Chapter 18

SYSTEMIC BACTERIAL SYNDROMES

BRUCELLOSIS

Brucellosis is a zoonotic infection transmitted to humans by contact with fluids from infected animals (sheep, cattle, goats, pigs or other animals) or derived food products such as unpasteurised milk and cheese. High risk persons include veterinarians, farmers, meat handlers and abattoir workers. Several species are recognised within the genus *Brucella*, although most human cases of Brucellosis are caused by *Brucella melitensis*.

CLINICAL PRESENTATION

Brucellosis is a systemic infection with a broad clinical spectrum, ranging from asymptomatic infection to a severe and potentially fatal illness. The presentation is often vague and a high index of suspicion is required. The main presentations are an acute illness or one of subacute onset and a tendency to become chronic or relapsing. Patients may present with a febrile illness with constitutional symptoms such as malaise and headaches. Back pain and abdominal pain are commonly reported. A localised infection may occur in up to 30% of cases and may involve any organ system with osteoarticular disease being the most common focal infection, typically affecting the sacroiliac joints or the joints of the lower limbs. Chronic brucellosis refers to patients with clinical manifestations for more than one year after the diagnosis of brucellosis has been established and is often characterised by localised infection or relapsing symptoms.

LABORATORY DIAGNOSIS

The laboratory diagnosis of brucellosis is made by:

- Culture of the organism from blood, bone marrow or tissue specimens.
- Serology by demonstrating a four-fold rise in antibody titre in paired sera collected two to four weeks apart.
- PCR on blood or other body tissue.

Culture and PCR have limited sensitivity and serology is often helpful to make a presumptive diagnosis of brucellosis by demonstrating a significant rise in specific serum antibodies. False-positive results are common and failure to demonstrate a four-fold rise in antibody titre in paired sera usually excludes a recent infection. Laboratory findings should be interpreted together with clinical manifestations, exposure history, occupation, and history of past infection.

TREATMENT OF BRUCELLOSIS

ADULTS WITH UNCOMPLICATED INFECTION (NO SPONDYLITIS, NEUROBRUCELLOSIS, ENDOCARDITIS)

Doxycycline 100 mg PO 12 hourly

AND

Rifampicin 600–900 mg (15 mg/kg) PO daily

Treat for 6 weeks

Rifampicin may be substituted with parenteral gentamicin 5 mg/kg given for the first seven days of treatment.

ADULTS WITH SPONDYLITIS OR SACROILIITIS

Doxycycline 100 mg PO 12 hourly

AND

Streptomycin 1 g IMI once daily for the first 14–21 days

Treat for at least 12 weeks

Streptomycin may be substituted with rifampicin 600–900 mg (15 mg/kg) PO daily given with doxycycline for at least 12 weeks.

An alternative regimen is rifampicin and ciprofloxacin 500 mg PO 12 hourly for at least 12 weeks.

ADULTS WITH NEUROBRUCELLOSIS

Three drugs that cross the blood brain barrier should be given:

Doxycycline 100 mg PO 12 hourly

AND

Rifampicin 600–900 mg (15 mg/kg) PO daily

AND

Ceftriaxone 2 g IV 12 hourly

The duration of therapy is generally a few months and needs to be individualised. In general, it should be continued until CSF parameters have returned to normal.

ADULTS WITH ENDOCARDITIS

Most patients with endocarditis due to brucellosis require both surgery and antimicrobial agents. A combination of antibiotics that include an aminoglycoside should be used:

Doxycycline 100 mg PO 12 hourly

AND

Rifampicin 600–900 mg (15 mg/kg) PO daily

AND

Cotrimozaxole 1 double strength tablet PO 12 hourly

AND

Gentamycin 5 mg/kg per day IV divided in one to three doses

The gentamicin is given for two to four weeks and the remaining oral antibiotics for between 6 weeks and 6 months (mean duration 3 months).

PREGNANCY

There is little data to guide recommendations. Rifampicin 900 mg PO daily with or without cotrimoxazole 1 double strength tablet PO 12 hourly for 6 weeks. Use of cotrimoxazole during the last week before delivery is associated with kernicterus and should be avoided if possible.

CHILDREN

Combination therapy with a tetracycline (for children ≥ 8 years) or cotrimoxazole (for children < 8 years) and at least one other agent (rifampicin, gentamicin or streptomycin) should be used.

