

Biological incidents

Biological incident action guide

Overview

- A deliberate release may be **overt** (announced openly by perpetrators, eg the envelopes containing threatening notes and anthrax spores distributed through US Postal Service in 2001), or **covert** (unannounced, without any warning or indication of the organism involved) eg 1984 *Salmonella typhimurium* contamination of salad bars in restaurants in Dalles, Oregon, by followers of Baghwan Shree Rajneesh, when 751 people developed gastroenteritis
- Many different organisms could, in theory, be used deliberately, and be distributed through food, water, or the air (by an explosive device, aerosol canister, or crop duster); this manual focuses on organisms that could be aerosolised and/or would cause serious or fatal infections
- Intentional and naturally occurring outbreaks may be indistinguishable initially
- Symptoms of some forms of intentional or accidental chemical poisoning may mimic some infections (eg arsenic-contaminated coffee, Maine, 2003, and nicotine-contaminated minced meat, Michigan, 2003, both initially thought to be gastroenteritis; thallium poisoning, Florida, 1988, initially thought to be botulism)
- **Early recognition of a covert release of a biological agent will be achieved only if clinicians remain aware of the possibility, and are willing to alert and consult with their microbiologist, ID physician and Health Protection Team on suspicion, and before a definitive diagnosis has been reached**
- **Be alert to the unusual, the unexpected, and the case that 'just doesn't fit':**
 - an unusual illness (eg sudden unexplained febrile death, critical illness or pneumonia death in a previously healthy young adult)
 - an unusual number of patients with the same symptoms
 - an illness unusual for the time of year (eg 'flu' in summer)
 - an illness unusual for the patient's age group (eg 'chickenpox' in a middle-aged adult)
 - an illness in an unusual patient (eg cutaneous anthrax in a patient with no history of contact with animals, animal hides or products)
 - an illness acquired in an unusual place (eg tularemia acquired in the UK)
 - unusual clinical signs (eg mediastinal widening on CXR; sudden onset of symmetrical flaccid paralysis)
 - unusual progression of an illness (eg lack of response to usually effective antibiotics; 'chickenpox' rash predominant on extremities)
- Any confirmed case of smallpox, plague, pulmonary anthrax, glanders, tularemia, Venezuelan equine encephalitis (VEE) or viral haemorrhagic fever (VHF) in the UK should be assumed to be the result of a deliberate release until proven otherwise
- Use the action list below in conjunction with the handsheets on infection control (standard precautions, respiratory precautions, airborne infection isolation) and PPE in the section on generic incident management, and those on microbiological testing and specific infections in this section

Action list												
Actions	Infections											
	Anthrax	Botulism	Brucella	Clanders	Melioidosis	Plague	Q fever	SARS	Smallpox	Tularemia	VHF	VEE
Important actions to take for health protection when a diagnosis suspected or confirmed ● If smallpox is the suspected diagnosis, Smallpox Diagnostic Expert will take specimens ■ If VHF is the suspected diagnosis, seek expert advice and assessment before taking specimens ▲												
At presentation of a patient in whom the diagnosis is SUSPECTED												
Discuss with senior emergency medicine clinician and on-call medical microbiologist	●	●	●	●	●	●	●	●	●	●	●	●
Immediately ISOLATE patient in SINGLE ROOM and restrict entry to essential personnel only						●		●	●	●		
Doctor, triage nurse and others who had close contact with patient to remain in room with patient									●			
Ask other patients and their relatives/friends to remain until diagnosis confirmed or excluded									●			
Ensure ambulance used by case is not used again until decontaminated or diagnosis excluded									●	●		
Enforce STANDARD and AIRBORNE infection control precautions (including appropriate PPE)								●	●	●		
Enforce STANDARD and RESPIRATORY infection control precautions (including appropriate PPE)						●						
Enforce STANDARD infection control precautions (including appropriate PPE)	●	●	●	●	●	●			●	●		●
Arrange IMMEDIATE clinical assessment by Smallpox Diagnostic Expert (■) or ID physician (●)		●				●		●	■	●		●
Arrange URGENT ID consultation/assessment	●		●	●	●	●				●		●
Alert Infection Control Doctor, Trust senior management and nursing staff, & Occupational Health						●		●	●	●		●
Immediately alert local Health Protection Team (HPT)	●	●		●	●	●		●	●	●	●	●
Label ALL specimen containers and ALL request forms 'high risk', and warn laboratory in advance	●	●	●	●	●	●	●	●	■	●	▲	●
Transport clinical specimens to the laboratory according to local protocols for high-risk specimens	●	●	●	●	●	●	●	●	■	●	▲	●
With HPT, identify case contacts for follow up (+/- post exposure prophylaxis or vaccination)						●		●	●	●		
See disease-specific fact sheet for history taking, investigation, treatment and further management	●	●	●	●	●	●	●	●	●	●	●	●
This disease is notifiable by law (or maybe depending on presentation ◆)	●	◆				●			●		●	◆
When/if the diagnosis is CONFIRMED												
Inform local Health Protection Team	●	●	●	●	●	●	●	●	●	●	●	●

Biological agents: syndromes and differential diagnosis

Overview

- Be alert to the unusual, the unexpected, and the case that 'just doesn't fit'
- Take a thorough clinical history. Remember to ask the patient about:
 - Occupation (what is their job and where do they do it?)
 - Travel abroad (countries and areas visited, with dates; rural or urban; use of antimalarial drugs, bed nets, insect repellents; immunisations; unprotected sex; unusual events eg animal bite)
 - Family and other contacts (has anyone had similar symptoms?)
 - Hobbies, recreations, contact with pets or other animals, insect bites, food
 - What they think might have caused their illness
- Have a low threshold for seeking advice from the senior emergency medicine clinician, and your consultant microbiologist, CCDC, or ID physician
- The tables below show the differential diagnoses for some important syndromic presentations. Those marked* are covered in this manual

<p>Neurological symptoms/signs (symmetrical descending flaccid paralysis)</p>	<p>→</p> <p>Differential diagnosis includes:</p> <p>Guillain-Barre syndrome CVA Chemicals & toxins: organophosphates, carbon monoxide, mushrooms, thallium, alcohol CNS viral infection, polio, transverse myelitis Myasthenia gravis Psychiatric illness Botulism*, nerve agents*</p>
<p>Fever and... chest symptoms/signs (cough, and/or sputum, chest pain, dyspnoea)</p>	<p>→</p> <p>Differential diagnosis includes:</p> <p>Exacerbation COPD (often <i>Haemophilus influenzae</i>) Lobar pneumonia (<i>Streptococcus pneumoniae</i>, rusty sputum, cold sore/s) Atypical pneumonia (<i>Mycoplasma pneumoniae</i>, <i>Chlamydia pneumoniae</i>, <i>Chlamydia psittaci</i>, <i>Legionella pneumophila</i>, influenza, RSV, chickenpox, Q fever* [<i>Coxiella burnetii</i>]) Lung abscess, empyema TB SARS*, pulmonary anthrax*, plague*, tularemia*, melioidosis*, glanders*, ricin*, radiation*</p>
<p>Fever and... generalised rash</p>	<p>→</p> <p>Differential diagnosis includes:</p> <p><i>Erythematous/maculopapular rash</i>: rubella, measles, parvovirus B19, enteroviral infections, scarlet fever, typhoid (rose spots), dengue and arboviral infections, syphilis, and smallpox* <i>Vesicular/pustular rash</i>: chickenpox, disseminated HSV, disseminated herpes zoster, hand foot and mouth disease, molluscum contagiosum, monkeypox, drug rash, impetigo, contact dermatitis, erythema multiforme, Stevens Johnson syndrome, scabies, acne, complications of smallpox vaccination, smallpox*</p>
<p>Fever and... localised skin signs and/or local lymphadenopathy</p>	<p>→</p> <p>Differential diagnosis includes:</p> <p>Impetigo, erysipelas Fixed drug eruption, local reaction to vaccine/BCG Orf, cowpox, necrotic recurrent herpes simplex virus (HSV) infection (cold sore) Lymphogranuloma venereum, granuloma inguinale, chancroid, bubonic plague* Tick bite, spider bite, infected insect bite Cutaneous anthrax*, tularemia*, glanders*, melioidosis*</p>
<p>Fever and... shock and/or bleeding tendency or DIC</p>	<p>→</p> <p>Differential diagnosis includes:</p> <p>Gram negative sepsis Meningococcal infection (<i>Neisseria meningitidis</i>) Toxic shock syndrome (<i>Staphylococcus aureus</i>) Malaria, typhoid, leptospirosis, rickettsial infection (typhus, spotted fever), dengue, haemolytic uraemic syndrome (enterotoxigenic <i>E coli</i>); viral haemorrhagic fevers*, anthrax*, plague*, tularemia*, glanders*, melioidosis*, smallpox*, ricin* Other causes of DIC, including leukaemia, solid tumour, intrauterine death, liver failure</p>

