Japanese B encephalitis was the name assigned to an epidemic which occurred in 1924, in order to distinguish it from von Economo's disease (type A encephalitis or encephalitis lethargica). The Japanese Encephalitis (JE) virus is now the leading cause of viral encephalitis worldwide, with an estimated 45 - 50,000 cases occurring annually in Asia.<sup>1,2,3</sup> It is known to occur in many parts of Asia, including Japan, China, Korea and South East Asia.<sup>3</sup> The disease has recently emerged in Australia, with reported outbreaks in the Torres Strait<sup>4</sup> and north Queensland.<sup>5</sup> Along with Murray Valley Encephalitis virus, the major cause of arboviral encephalitis in Australia,<sup>4</sup> JE virus is a member of the family *Flaviviridae*.

*Flaviviridae* are enveloped, positive, single-stranded RNA viruses.<sup>1</sup> The natural circulation of the virus is between water birds (egrets, herons) and mosquitoes.<sup>3,4,6</sup> Pigs are important amplifying hosts,<sup>3,4</sup> and are often implicated in outbreaks.<sup>4</sup> In Asia, the most efficient vector is the mosquito *Culex tritaeniorhynchus*.<sup>3,4</sup> In the Torres Strait outbreak, the ornithophilic mosquito *Culex annulirostris* was implicated as the major vector.<sup>4</sup> Circumstantial evidence suggested the possibility of aerial carriage of infected mosquitoes from Papua New Guinea to northern Australia.<sup>5,7</sup> Less intensive pig husbandry, fewer mosquitoes and other ecological circumstances appear to have limited transmission of JE onto the Australian mainland.<sup>5</sup>

Large vertebrates such as humans are inefficient amplifying hosts.<sup>4,8</sup> As "dead-end" hosts,<sup>2</sup> humans have a low level of viraemia of short duration.<sup>4,8</sup> Infection with the JE virus is usually asymptomatic.<sup>3,4,8</sup> The case to infection ratio is of the order of 1:200 to 1:300.<sup>9</sup> The incubation period ranges from 4 - 14 days. As with other viral encephalitides, the initial viraemia probably originates in the lymphoid system, with little or no clinical disease during this phase.<sup>9</sup> CNS invasion then most likely occurs through infection of olfactory neuroepithelium or infection of brain capillaries.<sup>9</sup> When manifest, clinical features of the acute illness include headache, meningism, fever, weight loss, convulsions, rigidity, decreased level of consciousness and coma.<sup>4,9,10</sup>

The typical pathological picture of viral encephalitides includes focal necrosis of neurones, inflammatory glial nodules and perivascular lymphoid cuffing, with the involved areas displaying "luxury perfusion" (normal or increased total blood flow, with low oxygen extraction).<sup>9</sup> Biphasic illness patterns have been described, possibly related to early relapses.<sup>10</sup> Infection in the first or second trimesters of pregnancy may cause intrauterine infection and miscarriage.<sup>3</sup>

The elderly may be more susceptible to developing neuroinvasive disease.<sup>3</sup> Reported case fatality rates are of the order of 20-50%.<sup>1,3,9,11</sup> Risk factors that may be associated with a fatal outcome include isolation of virus in the CSF, low levels of JE virus-specific IgG and IgM in both CSF and serum, and a severely depressed sensorium.<sup>11</sup> In survivors, long-term neuropsychiatric sequelae occur in approximately 30 - 50%.<sup>1,3,9</sup>

Cerebral CT scanning, cerebral magnetic resonance imaging and EEG are not usually specific in JE. In severe cases, bilateral haemorrhagic thalamic lesions have been reported.<sup>9</sup> The organism usually cannot be isolated from blood or CSF, although it can be obtained from brain tissue and has been recovered from the CSF in severe cases.<sup>9</sup> The EEG may show diffuse continuous delta slowing or a diffuse delta pattern with spikes.<sup>12</sup> There appears to be no correlation between the EEG changes and either the severity of the disease or the outcome.<sup>12</sup> Serology remains important for confirmation of the diagnosis of JE, with detection of IgM in serum or CSF by enzyme-linked immunosorbent assay (ELISA) being the standard diagnostic test.<sup>12,13,14</sup> There is some cross-reactivity with other flaviviruses.<sup>12</sup>

The treatment of JE is supportive. There has been a report of benefit on the course of JE from human alpha interferon and of the use of 10-carboxymethyl-9-acridanone (an interferon inducer) in mice with JE infection.<sup>1</sup> Dexamethasone has not been shown to prevent deaths from cerebral oedema induced increases in intracranial pressure in patients with severe JE.<sup>1</sup> Preventative measures include an inactivated JE vaccine,<sup>3,4</sup> as well as the use of protective clothing, bed nets and insect repellents, and living in air-conditioned or well screened rooms.<sup>3</sup> Although the overall risk for acquiring JE among most travellers to Asia is extremely low, the risk for an individual traveller is highly variable.<sup>3</sup>