Children without osteoarticular disease, neurobrucellosis or endocarditis:

< 8 years: oral cotrimoxazole and rifampicin for four to six weeks

≥ 8 years: oral doxycycline and rifampicin for 6 weeks

Children with osteoarticular disease, neurobrucellosis or endocarditis:

< 8 years: oral cotrimoxazole for at least 6 weeks (up to 6 months for severe infections) **AND** parenteral gentamicin for the first two weeks of treatment

≥ 8 years: oral doxycycline for at least six weeks (up to 6 months for severe infections) **AND** parenteral gentamicin for the first two weeks of treatment

Rifampicin can be added to reduce the risk of relapse

DOSES

Cotrimoxazole: 10 mg/kg/day PO of the trimethoprim component (max 480 mg/day) and 50 mg/kg/day PO of the sulfamethoxazole component (max 2.4 g/day) given 12 hourly

Doxycycline: 2–4 mg/kg per day PO given 12 hourly

Rifampicin: 15–20 mg/kg/day PO (max 900 mg/day) given as one or two divided doses

Gentamicin: 5 mg/kg IV divided in one to three doses

TICK-BITE FEVER

In South Africa, tick-bite fever (TBF) is caused by *Rickettsia conorii* and *Rickettsia africae*.

CLINICAL PRESENTATION

- The clinical triad of fever, rash and eschar occurs in 50–75% of cases.
- The eschar may not be present or resemble an insect bite or trauma.
- The rash may resemble many other infections such as rubella, measles, and enterovirus or arbovirus infections.

SUMMARY TABLE: R. CONORII AND R. AFRICAE INFECTIONS

	RICKETTSIA CONORII	RICKETTSIA AFRICAE
Transmission	Transmitted by dog ticks	Transmitted by cattle and game ticks
Incubation	Five to seven days	Five to seven days
Prodrome	Malaise, fever, headache	Malaise, fever, headache
Eschar	Typically single, may not be apparent	May have multiple eschars
Disease	Classic Mediterranean spotted fever	African TBF is a separate, milder disease
Rash	Maculopapular rash appearing three days into the illness. Involves palms and soles.	May not have a rash or may be mild maculopapular rash, sometimes with vesicular elements.

Complications	Varies from mild to severe and sometimes fatal. Complications may include coma, pneumonia, bleeding, hepatitis, renal failure, and myocarditis. Severe cases can be confused with meningococcemia or Crimean-Congo haemorrhagic fever and more commonly affect the young and elderly.	A mild disease without life-threatening complications. Neuropsychiatric features and a neuropathy have been described.

LABORATORY DIAGNOSIS

- The diagnosis is usually based upon clinical features and epidemiological clues.
- The total white cell count is usually normal with a neutrophilia. In severe cases, a neutropenia and thrombocytopenia may be present.
- Serological tests for *Rickettsia* antibodies are usually negative during the acute illness and repeat testing is often needed to demonstrate an IgM or IgG response.
- Rickettsia PCR may be positive during the acute phase and confirms an infection, although as with serology, a negative result does not exclude the diagnosis and treatment should be given based on the clinical presentation and history of possible exposure.

TREATMENT OF TICK-BITE FEVER

ADULTS

Doxycycline 100 mg PO 12 hourly for 5–7 days is recommended

Alternatively, tetracycline 25–50 mg/kg/day PO in 4 divided doses for 5–7 days or for at least 48 hours after the resolution of the fever. A response to treatment should be seen with 48 hours. Failure to respond to treatment suggests an alternative diagnosis.

CRITICALLY ILL PATIENTS UNABLE TO TOLERATE ORAL MEDICATION

Chloramphenicol and a quinolone such as ciprofloxacin show in-vitro activity and are suggested in critically ill patients unable to tolerate oral medication since parenteral tetracycline is unavailable in South Africa.

PREGNANT WOMEN AND CHILDREN

Doxycycline is the recommended therapy, at least initially, in children and pregnant women as it is the most effective antibiotic and TBF may be fatal. Doxycycline should be used in children (dose 2.2 mg/kg per dose administered twice daily) and pregnant women for 2 days, followed by 3–5 days of a macrolide to complete the therapeutic course.