Taking samples

- Always use standard precautions when taking any specimen
- Use additional PPE (eg double gloves, eye and face protection, FFP3 mask) appropriate to the task and infection, or if the aetiology is uncertain
- If you are uncertain about what PPE to use, or which specimens to collect, seek expert advice
- Telephone the microbiology laboratory in advance to tell them to expect the specimens
- Pre-label specimen containers with the patient's name, hospital number, date and time of sample
- Use dry cotton wool balls (rather than alcohol swabs) to apply pressure to stop any bleeding from venepuncture sites
- Label all specimens and forms as 'high risk' or 'danger of infection' (or otherwise identify them as **high risk** using locally agreed method)
- If possible, take specimens for bacterial culture before starting antibiotic treatment. If antibiotics have already been given, mention this on the form
- Take at least 4 sets of blood cultures (2 sets from each of two venepunctures at different sites at least 1 hour apart)
- Avoid contaminating the outside of the specimen container during specimen collection. Screw container caps tight
- Put each specimen in a separate plastic specimen bag (ie 3 specimens, 3 specimen bags). Seal specimen bags with tape: do NOT use clips, staples or pins – this endangers the laboratory staff who open the bags
- Fill in all request forms fully and accurately, giving the working diagnosis and as much clinical information about the case as you can ('? tularemia' is helpful, but 'fever, skin nodules, pneumonia, laboratory worker, on ampicillin ? tularemia' much more so). Put each request form in a separate plastic bag. Never put a request form in the same bag as a specimen – use separate bags, then tape the bag containing the specimen and the bag containing the request form together
- Complete a chain of evidence form if necessary
- Transport specimens to the local microbiology laboratory as soon as possible, using locally agreed procedures for **high risk** samples
- Specimens should be transported to the laboratory by hand by a responsible person
- Do NOT use vacuum-tube systems for specimen transport
- Specimen packaging, labelling and transportation must comply with current national and international standards. See: Biological agents: managing the risks in laboratories and healthcare premises, ACDP/HSE 2005 www.hse.gov.uk
- The table below shows the specimens that are important (or that may be helpful, if it is clinically appropriate to obtain them) in the laboratory diagnosis of high consequence pathogens – but it is not all-inclusive, and if you suspect that a patient has any of these illnesses, you should discuss the case with a senior clinician and with the consultant microbiologist

Sample guide		Infections												
Clinical specimens		Anthrax	Botulism	Brucella	Glanders	Melioidosis	Plague	Q fever	Tularemia	SARS	Smallpox	VEE	VHF	Unusual illness
Important for laboratory confirmation of diagnosis, collect routinely ●														
Helpful for laboratory confirmation of diagnosis, if specimen clinically indicated ■														
Helpful for exclusion of an important differential diagnosis ▲														
Label ALL specimens and ALL request forms 'high risk' or 'danger of infection'														
Hazard Group of organism		3	2	3	3	3	3	3	3	3	4	3	4	3
Blood cultures		●		●	●	●	●	●	●	▲		▲		●
Paired sera (10mls clotted blood acutely and at least 14 days post onset)		●	●	●	●	●	●	●	●			●		●
Additional 20mls acute serum sample AND further sample at more than 21 days post onset										●				●
EDTA blood sample (5 x 4ml) on admission		●					●		●					●
Swab/aspirate of any skin lesion for microscopy, culture & sensitivity		●			●	●	●		●					■
Nasal swabs (dry swabs, not in transport medium, preferred) for microscopy, culture & sensitivity		●												
Throat and nasal swabs together (or throat washings) in virus transport medium										●	●			●
Nasopharyngeal aspirate or throat washings for rapid tests for influenza and RSV		▲					▲	▲	▲	▲				▲
Sputum for microscopy, culture & sensitivity		●			●	●	●	●	●	▲				■
Sputum for ZN stain and AAFBs		▲		▲	▲	▲	▲	▲	▲	▲				▲
Bronchoalveolar lavage or bronchial washings (in sterile container)		■	■		■	■	■	■	■	■				■
Urine (at least 20mls; 'clean catch' specimen into sterile container) for microscopy, culture & sensitivity		▲		▲	●	●	▲		▲			▲		▲
Urine (in sterile container) for legionella and pneumococcal antigens		▲			▲	▲	▲	▲	▲					▲
Faeces (at least 10g in sterile container)		■	●											
Vomit or gastric washings or gut contents (at least 10g in sterile container)		■	●											
CSF (in sterile containers)		■		■			■							■
Bone marrow aspirate (in sterile container)				■										
Specimens from other normally sterile sites that may be helpful for laboratory diagnosis include pleural fluid, pus, and tissue from debridement														
If in doubt, seek advice from your consultant microbiologist and/or infectious disease physician														
For detailed guidance on the identification, investigation, and management of 'unusual illness', see: www.hpa.org.uk														

Pre- and post- exposure prophylaxis

Overview

- The decision to offer post-exposure prophylaxis after a deliberate or accidental release should be taken after a risk assessment of the likelihood and extent of exposure has been made. If a deliberate release occurs, advice about the use of prophylaxis will be provided. Groups likely to need prophylaxis include persons exposed at the incident scene (including first responders and handlers of contaminated clothing) and, for smallpox and pneumonic plague, contacts of cases, laboratory workers and others
- For exposure outside the context of deliberate release (eg accidental exposure during laboratory work; accidental inoculation of the live brucella vaccine that is used in animals), follow local occupational health protocols (including those on exposure to HBV, HCV and HIV) on reporting, care provision, counselling and follow up, and seek expert advice if in doubt
- Before prescribing, check current recommendations via the HPA (www.hpa.org.uk) and DH (www.dh.gov.uk) websites, and check drug dosages, contraindications and interactions in the BNF
- The table shows the **drug/s of first choice** and **second choice** (for use when the drug of first choice cannot be prescribed because it is contraindicated or is not available), and alternatives for use (eg amoxicillin for anthrax) when the organism is known to be sensitive to the drug. Except where specified, antibiotic prophylaxis should begin, if possible, within 24 hours of exposure
- The Department of Health has prepared Patient Group Directions (PGDs) for use when members of the public may have been exposed to a biological agent. These provide for initial (first 3 days) post exposure prophylaxis with ciprofloxacin, and for completion of treatment with either ciprofloxacin or doxycycline
- Ciprofloxacin is not licensed for use in children or in pregnant women. There have been no formal studies of the use of ciprofloxacin in pregnancy, but it is unlikely to be associated with a high risk of abnormalities of foetal development. There is some evidence that the use of fluoroquinolones in children (including via breast feeding) may be associated with tendinitis and arthropathy. The risk of adverse effects of ciprofloxacin must be weighed against the risk of developing an infectious disease with significant morbidity and mortality. Doxycycline has adverse effects in children (deposition in growing bones and teeth, causing staining and, occasionally, dental hypoplasia), and should be used in children less than 12 years and in pregnancy only when no alternative antibacterial can be given, and when the risk of infection outweighs the risk of adverse effects. If given ciprofloxacin or doxycycline, lactating mothers should stop breast feeding
- For patient information sheets, patient group directions, and additional information on ciprofloxacin and doxycycline: www.dh.gov.uk