#### *Murine typhus*

In 1926 an outbreak of a typhus-like illness affected grain handlers near Toowoomba in Queensland. The illness coincided with a mouse plague and was therefore known locally as "mouse fever".<sup>15,16</sup> Earlier Australian reports of a similar illness involving wheat handlers was known colloquially as "wheat disease".<sup>16,17</sup> In 1931, the

causative organism, *Rickettsia typhi* (then known as *R. mooseri*) was isolated from rat fleas and rat brains.<sup>16,18</sup> By the end of World War II it was recognised as a global disease.<sup>18</sup> Now known as murine (or endemic) typhus, it is one of several rickettsial diseases found in Australia.<sup>16</sup>

Murine typhus tends to occur in clusters and is often associated with rat-infested premises. In Australia, outbreaks have been recorded in at least Western Australia, South Australia, and Queensland.<sup>16</sup> Although improved rodent control has resulted in an apparently decreased incidence, it is also likely that the disease is poorly recognised. The common vector for rats and humans is the Oriental rat flea, *Xenopsylla cheopis*. The fleas become infected when they ingest blood from diseased rats. The rickettsiae then multiply in the intestinal cells of the flea so that when it defecates, as it does when it takes further blood meals from its host, faeces containing *R. typhi* are introduced into the bite wound.<sup>16,18</sup> Exposure of the mucous membranes of the eye or upper respiratory tract to aerosolised dried flea faeces may also initiate human disease.<sup>16,18</sup>

The incubation period for murine typhus is eight to 16 days, with a mean of eleven days.<sup>18</sup> Prodromal symptoms last one to three days and commonly include headache, myalgia, nausea and malaise, followed by abrupt onset of fever and chills.<sup>18</sup> Once the disease is manifest, nausea and vomiting are common. Other features may include lymphadenopathy, constipation, abdominal pain, hepatomegaly, splenomegaly, confusion, seizures, ataxia, jaundice and coma.<sup>16,18</sup> Pulmonary involvement occurs frequently, with 35% of patients developing a non-productive cough and pulmonary densities being found on chest X-ray in 23% of patients who have this investigation performed.<sup>18</sup> A rash is found in 13% of patients at the time of presentation and develops during the course of the illness in many others, although approximately 50% of patients never develop a rash.<sup>18</sup>

The rash is initially macular and found in the axilla and the inner arm, but it is typically maculopapular when it spreads to involve the trunk, abdomen and proximal limbs.<sup>18</sup> The hands, feet and face are sparsely involved.<sup>16,18</sup> The clinical diagnosis can be confirmed in the laboratory by *R. typhi* specific indirect fluorescent antibody testing (IFAT), immunohistology or dot ELISA.

In many cases, murine typhus runs a self-limiting course even without treatment. In children, the illness is usually not severe, with around half only developing nocturnal fevers.<sup>18</sup> In adults, however, the disease can be associated with significant disability and often requires admission to hospital.<sup>16</sup> Of the hospitalised patients, approximately 10% require admission to an intensive

care unit.<sup>18</sup> Serious complications include respiratory failure, cerebral haemorrhage and haemolysis.<sup>18</sup> The reported mortality rate ranges from 1-5%.<sup>16,18</sup>

Death is usually the result of circulatory or renal failure, or secondary bacterial infections and is more likely in elderly and debilitated patients.<sup>18</sup> Nonetheless, murine typhus is easily treated with appropriate antimicrobial therapy. Oral doxycycline (200mg per day) is commonly used with the recommended duration of therapy ranging from 7 - 15 days.<sup>16</sup> There is evidence that ciprofloxacin is also effective.<sup>16</sup>

#### *Australian spotted fever (Queensland tick typhus)*

Australian spotted fever (ASF) is caused by the organism *Rickettsia australis* and is transmitted by bites from an infected tick. In Australia, two tick vectors of *R. australis* have been identified: *Ixodes holocyclus* (the paralysis tick) and *Ixodes tasmani*.<sup>19</sup> The disease was first described in 1946 in soldiers in north Queensland,<sup>20,21</sup> and occurs along eastern and south-eastern coastal areas of Australia from tropical to temperate climates.<sup>19</sup>