Prophylactic antibiotic therapy is not indicated for patients who have had recent tick bites and who are not ill.

Q FEVER

Q fever is a zoonotic infection caused by *Coxiella burnetii* with farmers, farm and abattoir workers as well as those living in or traveling to a country where *C. burnetii* is prevalent being at highest risk.

CLINICAL PRESENTATION

The clinical presentation varies widely from asymptomatic infection to mild disease to severe infections. Presentation can be either acute or chronic.

Acute infection follows an incubation period of approximately 20 days and may present with a flu-like illness (fever, headache and myalgia), lasting for between one and three weeks. Patients may develop pneumonia, hepatitis, endocarditis, rash, meningitis, encephalitis and a variety of other complications during the acute illness.

Less than 5% of patients with acute infections will develop a persistent infection with endocarditis, bone, joint and vascular infections being the most common presentations.

LABORATORY TESTING

The laboratory findings during acute Q fever are non-specific with a transaminitis frequently being present. Elevated CRP, ESR and a leukocytosis and thrombocytopaenia can be seen in approximately 25% of cases.

C. burnetii does not grow in routine blood culture and acute Q fever is typically diagnosed serologically with anti-phase II IgG $\geq$ 200 or a fourfold rise in anti-phase II IgG between serum samples collected during the acute and convalescent phases taken three to six weeks apart. Chronic localised infections should be suspected if the patient has an IgG titer $>$ 800 against phase I or has persistently high levels of anti-phase I antibodies six months after being treated for acute Q fever.

TREATMENT OF Q FEVER

ACUTE Q FEVER IN ADULTS

Doxycycline 100 mg PO 12 hourly for 14 days

PREGNANT WOMEN

Cotrimoxazole 1 double strength tablet PO 12 hourly. Treat until the end of the 7th month of pregnancy and stop to avoid the perinatal risks associated with cotrimoxazole. Give additional folic acid during treatment.

PERSISTENT LOCALISED DISEASE (ENDOCARDITIS, VASCULAR, BONE AND JOINT INFECTION)

A combination of doxycycline 100 mg PO 12 hourly and hydroxychloroquine 600 mg PO daily should be given for between 18 and 24 months.

TYPHOID FEVER

Typhoid fever or enteric fever is a potentially fatal multisystem illness caused primarily by *Salmonella enterica* subspecies *enterica* serovar *typhi*. Other salmonellae such as the related serovars *paratyphi* A, B, and C may cause a similar clinical illness. Typhoid is endemic in South Africa with sporadic cases reported in all provinces every year with occasional outbreaks. It is spread via the faecal-oral route and tends to occur where water quality and sanitation is poor.

CLINICAL PRESENTATION

Typhoid is a febrile illness with onset of symptoms five to 21 days after ingestion of the causative bacteria in contaminated food or water. Clinical symptoms include fever, headache, rigors and gastrointestinal symptoms (nausea, abdominal pain, constipation). Hepatomegaly and splenomegaly may be noted. Laboratory findings include anaemia, leucopaenia or leucocytosis (with a neutrophilia) and a mild thrombocytopenia. Raised liver enzymes are frequently seen.

LABORATORY DIAGNOSIS

The diagnosis of typhoid fever is made by culture of *Salmonella typhi* from blood cultures or bone marrow. Stool cultures only tend to become positive after the first week of the illness. Serological tests (such as the Widal test) are of limited clinical use.

TREATMENT

Optimal antimicrobial treatment of patients with typhoid fever depends on the local patterns of antibiotic resistance, and is enhanced by results of antimicrobial susceptibility testing of the *Salmonella typhi* from the individual patient.

TREATMENT OF TYPHOID FEVER

ADULTS

Ciprofloxacin 500 mg PO 12 hourly or 400 mg IV 12 hourly for 7 days

OR

Ceftriaxone 2 g IVI daily for 5 days

OR

Azithromycin 1 g PO then 500 mg PO once daily for 5–7 days

Dexamethasone should be used in severely ill patients. Dose is 3 mg/kg IV given just prior to antibiotic administration, then 1 mg/kg 6 hourly IV x 8 doses.