Protocols				
Disease/ Agent	Pre-exposure vaccine	Post-exposure prophylaxis Adults	Duration	Post-exposure prophylaxis Children
Anthrax	Available for those at occupational risk eg work with animal hides, laboratory work. 5 dose course (0, 3 and 6 weeks, 6 and 12 months)	Ciprofloxacin 500mg orally bd or Doxycycline 100mg orally bd or if organism shown to be sensitive Amoxicillin 500mg orally tds	60 days or 28 days*	Ciprofloxacin 10mg-15mg/kg orally bd (not to exceed 1g per day) or if organism shown to be sensitive Doxycycline 2.5mg/kg orally bd or Amoxicillin 25mg/kg orally tds
		Anthrax vaccine may be available and used post-exposure in combination with antibiotics in selected cases (eg first responders in incident 'hot zone'). * If anthrax vaccine is given, or a full course of vaccine has been completed previously, antibiotic prophylaxis is reduced to 28 days		
Botulism	Toxoid vaccine for research workers	Not indicated		
Brucellosis	No	Doxycycline 100mg orally bd and Rifampicin 600mg-900mg orally daily Pregnancy: use rifampicin alone	21 days (if low risk)- 6 weeks (high risk)	Doxycycline 2.5mg/kg orally bd and Rifampicin 10-15mg/kg orally daily
Glanders and melioidosis	No	Doxycycline 100mg orally bd or Co-trimoxazole 960mg orally bd	7 days	Co-trimoxazole 24mg/kg orally bd
Plague	Sub-unit vaccines in development but not yet evaluated in humans	Ciprofloxacin 500mg orally bd or Doxycycline 100mg orally bd	7 days	Ciprofloxacin 10mg-15mg/kg orally bd (not to exceed 1g per day) or Doxycycline 2.5mg/kg orally bd
		Health care and laboratory workers should continue therapy until 7 days after last known exposure		
Q fever	Not in UK	Doxycycline 100mg orally bd or Co-trimoxazole 960mg orally bd (particularly for pregnant/ breast-feeding women)	7 days	Co-trimoxazole 24mg/kg orally bd
		Begin prophylaxis 8-12 days after exposure (if taken earlier it will merely delay illness onset)		
Smallpox	Vaccinia vaccine – has been given to key workers	Vaccine given immediately or very soon after exposure reduces the severity of infection		
Tularemia	Vaccine has been given to selected laboratory workers	Ciprofloxacin 500mg orally bd or Doxycycline 100mg orally bd	14 days	Ciprofloxacin 10mg-15mg/kg orally bd (not to exceed 1g per day) or Doxycycline 2.5mg/kg orally bd
		Vaccine gives incomplete protection: antibiotics required after known laboratory exposure		
VEE	No	Not indicated		
Viral haemorrhagic fever	No current vaccine available	Ribavirin and active follow up for 21 days for any health care or laboratory worker with a high-risk exposure (eg needlestick injury, or skin, eye or mucous membrane contact with blood or body fluids) to a known source of Lassa fever virus or arenavirus, or to a VHF of uncertain aetiology		

Think of anthrax

In any **previously health patient** with:

- Rapid onset of severe febrile illness, sepsis or respiratory failure with wide mediastinum on CXR *or*
- Painless black-scabbed ulcer on arm, neck or face with extensive local swelling *or*
- Gram positive rods (or *Bacillus sp*) in blood or CSF assessed not to be contaminants *or*
- Haemorrhagic meningitis *or*
- Unexplained febrile death
- **Inhalational anthrax is very rare indeed: a single confirmed case in the UK suggests deliberate release**

Key facts

- Caused by *Bacillus anthracis* (Gram positive bacterium with hardy spore form that can survive in soil for decades)
- Zoonosis (disease that affects animals and humans) – mainly of sheep, cattle, and goats
- Human anthrax now rare in UK (< 1 case/year) but still occurs in parts of Europe, the Americas and in the Middle East and Africa
- Naturally acquired human anthrax is the result of contact with an infected animal, carcass or animal product
- Clinical features depend on route of exposure: contact with abraded skin causes cutaneous anthrax; breathing in the spores causes inhalational anthrax; eating under cooked anthrax-contaminated meat causes gastrointestinal anthrax
- Occupational risks: working with animals or animal hides, skins or hair, as in Hawick, Scotland in 2006 where there was one death, or working with the organism in the laboratory. Working in a postal sorting office or as mail handler was a risk in the 2001 outbreak, when deliberate release of letters containing anthrax spores via the US Postal Service caused 22 cases (five deaths)
- Other risks: threatening letters or suspicious packages
- Incubation period usually 1-7 days (range < 24 hours – 60 days post exposure)

Symptoms and signs

Cutaneous anthrax	Inhalational anthrax	Gastrointestinal anthrax
<ul style="list-style-type: none"> • Initial pimple/papule enlarges, blisters, ulcerates over 2-6 days to form a black scab (eschar) • Painless, not tender (may itch) • Extensive local swelling • Commonest on hands, forearm, neck, or face • Local lymphadenopathy • Systemic malaise: headache, chills • With antibiotics, recovery usual 	<ul style="list-style-type: none"> • Febrile, flu-like prodrome <ul style="list-style-type: none"> – Fever, drenching sweats – Malaise, myalgia – Nausea, vomiting – Non-productive cough – Headache, confusion – No coryza (cf URTI, flu) • 1-2 days later severe sepsis, acute dyspnoea, chest pain, respiratory failure, meningism • 100% mortality if untreated 	<ul style="list-style-type: none"> • Acute abdomen • Severe abdominal pain • Nausea, vomiting • Bloody diarrhoea • Sepsis, shock • High mortality even with treatment

Management

- If diagnosis suspected, discuss with senior emergency medicine clinician and consultant microbiologist, arrange urgent ID consultation, and alert local Health Protection Team (HPT)
- NO risk of person to person spread: use STANDARD precautions
- Culture (and Gram stain) of: blood, swab /aspirate of any skin lesion, sputum, other (eg pleural fluid, CSF); 10mls clotted blood for serology (and further sample at least 14 days post onset); 20mls blood in EDTA tubes for PCR; nasopharyngeal aspirate or throat washings for rapid tests for influenza and RSV (positive results may exclude diagnosis); Hazard Group 3 organism, label all samples 'danger of infection'
- If possible take cultures BEFORE starting antibiotics
- CXR +/- or CT scan chest (look for wide mediastinum, pleural effusion/s, pulmonary infiltrates)
- Dermatology/ID referral for biopsy of any skin lesion (histology, PCR)
- Systemic anthrax: ABGs: (low PaO₂); FBC (high white cell count); U & Es (low sodium); LFTs (high transaminases, low serum albumin)
- Initial treatment for adults with systemic anthrax: ciprofloxacin 400mg IV bd (or doxycycline 100mg IV bd) plus 1 or 2 additional antibiotics (rifampicin/vancomycin/clindamycin/penicillin or amoxicillin/imipenem or meropenem/chloramphenicol)
- Initial treatment for children with systemic anthrax: ciprofloxacin 10mg/kg IV bd, not to exceed 800mg per day (or doxycycline: if at least 8 years old and body weight 45kg: 100mg IV bd; if less than 8 years and body weight less than 45kg, or less than 8 years: 2.2mg/kg IV bd) plus 1 or 2 additional antibiotics as above
- Initial treatment for adults with cutaneous anthrax and no systemic symptoms: ciprofloxacin 500mg orally bd or doxycycline 100mg orally bd for 7 days; change to amoxicillin 500mg orally tds if organism sensitive
- Initial treatment for children with cutaneous anthrax and no systemic symptoms: ciprofloxacin 10mg/kg-15mg/kg orally bd or doxycycline 2.5mg/kg orally bd or, if organism penicillin sensitive, amoxicillin 80mg/kg/day orally in three divided doses
- Anthrax is NOT sensitive to cephalosporins