The incubation period for ASF is around 5 days from the tick bite. Clinical manifestations include bite-site eschar, rash, fever, headache, myalgia, lymphadenopathy, arthralgia, conjunctivitis, pharyngitis and neurological involvement.<sup>19,21</sup> The rash is classically maculopapular, although it is not uncommonly vesicular,<sup>19,22</sup> and is not always present. In a recently reported severe case, the clinical presentation featured seizures and acute confusion.<sup>21</sup> Although the illness is usually mild,<sup>19</sup> deaths have been reported.<sup>23</sup> The recommended antimicrobial therapy is doxycycline (age > 8 years: 2 mg/kg up to 100 mg orally twice daily) or chloramphenicol for seven to ten days.<sup>24</sup>

#### **Vertebrate borne infections**

##### *Australian bat lyssavirus*

Australian bat lyssavirus (ABL) is a new genotype (genotype 7) in the *Lyssavirus* genus (family *Rhabdoviridae*), more closely related to the classic *rabies virus* (genotype 1) than any of the other known genotypes<sup>25,26,27</sup> (e.g. *Lagos bat virus*, *Mokola virus*, *Duvenhage virus* and the two *European bat lyssaviruses*). This new rhabdovirus was first isolated in 1996 from a sick juvenile black flying-fox (*Pteropus alecto*).<sup>28</sup> There have now been reported human cases of ABL infection following bites from the yellow-bellied sheath-tail bat (*Saccolaimus flaviventris*) and the fruit bat, or flying-fox (*Pteropus* spp.).<sup>27</sup> At present, it must be assumed that any Australian bat could transmit ABL,<sup>27,29</sup> especially those that are unwell.

There is little information on the pathogenesis of

lyssaviruses in bats, although it seems that mortality in naturally infected bats is low and seroconversion occurs in many survivors.<sup>30</sup> In a screening of 366 sick, injured or orphaned bats from south Brisbane and the South Coast of Queensland, the prevalence of Lyssavirus detected by fluorescent antibody testing was 6%.<sup>31</sup> Lyssaviruses are usually transmitted to humans by bites or scratches that provide direct contact between the virus in the saliva or blood of infected animals, and exposed tissue, nerve endings or mucous membranes of the victim.<sup>29</sup> For ABL, at-risk exposure does not include patting bats, contact with the urine or faeces of bats, or contact with bats that have been dead for more than four hours.<sup>25,29</sup>

In a recent review of 205 potentially exposed persons,<sup>31</sup> volunteer animal handlers accounted for 39% of the potential exposures to ABL, their family members for 12%, and community members who intentionally handled bats for 31%. On the other hand, professional animal handlers accounted for 14%, and community members with contact initiated by bats only 4%. These potential exposures highlight the importance of educating the public that Australian bats should not be handled.

The incubation period is not yet well defined. For rabies, the incubation period is typically 20 - 90 days.<sup>27</sup> In one of the reported deaths from ABL, the apparent incubation period was 27 months.<sup>27</sup> The clinical picture of ABL infection in humans is similar to rabies. In a recently reported case, there was a short, non-specific prodrome followed by drooling, dysphonia and dysphagia, painful muscular spasms, autonomic instability, coma and ultimately death.<sup>27</sup> The post-mortem examination revealed widespread encephalitis, with the inflammation and necrosis most severe in the hippocampi and brainstem. There were a few Negri-like cytoplasmic inclusion bodies, especially in the hypothalamus.

In the first reported case of human encephalitis due to ABL, the post-mortem results were similar, showing meningoencephalomyelitis and Negri-like neuronal intracytoplasmic inclusions.<sup>32</sup> In bats, the main lesion is non-suppurative meningoencephalomyelitis and ganglioneuritis similar to that seen in rabies, except that the number of Negri bodies is more variable.<sup>33</sup>

Proper cleansing of the wound is an effective measure for reducing the transmission of classic rabies virus.<sup>25,29</sup> Following a bite or scratch from a bat, the wounds should be immediately and thoroughly washed with soap and water,<sup>25,27</sup> and, if possible, a virucidal preparation such as povidone-iodine solution.<sup>25</sup>