CHILDREN

Ceftriaxone 50 mg/kg/day IV for 5 days

OR

Azithromycin 10 mg/kg PO once daily for 7 days

Dexamethasone should be used in severely ill patients. Dose is 3 mg/kg IV given just prior to antibiotic administration, then 1 mg/kg 6 hourly IV x 8 doses.

LEPTOSPIROSIS

Leptospirosis is a zoonotic infection caused by spirochetes of the genus *Leptospira.* Various mammals are natural hosts and humans are infected incidentally after animal or environmental exposure. Rodents are the most important reservoirs and shed the organism in their urine resulting in contamination of the environment, particularly water sources. Leptospirosis is seen worldwide, however is not commonly diagnosed in South Africa. Most cases are mild and self-limited or subclinical, while some are severe and potentially fatal.

CLINICAL PRESENTATION

Leptospirosis presents typically with the abrupt onset of fever, rigors, myalgias and headache following an incubation period of two to 26 days. Conjunctival suffusion is seen in more than 50% of patients and is an important clue to the diagnosis. Other symptoms include cough, nausea, vomiting and diarrhoea. Signs include splenomegaly, lymphadenopathy, pharyngitis, hepatomegaly, muscle tenderness and a skin rash. Severe cases may develop jaundice and renal failure (Weil's disease), pulmonary haemorrhage, acute respiratory distress syndrome (ARDS), myocarditis, rhabdomyolysis and uveitis.

LABORATORY DIAGNOSIS

Routine laboratory tests are typically non-specific and may include a leucocytosis with a left shift, thrombocytopenia, elevated serum bilirubin, elevated serum creatinine, elevated creatinine kinase and elevated amylase. Urinalysis may show proteinuria, leucocytes, erythrocytes and casts.

A laboratory diagnosis may be made by demonstrating a positive *Leptospira* IgM, isolating the bacteria from a blood culture or other clinical specimen, or positive PCR on a blood specimen in the first few days of the illness.

Mild cases of leptospirosis may not require treatment and if the patient has defervesced by the time the diagnosis is confirmed, no antibiotics are required. Treatment for more severe forms of leptospirosis is recommended and should be instituted early when suspected, rather than when the diagnosis is proven.

TREATMENT OF LEPTOSPIROSIS

SEVERE ILLNESS

Benzylpenicillin (penicillin G) 1.5 million units IV 6 hourly for 7 days (children: 30 mg/kg up to 1.2 g per dose)

OR

Ceftriaxone 1-2 g IV once daily for 7 days (children: 25 mg/kg up to 1 g per dose)

MILD ILLNESS

Doxycycline 100 mg PO 12 hourly for 5–7 days (children > 8 years: 2.2 mg/kg/day up to 100 mg per dose)

OR

Azithromycin 500 mg PO once daily for 3 days (children: 10 mg/kg on day one [max 500 mg/day] followed by 5 mg/kg/day once daily on subsequent days [max 250 mg/day])

LYME DISEASE

Lyme disease is caused by the spirochaete *Borrelia burgdorferi* and is not known to be endemic in South Africa. Most cases appear to be imported in travellers who have visited Europe and the USA where it is a common tick-borne illness.

CLINICAL PRESENTATION

The symptoms of Lyme disease vary widely and include a rash at the site of the tick bite, flu-like symptoms, and arthritis, cardiac and neurologic symptoms. The infection may also be asymptomatic or mildly symptomatic in a small percentage of infected people. Lyme disease can be divided into three phases: early localised disease (erythema migrans), early disseminated, and late Lyme disease.

LABORATORY DIAGNOSIS

A diagnosis of Lyme disease is based on an individual's travel history and possible exposure to ticks, characteristic signs and symptoms, and the results of specific laboratory tests. Laboratory tests for Lyme disease should only be performed in individuals who reside in or who have travelled to an endemic area, who have a history of possible tick exposure and who have compatible signs and symptoms as false positive laboratory test results are frequently seen. Serological testing by means of an IgG and IgM ELISA is commonly performed and positive results need to be confirmed by means of a more specific Western blot (which has specific diagnostic criteria for positive IgG and IgM results).