See also

- Emergency contacts, personal protective equipment, infection control, post-exposure prophylaxis, biological incident action guide, microbiological testing, picture gallery

Think of botulism

In any **previously healthy patient** with:

- Symmetrical descending flaccid paralysis, with prominent bilateral cranial nerve signs, without fever and without sensory loss
- **A single suspected case of botulism is a public health emergency, regardless of the circumstances**

Key facts

- Caused by neurotoxins of *Clostridium botulinum* (spore forming Gram positive anaerobic bacillus)
- *Clostridium botulinum* occurs in soils and marine sediments worldwide; in anaerobic conditions, the spores germinate and the growing bacterial cells then produce toxin
- Botulinum toxin has 7 antigenically distinct forms, A-G (A and B most common in natural human disease)
- Toxin acts by blocking acetylcholine release at the neuromuscular junction
- Toxin is amongst the most lethal known, but is inactivated by normal cooking of food and by chlorination of water
- Botulism follows absorption of toxin into bloodstream after eating toxin-containing food, or following local production of toxin by *C botulinum* in a wound (or, in infant botulism, intestine), or breathing in pure toxin
- Naturally acquired food-borne botulism is rare in the UK, but can occur (27 cases in 1989 outbreak associated with hazelnut yoghurt); more common in Europe where home-canning/preservation of food more widespread; wound botulism has occurred after gun-shot wounds, and in UK drug users who have injected with contaminated heroin; infant botulism usually affects infants aged less than 6 months, and is associated with feeding of honey containing *C botulinum* spores, with subsequent gut colonisation and toxin production
- Inhalation botulism does not occur naturally but could follow the deliberate release of aerosolised toxin
- All forms of botulism have the same neurological symptoms and signs
- Speed of onset and severity of illness are related to dose and route of exposure: 6 hours-8 days after ingestion of toxin: onset might be more rapid after inhalation

Symptoms and signs

Early symptoms and signs

- No fever
- Facial weakness
- Ptosis, drooping eyelids
- Difficulty speaking, seeing, or swallowing
- 4 Ds: dysphonia, dysarthria, diplopia, dysphagia
- Dry mouth
- Pupils dilated and sluggishly reacting
- Normal sensation and alertness
- Nausea, vomiting and diarrhoea sometimes accompany food-borne botulism

Late symptoms and signs

- Neck weakness – loss of head control
- Descending weakness – pharynx, arms, accessory muscles of respiration, diaphragm, lower body
- Respiratory failure may be the first sign if onset is very rapid
- Loss of gag reflex and tendon reflexes
- Autonomic disturbance
- Death from airways obstruction and respiratory muscle paralysis
- Mortality reduced by early administration of antitoxin and good supportive care

Note Often diagnosed late: misdiagnoses have included anxiety, Guillain-Barre syndrome (preceding febrile illness, ascending paralysis, paraesthesiae, CSF/EMG findings); myasthenia gravis (recurrent paralysis, sustained response to anticholinesterase test, EMG); intoxication eg carbon monoxide, organophosphates, mushrooms, magnesium, alcohol (history, toxicology); stroke (usually asymmetric, abnormal brain scan); and rarely, polio (fever, asymmetry), tick paralysis (ascending paralysis, tick on skin), CNS viral infections (altered consciousness, CSF, EMG), and psychiatric illness

Management

- If diagnosis suspected, discuss with senior emergency medicine clinician and consultant microbiologist, arrange immediate assessment by ID physician, and immediately alert local Health Protection Team
- NO risk of person to person spread: use STANDARD precautions
- Take a clear and detailed food history
- Obtain 10mls serum; 10g faeces (in sterile container) and other (gastric washings/lavage; bronchial washings/lavage; pus from abscess/wound; wound swab in transport medium) as appropriate, for urgent toxin detection by reference laboratory
- Obtain samples for toxin detection before giving any antitoxin
- Tests that may help in excluding diagnosis include: brain scan, EMG, CSF examination, Tensilon™ test
- ID physician will provide expert advice about further management, and about giving antitoxin (botulinum antitoxin is held in regional centres and HPA Centre for Infections)
- Decision to give antitoxin is made clinically, and not on laboratory test results
- Antibiotics (penicillin with metronidazole) indicated only for wound botulism; if wound botulism, may also need surgical debridement
- Monitor and support respiratory function: intubate, ventilate (possibly long term); treat secondary infection

See also

- Emergency contacts, personal protective equipment, post-exposure prophylaxis, infection control, microbiological testing, biological incident action guide, picture gallery

Think of brucellosis

In any with **previously healthy patient** with:

- Fever of unknown origin, *or*
- Endocarditis (culture negative), *or*
- Hepatitis (negative for HAV, HBV, HCV markers with granulomata on biopsy)
- **A single confirmed case with no history of travel to endemic area or of occupational exposure suggests deliberate release**

Key facts

- Caused by *Brucella abortus*, *Brucella melitensis*, or *Brucella suis* (tiny Gram negative coccobacilli)
- Zoonosis (disease that affects animals and man), affecting cows (*Brucella abortus*), sheep, goats and camels (*B melitensis*), pigs (*B suis*), and other mammals
- Animal disease is now rare in UK, but still common in some parts of Europe, M East, Africa, Asia, S and C America (including Mexico), and the Caribbean
- Naturally acquired human infection follows drinking unpasteurised milk or eating unpasteurised milk products from infected animals; breathing in the organism or directly contaminating the eyes, nose, mouth or abraded skin during close contact with infected animals, products of conception, or carcasses, or while working with the organism in the laboratory, and the accidental inoculation of live attenuated animal vaccine
- Human disease uncommon in UK (< 20 reported cases each year, usually acquired abroad)
- *B melitensis*, *B abortus* and *B suis* cause similar human illnesses (*B melitensis* causes the most severe disease); clinical features do not depend on route of exposure
- Occupational risks for: animal handlers, vets, meat packers and abattoir workers exposed to infected animals, carcasses, or contaminated dust (eg when washing down buildings); laboratory workers
- Incubation period usually 1-3 weeks, but may be longer (up to 6 months)
- Diagnosis easily missed as symptoms are variable and non-specific

Symptoms and signs

Acute brucellosis

- Fever, often undulant/irregular
- Chills, sweats, malaise, fatigue, exhaustion
- Loss of appetite, weight loss
- Headache
- Myalgia, joint pain (sacroiliac and other large joints)
- Low back pain (lumbar tenderness)
- Dry cough, pleuritic chest pain
- Depression, mood change, irritability
- Physical examination usually normal but may have:
 - Hepatosplenomegaly, generalised lymphadenopathy
 - Meningoencephalitis (rare, < 5% of all cases)
 - Endocarditis (rare, 1-2% of all cases)

Chronic brucellosis (symptoms for at least 1 year)

- Intermittent low grade fever, chills, sweats
- Malaise, fatigue
- Weight loss
- Depression (may be severe, or main symptom)
- Arthritis
- Back pain (vertebral osteomyelitis, paravertebral abscess)
- Hepatosplenomegaly
- Endocarditis
- Mortality low (< 5%) but morbidity considerable