Regardless of the severity of exposure, appropriate medical advice should be sought.<sup>27</sup> If possible, the bat should be kept for testing, provided that the capture of

the bat does not place the injured party, or others, at further risk of exposure. Rabies vaccine and immune globulin appear to be protective against lyssavirus in animal models and are recommended after human exposure.<sup>25,29</sup> The current recommendations are available in detail through the Commonwealth Department of Health and Aged Care,<sup>29</sup> the Australian Immunisation Handbook<sup>25</sup> or through local public health authorities. Essentially, pre-exposure vaccination with rabies vaccine is recommended for those occupationally or recreationally exposed to bats, such as bat researchers, wildlife officers, veterinarians and their assistants, power line workers, members of indigenous communities who may catch bats and cavers. Pre-exposure vaccination consists of three deep subcutaneous or intramuscular doses (1 mL) of rabies vaccine on days 0, 7 and 28. The preferred intramuscular site is the deltoid, as antibody titres may be reduced if administration is via other sites. The anterolateral aspect of the thigh is an alternative in children. Post-exposure vaccination consists of five deep subcutaneous or intramuscular (as above) doses of rabies vaccine (days 0, 3, 7, 14 and 28). Rabies immunoglobulin (RIG) should be given as a single dose (20 International Units/kg) at the same time as the first dose of vaccine. RIG must not be given at the same site as the vaccine, nor administered later than seven days after rabies vaccine has started. As much of the dose of RIG as possible should be infiltrated into and around the wound and the rest given intramuscularly in a site close to the wound. For large wounds, the RIG can be diluted in saline so that an adequate volume for infiltration can be obtained.<sup>25</sup>

### *Leptospirosis*

The *Leptospira* genus belongs to the *Leptospiraceae* family of the order *Spirochaetales*. Traditionally, the genus *Leptospira* is divided into two species, *L. interrogans* and *L. biflexa*, of which *L. interrogans* is designated as pathogenic.<sup>34,35,36</sup> However, there are a number of recognised serovars and serogroups of pathogenic leptospires, and *L. interrogans* is now divided into seven named species (e.g. *L. interrogans*, *L. weilii*, *L. santarosai*, *L. noguchi*, *L. borgpetersenii*, *L. inadai* and *L. kirschner*) and five unnamed species (*Leptospira* species 1, 2, 3, 4 and 5).<sup>36</sup> Regardless, it may remain practical to use the traditional classification based on serologic differences,<sup>35</sup> with more than 200 serovars making up the 23 serogroups of *L. interrogans*.

In Australia, serovar *australis* and serovar *zanoni* are important causes of clinical leptospirosis in humans.<sup>37</sup> The highly motile spirochete is common in tropical Australia, especially in Queensland. An outbreak in north Queensland during the first half of 1999 resulted

in 184 notifications with over half of the cases requiring hospitalisation.<sup>37</sup>

Leptospirosis was first described by Weil in 1886,<sup>36</sup> and is probably one of the world's most widespread zoonoses.<sup>38</sup> Leptospire are likely to be ubiquitous in tropical countries.<sup>39</sup> The major animal vector for leptospirosis is the rat,<sup>36</sup> but others include cattle, pigs, goats, dogs and marsupials.<sup>34</sup> Although a number of serotypes are associated with particular animals,<sup>35</sup> such as *canicola* (dogs), *hardjo* (cattle) and *pomona* (pigs), individual animals may carry multiple serovars.<sup>36</sup> Whilst the infection in animals is often subclinical,<sup>36</sup> leptospira are found in large numbers in the kidneys of the infected animals,<sup>40</sup> and can be shed in the urine for prolonged periods.<sup>35,41</sup> Furthermore, leptospire can survive in soil or surface water for many weeks,<sup>34,36</sup> and floodwaters have been implicated in a number of recent outbreaks.<sup>41,42</sup>

Transmission of the disease to humans usually follows contact of mucous membranes or skin abrasions with urine, blood or tissue of infected animals, either directly or indirectly via contaminated soil or water.<sup>34,36,41,42</sup> The organisms can then spread rapidly through the bloodstream to affect major organ systems.<sup>34,36</sup> The most consistent pathologic finding is vasculitis with endothelial oedema, necrosis and lymphocytic infiltration.<sup>36</sup> The degree of multiple organ involvement is not necessarily related to the number of leptospire found on tissue microscopy, so a number of mediators have been suspected as contributing to the pathogenesis of the disease.<sup>36</sup>

The incubation period for leptospirosis is usually 5 - 14 days, with a range from 2 - 30 days.<sup>35,36,43</sup> Approximately 90% of symptomatic patients have the mild and self-limited (anicteric) form of the disease,<sup>35,36</sup> where the common clinical manifestations include fever, chills, headache, conjunctivitis, nausea, vomiting and myalgia,<sup>34,36,43,44</sup> After a brief asymptomatic phase the immune stage of leptospirosis with prominent aseptic meningitis occurs.