TREATMENT OF LYME DISEASE

EARLY LYME DISEASE (ERYTHEMA MIGRANS)

Doxycycline 100 mg PO 12 hourly (children ≥ 8 years: 2 mg/kg/dose 12 hourly [max. 100 mg/dose])

OR

Amoxycillin 500 mg PO 8 hourly (children 50 mg/kg per day in three divided doses [max. 500 mg/dose])

Treat for 14–21 days

EARLY DISSEMINATED DISEASE (WITH NEUROLOGIC OR CARDIAC DISEASE)

Ceftriaxone 2 g IV given once daily (children: 50–75 mg/kg intravenously once daily [max. 2 g])

Treat for 14–21 days

LATE DISEASE (ARTHRITIS, ACRODERMATITIS CHRONICA ATROPHICANS, LATE NEUROLOGICAL DISEASE)

Treat with oral doxycycline or amoxycillin as above for 21–28 days except late neurological disease which requires IV ceftriaxone for up to 28 days.

BARTONELLA INFECTIONS

Bartonella species are fastidious Gram-negative bacteria that cause a range of manifestations including cat scratch disease, bacillary angiomatosis and other infections in HIV-infected patients, as well as endocarditis. The three most important *Bartonella* species known to cause human disease are *Bartonella henselae*, *Bartonella quintana* and *Bartonella bacilliformis*.

BARTONELLA SPECIES	RESERVOIR/VECTOR	ASSOCIATED DISEASES
Bartonella henselae	Domestic cat (reservoir) and its fleas (vector)	Cat scratch disease (CSD), bacillary angiomatosis, meningoencephalitis and chronic bacteraemia.
Bartonella quintana	Human body louse (vector)	Trench fever, bacillary angiomatosis (particularly in HIV-infected patients), chronic bacteraemia, internal organ disease (bacillary peliosis) and culture-negative endocarditis.
Bartonella bacilliformis	Female sandfly (vector)	Carrion's disease in certain Andean regions of South America.

LABORATORY DIAGNOSIS

Cat scratch disease is suggested by compatible signs and symptoms and a history of exposure. Serology may be used to support the diagnosis, although false positive antibody results may be seen. For the other clinical presentations a diagnosis may be made in patients with a clinically compatible illness by serology, histology of biopsy or other tissue specimens and *Bartonella* PCR on blood or other appropriate clinical specimens. *Bartonella* are fastidious organisms and laboratory culture requires specific media and prolonged incubation. Blood cultures should be incubated for at least 21 days. *Bartonella* endocarditis can be confirmed by PCR on resected heart valve tissue.

TREATMENT

A number of antibiotics are effective against *Bartonella* infections including penicillins, tetracyclines, cephalosporins and aminoglycosides. With serious infections more than one antibiotic is used.

TREATMENT OF BARTONELLA INFECTIONS

CAT SCRATCH DISEASE

Azithromycin 500 mg PO (children: 10 mg/kg) x 1 dose then 250 mg PO (children: 5 mg/kg) given daily for 4 days

BACILLARY ANGIOMATOSIS, BACILLARY PELIOSIS

Doxycycline 100 mg PO 12 hourly (children: > 8 years: 2.5 mg/kg up to 100 mg per dose)

OR

Azithromycin 250 mg PO once daily (children: 5 mg/kg)

If there is CNS involvement, add rifampicin 300 mg PO 12 hourly (children: 7.5 mg/kg up to 300 mg per dose)

Treat for at least 3 months

ENDOCARDITIS

Doxycycline 100 mg PO 12 hourly for 6 weeks (children: > 8 years: 2.5 mg/kg per dose)

AND

Gentamicin 1 mg/kg IV 8 hourly OR rifampicin 300 mg PO 12 hourly (children: 7.5 mg/kg up to 300 mg per dose) for 14 days

Surgical resection of the infected valve is usually required

NEUTROPENIC SEPSIS IN CANCER AND TRANSPLANT PATIENTS

Antineoplastic therapy used in cancer patients adversely affects myelopoiesis as well as the integrity of the gastrointestinal mucosa. Patients are thus at risk for invasive infection from bacteria or fungi that translocate across intestinal mucosal surfaces. Patients with severe prolonged neutropenia are at particularly high risk for serious infections. Neutropenia is usually defined as an absolute neutrophil count < 1.5 x 10^9/L and severe neutropenia is usually defined as a neutrophil count less than 0.5 x 10^9/L. High-risk patients are those with severe, prolonged neutropenia (> 7 days) which is most likely to occur in the pre-engraftment phase of hematopoietic cell transplantation and in patients undergoing induction chemotherapy for acute leukemia.