Management

- Discuss with senior emergency medicine clinician and consultant microbiologist, arrange urgent ID consultation; inform local Health Protection Team if diagnosis confirmed
- NO risk of person to person spread: use STANDARD precautions
- Diagnosis most often made serologically: 10mls clotted blood (and further sample at least 14 days post onset); culture blood (multiple sets, which will need prolonged incubation in laboratory – make sure request forms mention the possible diagnosis), bone marrow aspirate, other (eg joint aspirate, pleural fluid); high risk of laboratory-acquired infection, label all samples 'danger of infection'
- If possible take cultures BEFORE starting antibiotics
- CXR: usually normal, rarely enlarged hilar nodes, pleural effusion; LFTs: often mildly abnormal; FBC: sometimes anaemia, leucopaenia, thrombocytopenia
- If neurological signs consider brain scan, CSF; refer cardiology if signs of endocarditis (surgical treatment may be required)
- Initial treatment for adults:
 - Doxycycline 100mg orally or IV bd
 - and either
 - Rifampicin 600mg-900mg orally *or* streptomycin 1g/day IM [maximum 3 weeks] *or* gentamicin 5mg/kg/day IM or IV
 - Check drug levels of streptomycin or gentamicin if used; monotherapy with rifampicin preferred for pregnant women
 - Duration of treatment depends on disease severity, patient age and response to treatment
- Initial treatment for children: gentamicin 5mg/kg/day IM for 5 days and cotrimoxazole (standard paediatric dose) orally for 3 weeks
- Treatment response indicated by resolution of fever and other symptoms, and weight gain
- Relapses may occur: follow up (check compliance) at 3 weeks and 6 weeks, then every 3 months for 1 year

See also

- Emergency contacts, personal protective equipment, post-exposure prophylaxis, infection control, biological incident action guide, microbiological testing

Think of glanders

In any **previously healthy patient** with:

- Cavitating pneumonia unresponsive to standard antibiotic or antituberculous therapy, *or*
- Severe unexplained sepsis, especially if cluster of linked cases, *or*
- Severe febrile illness with bloody nasal discharge or eye infection or visceral abscesses
- **In UK, a single confirmed case with no history of laboratory exposure suggests deliberate release**

Key facts

- Caused by *Burkholderia mallei* (formerly *Pseudomonas mallei*), a small Gram negative bacillus
- Zoonosis (disease of animals and man); primarily a disease of horses, donkeys, and mules
- Animal disease no longer occurs in the UK, but still occurs in Turkey, M East, parts of Africa, and S and SE Asia
- Naturally acquired human disease is the result of close contact with an infected animal or carcass, or a laboratory exposure; there is no environmental reservoir
- Infection acquired by direct contact of organism with cut or abraded skin, or eyes, nose or mouth, or by inhalation
- Occupational risks: work with organism in laboratory; in endemic areas, risk for stablehands, muleteers, vets and abattoir workers exposed to infected animals or carcasses
- Considered as a bioweapon in both World War I (eg to infect mules on Eastern front) and World War II
- Incubation period for human disease usually 10-14 days
- Human disease rare; very little recent clinical experience on which to base recommendations

Symptoms and signs

Localised glanders	Pulmonary glanders	Septicaemic glanders
<ul style="list-style-type: none"> • Fever, chills, malaise • Headache, myalgia • Local or generalised pustular ulcers • Local lymphadenopathy • Purulent or bloody nasal discharge 	<ul style="list-style-type: none"> • Fever, chills, malaise • Headache, myalgia • Productive cough • Dyspnoea • Chest pain • CXR: multifocal consolidation, effusion, cavitation, lung abscess 	<ul style="list-style-type: none"> • Fever, chills, malaise • Headache, myalgia • Septic shock • Multiple abscesses – common sites are liver, kidney, spleen • Multi-organ failure • High mortality if untreated

Management

- If diagnosis suspected, discuss with senior emergency medicine clinician and consultant microbiologist, arrange urgent ID consultation, and alert local Health Protection Team (HPT)
- Very low risk of person to person spread: use STANDARD precautions and exclude immunocompromised staff (including diabetics) from direct patient care
- Culture blood, urine, sputum, other (eg pus if suppurative lesions present), 10mls clotted blood for serology (and further sample at least 14 days post onset); exclude pulmonary TB if lung lesions (sputum for AAFBs and culture)
- If possible take cultures BEFORE starting antibiotics
- Initial treatment of severe disease: minimum 2 weeks IV therapy with:
 - Ceftazidime 120mg/kg/day (usual adult dose 2g IV tds) *or*
 - Meropenem 50mg/kg/day (usual adult dose 1g IV tds) *or*
 - Imipenem/cilastatin 50mg/kg/day (usual adult dose 1g IV tds) *or*
 - Gentamicin 5mg/kg IV once daily and oral co-trimoxazole 8/40mg/kg/day
 - Ciprofloxacin is NOT recommended
- For initial oral treatment of mild disease or oral eradication treatment of severe disease (20 weeks treatment in total):
 - Doxycycline 4mg/kg/day and co-trimoxazole 40/8mg/kg/day *or*, particularly for children and pregnant women, co-amoxiclav, expressed as amoxicillin, 60mg/kg/day (adult dose, expressed as amoxicillin, 500mg orally tds)
- Consider surgical drainage of abscesses
- Disease may relapse or recur: long term (minimum 5 years) follow up required

See also

- Emergency contacts, personal protective equipment, infection control, post exposure prophylaxis, microbiological testing, biological incident action guide

Think of melioidosis

In any **previously healthy patient** with:

- Cavitating pneumonia unresponsive to standard antibiotic or antituberculous therapy, *or*
- Rapid onset of severe unexplained sepsis, especially if cluster of linked cases
- **In UK, a single confirmed case with no history of laboratory work or of travel to endemic area suggests deliberate release**

Keys facts

- Caused by *Burkholderia pseudomallei* (formerly *Pseudomonas pseudomallei*), a small Gram negative bacillus
- Does not occur naturally in the UK, 1-2 imported cases each year
- Common in South Asia and SE Asia particularly in paddy-rice growing areas, and Northern Australia; cases also reported from Africa and Central and Southern America
- Naturally acquired infection follows contact of contaminated water with cut or abraded skin, swallowing/aspirating contaminated water (eg in near-drowning incidents), or breathing in contaminated dust
- Clinical features of primary disease (skin/soft tissue infection or pneumonia) depend on route of exposure, but presentation is highly variable
- Incubation period extremely variable: for acute infection, 1-21 days (mean 9 days) but disease may occur years after exposure, particularly in the immunocompromised (diabetes, chronic renal failure, steroid treatment, cystic fibrosis)
- Occupational risks for: laboratory workers; in endemic areas, rice farmers and agricultural workers
- *B pseudomallei* is intrinsically resistant to many antibiotics. Think of melioidosis if a Gram negative oxidase positive non-fermenter resistant to gentamicin and colistin but sensitive to co-amoxiclav is grown from blood, pus or sputum

Symptoms and signs

Skin and soft tissue melioidosis	Pulmonary melioidosis	Septicaemic/disseminated melioidosis
<ul style="list-style-type: none"> • Primary site of infection after trauma/inoculation or result of metastatic spread through bloodstream • Fever, chills, malaise • Local lymphadenopathy • Cellulitis • Subcutaneous nodules • Abscess (parotid gland in children) • Skin pustules 	<ul style="list-style-type: none"> • Primary site of infection after inhalation or result of metastatic spread through bloodstream • Fever, chills, malaise • Productive cough • Dyspnoea • Chest pain • CXR: multifocal consolidation, often of upper lobes with apical sparing, cavitation, lung abscess 	<ul style="list-style-type: none"> • Fever (may be high, swinging) • Chills, malaise, sweats • Multiple abscesses – common sites are liver, spleen, kidney; also bone, prostate, brain • Septic shock • Multiple organ failure • 100% mortality if untreated • 40% mortality with treatment