In severe cases (Weil's syndrome or icteric leptospirosis) jaundice, acute renal failure, thrombocytopenia, meningitis, pulmonary haemorrhage, myositis and conjunctival haemorrhage can occur.<sup>34,36,41,43,44</sup> Histologically, skeletal muscle involvement can include swelling, vacuolation of myofibrils and focal necrosis.<sup>35</sup> A case of leptospirosis associated with massive rhabdomyolysis was recently reported.<sup>45</sup> In the kidneys, involvement may include capillary vasculitis, acute tubular necrosis and interstitial nephritis, with relative sparing of the glomeruli.<sup>36</sup> In the heart, post-mortem findings include epicardial and endocardial petechiae, myocardial interstitial oedema, myocarditis and coronary arteritis.<sup>36</sup> Although extrapulmonary comp-

laints dominate the clinical picture,<sup>41,44</sup> pulmonary changes are not uncommon,<sup>41,46</sup> and fulminant leptospiral pneumonia<sup>44</sup> and acute respiratory distress syndrome<sup>45,46</sup> have been reported.

The haemorrhagic manifestations tend to occur relatively early in the disease process as a consequence of vascular endothelial damage.<sup>34,35</sup> In the lungs this damage is manifest predominantly as haemorrhagic pneumonitis with alveolar infiltrates on chest X-ray developing three to nine days after illness onset, especially in the lower lobes and peripheral lung fields.<sup>35,44</sup> With therapy, resolution of these infiltrates can occur rapidly.<sup>44</sup> In Australia, a polymorphic presentation with pulmonary haemorrhage is particularly associated with the *australis* serovar.<sup>37</sup>

Serum biochemistry may be helpful in the diagnosis of leptospirosis. Abnormalities include elevation of bilirubin, alkaline phosphatase, aminotransferases and creatine phosphokinase.<sup>35</sup> Leptospire can be isolated from the blood and cerebrospinal fluid (CSF) during the first 4 - 10 days of the disease and many patients have a CSF pleocytosis, even in the absence of clinical meningism.<sup>35</sup> Cultures of the urine and affected organs may also be positive from the second week of the illness.<sup>36</sup> Unfortunately, culture of the organism is slow,<sup>48</sup> and may take weeks to become positive.<sup>35</sup> Hence, serology plays an important role in the diagnosis of leptospirosis. Once antibodies are produced, the leptospire are eliminated from most sites in the body, with the exception of the eye and proximal renal tubules and possibly the brain.<sup>35</sup> Thus, the acute leptospiraemic phase is followed by an immune leptospiruric phase. The standard serologic tests for leptospirosis are the microscopic and macroscopic agglutination test (MAT) and the enzyme-linked immunosorbent assay. Polymerase chain reaction detection assays have also been developed in some laboratories.<sup>35,36,48</sup>

Leptospirosis can progress rapidly, so patients with severe disease require admission and monitoring in an appropriate critical care unit. The mortality rate for severe leptospirosis is of the order of 10%,<sup>36</sup> and is highest in the elderly and in those with Weil's syndrome.<sup>35</sup> In one series of 222 cases in a three-year period, an overall fatality rate of 22.6% was reported.<sup>49</sup> Whilst mild infections can be treated with oral doxycycline (age > 8 years: 2 mg/kg up to 100 mg twice daily) for five to seven days,<sup>24,36</sup> severe infections require intravenous benzylpenicillin (30 mg/kg up to 1.2g 6-hourly) for five to seven days.<sup>24,36,41,43</sup> A Jarisch-Herxheimer reaction may occur following the start of antimicrobial therapy.<sup>35</sup> Treatment with intravenous penicillin can be of benefit even late in the disease process. In a randomised, placebo-controlled, double-blind trial involving 42 patients, the effect of a seven

day course of intravenous penicillin (6 million units/day) on severe, advanced leptospirosis was examined.<sup>50</sup> As well as preventing leptospiuria, penicillin was found to shorten the duration of fever, rise in creatinine and hospital stay. Several studies suggest that pre-exposure chemoprophylaxis using oral doxycycline (200 mg once a week) can be efficacious.<sup>47,51</sup> The role of corticosteroids in the treatment of pulmonary haemorrhage associated with leptospirosis is not established, although there have been anecdotal reports of benefit.<sup>34</sup>

#### *Capnocytophaga canimorsus*

*Capnocytophaga canimorsus* (formerly known as dysgonic fermenter type 2 or DF-2) is a capnophilic, fusiform gram-negative bacillus<sup>52</sup> that is part of the normal oral flora of a number of animals.<sup>53</sup> The organism is found in the gingival mucosa of 16% of dogs and 18% of cats.<sup>54</sup> Dog bites, which are often trivial, account for 50% of cases of *C. canimorsus* infection in humans<sup>54</sup> (*canimorsus* being derived from the Latin for "dog bite").<sup>53</sup> Nevertheless, other animals have also been implicated, including cats.<sup>55</sup>