Neutropenic patients are unable to mount robust inflammatory responses and serious infection can occur with minimal symptoms and signs. In such patients, fever is often the only sign of infection and empiric systemic antibiotic therapy must be given promptly (within 30–60 minutes) to prevent sepsis and possible death. Fever is defined as a single oral temperature of > 38.3°C or a temperature of > 38.0°C sustained for more than one hour.

Usual organisms include Enterobacteriaceae, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and streptococci. Initial antibiotic selection should be guided by the patient's history, symptoms, signs, recent antibiotic use and culture data and local hospital and unit microbiology and susceptibility patterns. Ideally, antibiotics used should be bactericidal.

MICROBIOLOGY TESTING

- At least two sets of blood cultures. Two sets of blood cultures are typically repeated daily for persistent fevers/rigors at least during the first two days following initiation of empiric antibiotics.
- MC&S from other sites as clinically indicated, e.g.
  - Stool MC&S and *Clostridiidium difficile* toxin by PCR in patients with diarrhoea.
  - Urine MC&S if symptoms of urinary tract infection are present.
  - Skin aspirate or biopsy for MC&S and fungal stains and cultures, HSV PCR and VZV PCR if skin lesions or vesicles are present.
  - Sputum MC&S if a productive cough is present. Bronchoscopy with bronchoalveolar lavage may be pursued in patients with pulmonary infiltrates if a productive cough is absent.
  - CSF for MC&S, HSV PCR, CMV PCR, VZV PCR, and HHV6 PCR in patients with symptoms and/signs of meningitis or encephalitis.
- *Aspergillus* galactomannan antigen and serum plasma (1→3)-β-D-glucan (Fungitell®) should be considered in at risk patients.

EMPIRIC TREATMENT OF NEUTROPENIC FEVER

EMPIRIC ANTIBIOTIC TREATMENT

Transplant and oncology units typically have their own protocols for empiric antimicrobial therapy in patients with neutropenic fever. This is based largely on local microbiology and antimicrobial susceptibility patterns.

Examples of empiric therapy used include:

Amikacin 15 mg/kg IV once daily (children: 15 mg/kg once daily)

AND

Piperacillin-tazobactam 4.5 g (4 + 0.5 g) IV 8 hourly (children: 100 + 12.5 mg/kg up 4 + 0.5 g per dose)

OR

Amikacin 15 mg/kg IV once daily (children: 15 mg/kg once daily)

AND

Cefepime 2 g IV 8–12 hourly (children: 50 mg/kg/dose)

OR

Imipenem 0.5–1g IV 6–8 hourly (children: 15–25 mg/kg 6–8 hourly)

OR

Meropenem 1–2 g IV 8 hourly (children: 20–40 mg/kg/dose 8 hourly)

Vancomycin 15 mg/kg IV 12 hourly should be added empirically in patients with severe mucositis, catheter-related infection, hypotension, colonised with MRSA and in those that fail to respond to empiric antibiotics.

EMPIRIC ANTIFUNGAL TREATMENT

Antifungal therapy is typically added for patients who fail to respond within 3–7 days of empiric antibiotic therapy (persistent or recurrent fever) and in whom reassessment does not find a cause. The choice of agent for empiric antifungal therapy depends upon which fungi are most likely to be causing infection. *Candida* species are the most likely cause of invasive fungal infections and caspofungin (or another echinocandin) is often used as the initial antifungal agent. Voriconazole or amphotericin B (ideally liposomal), are preferred in patients with pulmonary findings suggestive of an invasive mould infection.

ANTIFUNGAL DOSING

Caspofungin: loading dose of 70 mg IV on day 1, then 50 mg IV once daily

Micafungin: 100 mg IV once daily

Anidulafungin: loading dose of 200 mg IV on day 1, then 100 mg IV once daily

Voriconazole: loading dose of 6 mg/kg IV 12 hourly on day 1, followed by 4 mg/kg IV 12 hourly

Liposomal amphotericin B: 3–5 mg/kg IV once daily

Amphotericin B deoxycholate: 0.5–1 mg/kg IV once daily