Management

- If diagnosis suspected, discuss with senior emergency medicine clinician and consultant microbiologist, arrange urgent ID consultation, and alert local Health Protection Team (HPT)
- Very low risk of person to person spread: use STANDARD precautions and exclude immunocompromised staff (including diabetics) from direct patient care
- Culture blood, urine, sputum, other (eg pus if suppurative lesions present); 10mls clotted blood for serology (and further sample at least 14 days post onset); exclude pulmonary TB if lung lesions (sputum for AAFBs and culture)
- If possible take cultures BEFORE starting antibiotics
- *B pseudomallei* is NOT sensitive to aminoglycosides (eg gentamicin, amikacin); ciprofloxacin is not recommended as treatment
- Initial treatment of severe disease: minimum 2 weeks IV therapy with:
 - Ceftazidime 120mg/kg/day (usual adult dose 2g IV tds) *or*
 - Meropenem 50mg/kg/day (usual adult dose 1g IV tds) *or*
 - Imipenem/cilastatin 50mg/kg/day (usual adult dose 1g IV tds)
- For initial oral treatment of mild disease, or oral eradication treatment of severe disease (20 weeks treatment in total):
 - Doxycycline 4mg/kg/day + co-trimoxazole 40/8mg/kg/day *or*, particularly for children and pregnant women, co-amoxiclav, expressed as amoxicillin, 60mg/kg/day (adult dose, expressed as amoxicillin, 500mg orally tds)
- Consider surgical drainage of abscesses
- Disease may relapse or recur: long term (minimum 5 years) follow up required

See also

- Emergency contacts, personal protective equipment, infection control, post exposure prophylaxis, microbiological testing, biological incident action guide

Think of plague

In any **previously healthy patient** with:

- Rapid onset of severe unexplained febrile respiratory illness, *or*
- Unexplained death following a short febrile or septicaemic illness, *or*
- Pneumonia with haemoptysis, especially if two or more linked cases
- **A single case of plague acquired in the UK suggests deliberate release**

Key facts

- Caused by *Yersinia pestis* (small Gram negative coccobacillus)
- Zoonosis (disease that affects animals and humans) – spread between fleas and small rodent reservoirs
- Does not occur naturally in UK
- 1500-3000 reported cases worldwide each year from Africa, Asia, and Americas (including US)
- Naturally acquired human disease usually the result of a bite from an infected flea
- Clinical features depend on route of exposure: bite of infected flea causes bubonic plague; breathing in organism causes pneumonic plague; direct inoculation of *Y pestis* into bloodstream, or progression of bubonic or pneumonic plague cause septicaemic plague
- Occupational risks: laboratory work on organism; in endemic areas outside UK, animal trapping, hunting, or skinning
- Deliberate release most likely to be via aerosol, causing pneumonic plague
- **Person to person spread of pneumonic (but not bubonic or septicaemic) plague CAN occur**

Symptoms and signs

Bubonic plague	Pneumonic plague	Septicaemic plague
<p><i>Incubation period 2-8 days</i></p> <ul style="list-style-type: none"> • Fever • Bubo – a swollen, very painful, tender lymph node draining the site of the flea bite (usually in the groin, axilla or on the neck); overlying skin is red and indurated • Buboes are usually unilateral • Hypotension, confusion • With antibiotics, 95% of cases recover • Untreated can progress to plague pneumonia, septicaemia or meningitis, and death • No person to person spread if no progression to pneumonia 	<p><i>Incubation period 2-4 days</i></p> <ul style="list-style-type: none"> • Fever, chills, sweats • Headache, severe malaise • Vomiting, diarrhoea • Cough, increasing dyspnoea • Watery sputum, may be bloody • Associated chest pain • CXR – multilobar consolidation, bilateral infiltrates, effusions • Rapid progression to shock/ARDS/ respiratory failure • 100% mortality if untreated • Early antibiotic Rx critical • Person to person spread by droplet infection occurs readily 	<p><i>Incubation period 1-8 days</i></p> <ul style="list-style-type: none"> • Most often from progression of untreated bubonic or pneumonic forms, but may occur without signs of infection elsewhere • Fever, chills, sweats • Gram negative shock • Purpura/peripheral gangrene • DIC • High mortality if untreated
		<p>Rare presentations</p> <ul style="list-style-type: none"> • Plague meningitis • Pharyngeal plague – cervical nodes + tonsillitis

Management

- If diagnosis suspected, discuss with senior emergency medicine clinician and consultant microbiologist, arrange immediate assessment by ID physician, and immediately alert local Health Protection Team (HPT)
- If pneumonic plague suspected (or confirmed) put patient in side room or cubicle, and enforce STANDARD and RESPIRATORY precautions for 72 hours after starting antibiotic treatment; with local HPT arrange post-exposure prophylaxis for close contacts
- Culture blood, sputum, other specimens (eg bubo aspirate, pleural fluid, CSF); 10mls clotted blood for serology (and further sample at least 14 days post onset); 20mls blood in EDTA tubes on admission for PCR
- If possible take cultures BEFORE starting antibiotics
- CXR: multilobar consolidation, bilateral infiltrates, pleural effusion/s
- Initial treatment:
 - Gentamicin at standard doses for severe sepsis according to local protocol, *or*
 - Ciprofloxacin 400mg IV bd (adults) or 15mg/kg IV bd (children)
- For mild adult cases: ciprofloxacin 500-750mg orally bd
- For mild paediatric cases: ciprofloxacin 20mg/kg orally bd
- For plague meningitis: use chloramphenicol 25mg/kg IV qds
- Check levels of gentamicin or streptomycin if used; expect clinical response in 36-48 hours

See also

- Emergency contacts, personal protective equipment, post-exposure prophylaxis, infection control, microbiological testing, biological incident action guide, picture gallery

Think of Q fever

In any **previously healthy patient** with:

- Community acquired pneumonia, especially if two or more linked cases, *or*
- Endocarditis (culture negative), *or*
- Hepatitis (negative for HAV, HBV, and HCV markers, with granulomata on biopsy)

Keys facts

- Caused by *Coxiella burnetii* (small Gram negative pleomorphic coccobacillus – difficult and dangerous to grow)
- Zoonosis (disease that affects animals and man): worldwide distribution, with reservoirs in sheep, cattle, goats, and other mammals – infected animals usually asymptomatic but shed the organism in large numbers in placental tissue, amniotic fluid, milk, urine and faeces
- *C burnetii* is resistant to heat and drying, so survives well in the environment
- Infectious dose is very low (can be just one organism)
- Naturally acquired human infections usually caused by breathing in organism (eg when birthing infected animal, from contaminated dust, from aerosols in laboratory work); rarely, from eating or drinking unpasteurised milk or unpasteurised milk products
- 50% human infections are asymptomatic; symptomatic infection may be more common in smokers
- In UK: 50-100 reported cases of human infection each year; 1% of all cases of community acquired pneumonia; most cases are sporadic, but outbreaks occur
- Incubation period of acute Q fever usually 18-21 days (range 4-40 days), may be shorter if large infective dose; chronic Q fever may occur years after untreated primary infection
- Occupational risks for: farmers, shepherds, vets and abattoir workers exposed to infected animals, their body fluids or carcasses, or contaminated dust (eg when washing down buildings); laboratory workers

Symptoms and signs

Acute Q fever

- Fever (often abrupt onset, high)
- Malaise, fatigue, sweats
- Headache, myalgia
- Dry cough (25% of symptomatic infections)
- No rash
- Hepatitis (30% of symptomatic infections)
- Often self-limiting after 1-2 weeks
- Rarely, aseptic meningitis, endocarditis

Chronic Q fever

- Fever
- Weight loss, malaise, fatigue
- Aseptic meningitis/meningoencephalitis
- Endocarditis (75% aortic valve; usually affects prosthetic valve or damaged native valve)
- Needs prolonged (minimum 2 years) antibiotic treatment, and usually, surgical valve replacement if endocarditis