Mechanisms of transmission, other than bites have also been described, including licking of wounds by dogs<sup>53,56</sup> and kissing dogs.<sup>57</sup> Other strains in the genus *Capnocytophaga* may also cause human illness following animal bites, including another canine oral commensal, *C. cynodegmi* (*cynodegmi* being derived from the Greek for "dog bite"), formerly known as the "DF-2 like organism".<sup>53,58</sup> Furthermore, a number of *Capnocytophaga* species are human oral commensals, including *C. gingivalis*, *C. ochraceus* and *C. sputigena* (DF-1).<sup>53</sup>

*C. canimorsus* septicaemia and meningitis secondary to dog bites was first described in 1976.<sup>59</sup> Since then, a variety of other clinical manifestations of *Capnocytophaga* infection have been described, including purpura,<sup>53,60</sup> cellulitis,<sup>54,58</sup> peripheral gangrene,<sup>53,54</sup> disseminated intravascular coagulation,<sup>53,54,56,61</sup> renal failure,<sup>53</sup> endocarditis,<sup>56,57</sup> myocardial infarction,<sup>61,62</sup> acute respiratory distress syndrome,<sup>53</sup> empyema,<sup>63</sup> haemolytic uraemic syndrome,<sup>64</sup> Waterhouse-Friderichsen syndrome,<sup>65</sup> lung abscess,<sup>66</sup> meningitis,<sup>56</sup> osteomyelitis,<sup>66</sup> peritonitis<sup>55</sup> and subphrenic abscess.<sup>66</sup> The period from contact with the dog and onset of symptoms ranges from one to eight days.<sup>56</sup> The common initial symptoms include fever, malaise, myalgia, vomiting, diarrhoea, abdominal pain, dyspnoea, confusion, headache and skin manifestations.<sup>56</sup> Most cases occur in adults,<sup>53</sup> especially in men, with a male:female preponderance of 2:1.<sup>54</sup> Infection appears to be more common in immuno-compromised patients,<sup>54,60</sup> including patients with asplenia,<sup>53,54,56,62</sup>

chronic alcoholism,<sup>53,54,56,62</sup> glucocorticoid therapy<sup>60</sup> and leucopaenia.<sup>66</sup> Nevertheless, it can occur in individuals with no apparent pre-existing illnesses, or no known animal exposure.<sup>56,63,65,66</sup> The mortality rate from *C. canimorsus* septicaemia is of the order of 30%.<sup>53,56</sup>

There are a number of other species of *Capnocytophaga* that are known to cause serious illness in humans. In a recently reported case, a diabetic man developed *C. cynodegmi* cellulitis following a dog bite, complicated by pneumonitis and bacteraemia.<sup>58</sup> Also recently described was an intra-amniotic infection by the human oral commensal *Capnocytophaga sputigena* that resulted in second-trimester miscarriage.<sup>67</sup> *Capnocytophaga* is often isolated as part of a polymicrobial infection with other oral commensals.<sup>66</sup>

In the laboratory, *C. canimorsus* can be a fastidious, slow growing organism.<sup>54,60</sup> Special requirements for isolating the organism include the use of heart infusion agar supplemented with 5% sheep or rabbit blood, and incubation at 35 - 37°C in the presence of carbon dioxide for up to one week.<sup>54</sup> It is usually sensitive to penicillin, third-generation cephalosporins, quinolones, tetracycline and clindamycin.<sup>53,60</sup> Penicillin is considered the drug of choice.<sup>53,54</sup> Most isolates are resistant *in vitro* to aminoglycosides,<sup>53,54,59,60</sup> metronidazole<sup>53</sup> and vancomycin.<sup>60</sup>

It remains controversial whether prophylactic antibiotics should be administered following dog bites.<sup>60,68</sup> In general, standard principles of wound management provide the best defence against bacterial contamination in wounds.<sup>68</sup> Regardless, the old Latin warning "*cave canem*" (beware of dog) must always be borne in mind, especially in immunocompromised individuals and high risk wounds (delayed presentation  $\geq$  8 hours, wounds unable to be adequately debrided, wounds on the hands, face or feet, wounds involving tendons, bones or joints).<sup>24</sup>

In these cases, in patients not hypersensitive to penicillin, the current Australian recommendations are for procaine penicillin 50 mg/kg (up to 1.5g) intramuscularly as a single dose, followed by amoxicillin/clavulanate orally for five days.<sup>24</sup>

#### Soil borne infections

##### *Chromobacterium violaceum*

*Chromobacterium violaceum*, a common soil saprophyte,<sup>69</sup> is a gram-negative bacillus found in the soil and water of tropical and subtropical areas.<sup>70</sup> It is the only *Chromobacterium* species currently known to be pathogenic to humans.<sup>71</sup> There are pigmented (violet) and non-pigmented colony types, with the non-pigmented strains representing less than 10% of strains.<sup>70</sup> Whilst there has been some debate regarding

the pathogenicity of the non-pigmented strains, it is possible that both types are of comparable infectivity.<sup>70</sup> Reports of human infection with *C. violaceum* date back to 1927.<sup>72</sup> Whilst most reported cases are from southeast Asia and the south-eastern United States of America, cases have recently been reported in tropical northern Australia.<sup>73</sup>

Although a virulent organism, the infectivity of *C. violaceum* is low,<sup>70</sup> and infection in humans usually follows exposure of breached skin to contaminated soil or water, especially during the wet season.<sup>70,73</sup> Infection is possible via the oral route<sup>70</sup> and has been reported following near drowning.<sup>73</sup> The incubation period ranges from one day to two months.<sup>73</sup> The clinical picture can resemble melioidosis (*Burkholderia pseudomallei*),<sup>71,73</sup> which is more common in Australia. Typically, local skin lesions, cellulitis and/or adenitis occur. Chromobacterial diarrhoea has been reported.<sup>74</sup>

When systemic, chromobacteriosis can be rapidly progressive with septicaemia, metastatic abscess formation (especially in the liver) and fatality rates as high as 60%.<sup>70,73</sup> Whilst some cases occur in immunocompetent individuals, immune deficiency predisposes to infection, especially in children and young adults with chronic granulomatous disease or other neutrophil defects.<sup>73</sup> Resistance of *C. violaceum* to penicillin and cephalosporins is common.<sup>70,73</sup> Initial empirical antibiotic therapy includes two of the following: gentamicin, cotrimoxazole, imipenem, tetracycline and ciprofloxacin.<sup>73</sup> Parenteral therapy should be for 2 - 4 weeks, followed by oral therapy (e.g. cotrimoxazole or ciprofloxacin) for 2 - 12 weeks.<sup>73</sup> Successful treatment of a four-month old infant with chromobacterial septicaemia using trimethoprim-sulfamethoxazole and ciprofloxacin was recently reported.<sup>75</sup> Surgical drainage of abscesses may be required, although it is not always necessary for splenic or hepatic abscesses.<sup>73</sup>

### Marine borne infections

#### *Edwardsiella tarda*

*Edwardsiella tarda* is a facultative anaerobic gram negative bacillus belonging to the family *Enterobacteriaceae*.<sup>76</sup> The organism is associated with aquatic environments and the animals that inhabit them, especially cold-blooded animals and reptiles.<sup>77,78</sup> It is a pathogen in many of these animals, including eels, catfish, and pet reptiles, and is a rare opportunistic pathogen in humans.<sup>77,79</sup>

In humans, the most common clinical manifestation is gastroenteritis,<sup>78,80,81</sup> which may be complicated by ulceration and bleeding.<sup>78</sup> The organism can also cause wound infections, ranging from mild cellulitis to necrosis,<sup>79,80</sup> and pus collections.<sup>77,78,82,83</sup> A penetrating

joint injury, for example via a catfish spine, can lead to septic arthritis.<sup>77</sup> Rarely, septicaemia, meningitis, cholecystitis, pancreatitis and/or osteomyelitis can occur.<sup>79,81,82</sup> Serious infections appear more likely in patients with pre-existing disease such as hepatic cirrhosis<sup>79,81,84</sup> or immune compromise.<sup>85</sup> Patients with sickle cell disease appear predisposed to osteomyelitis.<sup>78</sup> The mortality rate is as high as 44% in those patients with bacteraemia,<sup>78</sup> although this may be related in part to the presence of a serious underlying condition.<sup>76</sup>

Growth of *Edwardsiella* in the laboratory may require special culture. The organism grows best at temperatures in the range 22 - 26°C. It can be selected on enteric media and is distinguished from other *Enterobacteriaceae* by biochemical testing.<sup>77</sup>

Although most *E. tarda* isolates produce  $\beta$ -lactamase,<sup>78</sup> and are naturally resistant to benzylpenicillin,<sup>86</sup> they generally remain susceptible to antibiotics with activity against aerobic gram-negative bacilli, including amoxycillin, third-generation cephalosporins, gentamicin, trimethoprim-sulfamethoxazole, tetracyclines and oxyquinolones.<sup>77,79,86</sup>

#### *Non-cholera Vibrio infections*

The *Vibrio* species are oxidase-positive, gram-negative bacilli.<sup>87</sup> There are several strains of the most important non-cholera *Vibrio*, *Vibrio vulnificus*, with biogroup 1 being the main human pathogen,<sup>79</sup> and biogroup 3 another important human pathogen.<sup>88</sup> It is possible that not all of the other strains are virulent.<sup>89</sup> *V. damsela*, *V. parahaemolyticus* and *V. cholerae* are also human pathogens.