Management

- If diagnosis suspected, discuss with senior emergency medicine clinician and consultant microbiologist, arrange urgent ID consultation; if confirmed, alert local Health Protection Team (HPT)
- NO risk of person to person spread: use STANDARD precautions
- Diagnosis is usually serological: 10mls clotted blood for Q fever serology (and convalescent sample at least 28 days post onset); histology/immunocytochemistry (eg of liver biopsy) sometimes also helpful
- CXR: abnormal in 50% of symptomatic infections: patchy infiltrates, lobar consolidation, enlarged hilar nodes
- LFTs: raised (2-3 x normal) transaminases, bilirubin usually normal
- FBC: normal, or raised WCC, sometimes thrombocytopenia
- If neurological signs, consider brain scan, CSF; refer to cardiology if signs of endocarditis (surgical Rx may be required)
- Although untreated infection is usually self-limiting, antibiotic Rx reduces the risk of chronic infection and speeds recovery
- Initial treatment for acute Q fever for adults:
 - Doxycycline 100mg bd orally or IV, *or*
 - Tetracycline 500mg orally qds, *or*, if pregnant or breast-feeding,
 - Co-trimoxazole 960mg orally bd
- Initial treatment for children: Co-trimoxazole 24 mg/kg orally bd
- Treatment response (usually within 2-3 days) indicated by resolution of fever and of other symptoms
- Treatment of chronic Q fever or Q fever endocarditis requires long term combined antibiotic therapy: seek expert advice

See also

- Emergency contacts, personal protective equipment, post-exposure prophylaxis, infection control, biological incident action guide, microbiological testing

Severe acute respiratory syndrome (SARS)

Think of SARS

Any patient who meets this definition has SARS until proven otherwise:

Fever more than 38°C **AND** cough or dyspnoea or breathing difficulty **AND** in the 10 days before onset of illness, has:

- Travelled to/from a SARS zone of re-emergence (check www.hpa.org.uk), *or*
- Had close contact with other case(s) of severe respiratory illness from a SARS zone of re-emergence, *or*
- Worked in a laboratory with possible exposure to SARS coronavirus, *or*
- Had close contact with a health care worker with a severe unexplained respiratory illness

Key facts

- Caused by a human coronavirus discovered in 2003, SARS coronavirus does not occur naturally in the UK
- First cases were seen in Southern China in late 2002. Rapid person to person spread of virus caused outbreaks in Hong Kong SAR, Vietnam, Singapore and Canada in 2003, with more than 8000 cases in more than 30 countries
- Further cases in Singapore, Taiwan and China in late 2003 and 2004 were associated with laboratory-acquired infections
- Mortality during outbreaks 15% in hospitalised cases overall, higher in elderly and those with pre-existing illness; SARS in children less than 10 yrs was mild and uncommon
- Infection usually acquired by droplet transmission (breathing in virus particles from respiratory secretions) during close contact with a symptomatic case, or by contamination of eyes, mouth or nose with respiratory secretions, body fluids, or faeces of a case
- No antiviral drug (eg ribavirin) or other drugs, such as steroids, have been proven to be effective; treatment is essentially supportive
- Incubation period (from exposure to onset of fever): 3-7 days (range 2-10 days, average 5 days)
- Asymptomatic contacts are not infectious; cases are non-infectious from 10 days after resolution of fever
- **Health care workers caring for cases are at high risk of becoming infected if infection control is inadequate**
- Rapid detection and early isolation of cases, and early and effective infection control, are central to control of SARS

Symptoms and signs	Investigation (treat samples as 'high risk')
Initial symptoms <ul style="list-style-type: none">• Fever, chills, rigors• Malaise, myalgia, headache• Diarrhoea (sometimes)	<ul style="list-style-type: none">• CXR, pulse oximetry, ABG if O₂ saturation on air less than 95%• FBC & differential, U & Es, LFTs, creatinine, CK, LDH, CRP• Blood cultures• Clotted blood for acute serology (mycoplasma, legionella, chlamydiae, influenza A and B, adenovirus, RSV) + 20mls reserve; second sample at 21 days post onset• Sputum culture +/- Gram stain• Respiratory sample for rapid tests for influenza A and B, and RSV• Urine for legionella and pneumococcal antigens• Specialist investigations for SARS in liaison with local microbiologist and HPA Centre for Infections, Colindale
Followed, after 2-4 days by <ul style="list-style-type: none">• Cough• Breathing difficulty• Respiratory failure, ARDS, death• Rash, lymphadenopathy or CNS signs may make Dx less likely• Spectrum of disease – many cases will be relatively mild, and will not require hospital admission	

Management

- Assess all patients with febrile respiratory illness in a side room: patient to wear surgical mask; staff (including radiographer) to wear surgical mask, gown, gloves, pay scrupulous attention to handwashing and minimise hand-face or glove-face contact; restrict entry to essential staff and relatives
- Determine the date of onset of symptoms and obtain a travel, occupational, and contact history for the 10 days before onset
- If patient does not fit case definition, unlikely to be SARS: manage as condition indicates
- If patient satisfies case definition, and condition warrants hospital admission:
 - Discuss with senior emergency medicine clinician and consultant microbiologist; arrange immediate ID assessment; alert local Health Protection Team (HPT) and Occupational Health
 - Arrange admission to single isolation (ideally negative pressure) room, with AIRBORNE INFECTION ISOLATION precautions (use FFP3 mask)
 - Minimise aerosol-provoking procedures (high risk to health care workers of infection); avoid high flow (6L/min, or more) oxygen
 - Antibiotics according to local treatment protocol for community acquired pneumonia *or*
 - Co-amoxiclav 1.2G IV tds (*or* cefuroxime 1.5g tds) **and** erythromycin 500mg IV qds (*or* clarithromycin 500mg bd)
 - List patient's close contacts (household, face-to-face – within 1 metre, health care workers, others) in 10 days before onset
- Re-assess at 48 hours: if CXR and clinical course consistent with SARS, and no alternative diagnosis, send specialist Ix for SARS in liaison with HPA Centre for Infections, if not, remove from airborne infection isolation if appropriate, continue treatment and inform local HPT
- If patient fits case definition but condition does not warrant hospital admission, arrange follow up at 48 hours by primary care or local HPT to reassess and confirm recovery. Clinical staff should observe appropriate respiratory precautions when in patient's home (including wearing FFP3 mask)

See also

- Detailed HPA guidance on SARS can be found at: www.hpa.org.uk, and guidelines on clinical management can be found at the British Thoracic Society website at: www.brit-thoracic.org.uk
- Emergency contacts, personal protective equipment, infection control, microbiological testing, biological incident action guide, picture gallery

Think of smallpox

In any **previously healthy patient** with:

- Abrupt onset of moderate (to 39°C) fever and severe prostration *and*
- A characteristic rash: begins on third day of illness, densest on extremities and face, and with all pocks on any one part of body at the same stage of development
- **A single suspected case of smallpox is a public health emergency**

Key facts

- Caused by a DNA orthopox virus
- Smallpox eradication was certified in 1980; only remaining smallpox virus is secured in two laboratories in US and Russian Federation; there is no current evidence of illicit stocks of virus
- Only possible sources of infection now are an accidental release from a repository or deliberate release
- Routine vaccination ceased 30 years ago, and the population is no longer immune to smallpox
- May cause severe disease: mortality rate in outbreaks was 25-30%; highest in children less than 1 year, and the elderly
- Usually acquired by airborne route, but infection can follow direct contact of eyes, nose or mouth with vesicle fluid, respiratory secretions, saliva, or scabs
- Incubation period (from exposure to onset of illness) usually 10-16 days (range 7-19 days, median 12 days)
- Person to person spread occurs (secondary attack rate 10-25%); infectious dose low (probably 10-100 virions)
- Cases are infectious to others from onset of fever until all scabs have separated
- Asymptomatic afebrile contacts are not infectious
- Outcome of any release will be determined by speed of diagnosis and management of initial cases and contacts