Human infection with non-O1 (not agglutinated in O1 antiserum) *V. cholerae* is uncommon, however there has been a recent report in Australia of fatal disease caused by this organism.<sup>90</sup> The *Vibrio* species can produce a number of extracellular cytotoxins and enzymes capable of inducing extensive tissue damage.<sup>87</sup> A number of other mechanisms also contribute to the virulence of *V. vulnificus*, including production of siderophores.<sup>87</sup> Iron is an important growth factor for *V. vulnificus*,<sup>87</sup> and it has been demonstrated that survival of the organism in whole blood is positively correlated with serum ferritin concentration and transferrin iron saturation.<sup>91</sup>

Unlike *V. cholerae*, most aquatic vibrios are halophiles (salt loving)<sup>79,87</sup> and are widespread in warm salty or brackish waters. *V. vulnificus* is a marine/estuarine bacterium that is able to colonise the surfaces and internal organs of invertebrate and vertebrate marine animals.<sup>92</sup> *V. damsela* is a fish pathogen.<sup>79</sup> *Vibrio* infection in humans usually results from percutaneous inoculation, wound contamination or ingestion of raw or under-cooked seafood, especially

raw oysters.<sup>79,87,92,93</sup> *V. parahaemolyticus* is a common cause of gastroenteritis, and can also cause wound infections and septicaemia.<sup>87</sup> *V. damsela* wound infections usually remain localised, although fulminant septicaemia and deaths have been reported.<sup>79,94,95</sup> *Vibrio vulnificus* and non-O1 *V. cholerae* infections cause a range of manifestations in humans, including mild and self-limited wound infections,<sup>79</sup> corneal ulceration,<sup>96</sup> cellulitis,<sup>88,90</sup> bullous cellulitis,<sup>87,90,97</sup> necrotising fasciitis,<sup>79,87,88,90,93,97</sup> myositis,<sup>79,90</sup> severe necrotising wound infections,<sup>87,98</sup> compartment syndrome,<sup>99</sup> osteomyelitis<sup>88</sup> and septicaemia.<sup>87,90,97,100</sup> The latter is more commonly the result of ingestion of contaminated seafood, but may also follow wound infections.<sup>79,96</sup>

There appears to be a strong association between *Vibrio* septicaemia and chronic underlying conditions, especially chronic liver disease,<sup>79,87,90,91,93,100</sup> and, in the case of *V. vulnificus*, conditions associated with increased free iron, such as haemochromatosis and haemolytic anaemia.<sup>87</sup> In susceptible individuals, the mortality rate associated with *Vibrio* septicaemia may be as high as 50-60%.<sup>87,89,90</sup> Although *V. para-haemolyticus* is the most commonly reported non-cholera *Vibrio* species, over 90% of reported deaths are associated with *V. vulnificus*.<sup>87</sup>

The organisms can be isolated from stool cultures, blood cultures, wound swabs and cultures obtained from aspiration of bullae. Blood cultures are frequently positive in *V. vulnificus* infections.<sup>87</sup> In wound infections, histologic examination of the skin and/or soft tissues may reveal organisms.<sup>87</sup> There is considerable variability in antimicrobial sensitivity. Doxycycline (age > 8 years: 2 mg/kg up to 100 mg orally twice daily) should be included in the initial management.<sup>24</sup> Adjuncts to be considered include antipseudomonal penicillins, third generation cephalosporins, the fluoro quinolones, and carbapenems.<sup>79,87</sup> Management of the soft tissue infections includes early and appropriate incision, drainage and debridement.<sup>87,90</sup> Serial surgical intervention may be required, and skin grafting and reconstructive surgery may be indicated in the recovery phase.<sup>87</sup> Hyperbaric oxygen therapy has not been proven to be effective in the treatment of serious *Vibrio* infections.<sup>87</sup> Corneal ulceration from an injury sustained during oyster shucking has been successfully treated with ciprofloxacin, neosporin and fortified vancomycin.<sup>96</sup> Non-cholera *Vibrio* associated gastroenteritis is usually self-limiting, and antibiotic therapy has not been shown to shorten the course of the illness.<sup>87</sup>

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