Symptoms and signs

Clinical course of smallpox	Clinical course of chickenpox	Differential diagnosis of smallpox
<ul style="list-style-type: none"> • Febrile prodrome (days 1-3): sudden onset fever, malaise, headache, backache, prostration, vomiting, abdominal pain – patients are usually anxious and poorly • Erythematous rash (days 2-3) May become haemorrhagic • Maculopapular rash (days 4-6) • Vesicular rash becomes pustular (days 5-14+) as clear fluid in blisters becomes cloudy and thickens. Pustules are round, tense and deep in dermis, and feel like small hard peas in the skin. Rash may affect palms and soles, and is densest on face and extremities • Complications include haemorrhage, encephalitis, keratitis, multi-organ failure • Scabs form (days 10-14), separate (days 14-28), heal with scarring • Death can occur in first 48 hrs, before the rash develops 	<ul style="list-style-type: none"> • Incubation period 14-21 days • No history of chickenpox • Febrile prodrome usually mild or non-existent, patient usually not severely unwell • Rash is densest on trunk, with relative sparing of face and extremities, not usually present on palms and soles • Rash itches, evolves rapidly, lesions superficial, oval and appear in crops – macules, papules, vesicles and pustules at the same time on any one part of body • Scabs form quickly (day 4-7), separate rapidly (before day 15) • Caused by DNA herpes virus, can be distinguished from pox virus by electron microscopy • Aciclovir effective in treatment 	<ul style="list-style-type: none"> • Febrile prodrome: influenza, malaria, meningitis, typhoid • Erythematous stage: measles, rubella, parvovirus B19 • Papular stage: measles, chickenpox • Later rash: chickenpox, monkeypox, disseminated herpes simplex, disseminated herpes zoster, drug rash, contact dermatitis, hand foot and mouth disease, Stevens Johnson syndrome, erythema multiforme, molluscum contagiosum, scabies, impetigo

Management

- If you suspect smallpox, **IMMEDIATELY put a surgical mask on the patient and ISOLATE patient** (and any accompanying relatives or friends) **in a SINGLE room**. Close the door, and restrict entry to essential personnel. Admitting doctor to remain with patient, provide reassurance and any immediately necessary supportive care
- Senior emergency medicine clinician to assess patient in the room. If smallpox cannot be excluded, then:
 - If patient arrived by ambulance, ensure that ambulance is taken out of service until smallpox excluded or ambulance decontaminated
 - Alert consultant microbiologist, ICD, Trust Management, and local HPT and **IMMEDIATELY** arrange for URGENT assessment of case by local designated Smallpox Diagnostic Expert (SDE)
 - Enforce STANDARD and AIRBORNE infection control precautions
 - Current advice is to switch off air conditioning – and leave it off until smallpox excluded or system decontaminated
- If Smallpox Diagnostic Expert (SDE) suspects smallpox, SDE will alert Smallpox Management and Response Team (SMART) and assume responsibility for patient care and infection control until SMART arrives, when SMART will take over investigation, diagnosis, treatment planning and arrange any necessary vaccinations
- If SDE excludes smallpox, inform all those notified, stand down all action, arrange further patient management

See also

- Emergency contacts, personal protective equipment, post-exposure prophylaxis, infection control, biological incident action guide, microbiological testing, picture gallery
- Detailed special plans for investigation and treatment of smallpox can be found on www.dh.gov.uk

Think of tularemia

In any **previously healthy patient** with:

- Severe unexplained febrile illness or febrile death *or*
- Fever, single painful ulcer, with tender local lymphadenopathy, *or a*
- Cluster of cases of unexplained pneumonic or febrile illness

Key facts

- Caused by *Francisella tularensis* (tiny Gram negative coccobacillus, several biovars, difficult and dangerous to grow)
- Zoonosis (disease that affects animals and humans) – reservoirs in small mammals eg rabbit, lemming, vole
- Does NOT occur naturally in UK but common in parts of rural Europe, Asia, Americas and Australasia
- Naturally acquired human disease follows exposure by: bite of infected vector (tick, mosquito, deerfly); handling infected animal or carcass; breathing infected aerosol (from infected animal or carcass, contaminated hay, lawn mowing); eating contaminated food or water
- Clinical features depend on route of exposure: breathing in organism causes pneumonia; infection via bite or abraded skin causes ulcero/glandular disease; ingestion causes oropharyngeal disease; eye inoculation (eg by rubbing eyes with contaminated hands) causes oculoglandular disease
- Severity depends on infecting biovar (type A most severe, < 10 organisms can infect), and dose
- Occupational risks: in UK, laboratory work; outside UK, in endemic areas, hunting, trapping, or farming
- Deliberate release most likely to be via aerosol, causing pneumonic tularemia
- Incubation period usually 2-5 days (range 1-14 days)

Symptoms and signs

<p>Ulcero-glandular and glandular tularemia</p> <ul style="list-style-type: none"> • Fever, headache, myalgia, chills • Local lymphadenopathy – depends on site of inoculation – glands tender, painful, may be fluctuant • +/- Tender papule or ulcer at site of inoculation 	<p>Oculoglandular tularemia</p> <ul style="list-style-type: none"> • Fever, headache, myalgia, chills • Unilateral painful red eye • Eye exudate • +/- Corneal ulcer • Tender, swollen periauricular lymph nodes 	<p>Oropharyngeal tularemia</p> <ul style="list-style-type: none"> • Fever, headache, myalgia, chills • Sore throat • Exudate • Tender swollen cervical lymph nodes • +/- Pharyngeal/tonsillar ulcer/stomatitis
<p>Without antibiotics, infection will persist for weeks or months (fever, weight loss, malaise, fatigue) or may progress to:</p>		
<p>Pneumonic tularemia</p> <ul style="list-style-type: none"> • Follows inhalation of organism, or spread through bloodstream from primary site • Fever, chills, headache, myalgia, sore throat • Dry cough, pleuritic chest pain, dyspnoea • Physical signs and CXR variable • Untreated, can progress to respiratory failure, death 	<p>Septicaemic tularemia</p> <ul style="list-style-type: none"> • Follows primary exposure to organism, or spread through bloodstream from primary site • Fever, chills, headache, myalgia • Nausea, vomiting, diarrhoea, abdominal pain • Confusion, altered consciousness, coma • Septic shock, DIC, haemorrhage, ARDS 	

Management

- If diagnosis suspected, discuss with senior emergency medicine clinician and consultant microbiologist, arrange urgent ID consultation, and alert local Health Protection Team (HPT)
- Very low risk of person to person spread: use STANDARD precautions
- Culture: blood (organism hard-to-grow, take multiple sets and mention diagnosis on request form), and other specimens as appropriate eg sputum, throat swab/washings, fasting gastric aspirate, swab exudate/aspirate of any ulcer/local lesion; 10mls clotted blood + 20mls blood in EDTA tubes for serology/PCR (and further sample at least 14 days post onset); high risk of laboratory acquired infection: label all samples 'danger of infection'
- If possible take cultures BEFORE starting antibiotics
- Dermatology/ID referral for review and biopsy of any skin lesion (histology, PCR)
- CXR: may be near-normal, or multilobar infiltrates, enlarged hilar nodes, pleural effusions, adhesions
- Initial treatment if tularemia suspected but not confirmed:
 - Add aminoglycoside at standard doses to existing local protocol appropriate to presentation (eg community-acquired pneumonia, Gram negative sepsis)
- If diagnosis of tularemia confirmed by microbiology:
 - Gentamicin (first choice) 7mg/kg once daily IV (adults); 2.5mg/kg IV/IM tds (children) for 10 days, *or*
 - Streptomycin 1g IM bd (adults); 7.5mg/kg IM bd (children) for 10 days, *or*
 - Ciprofloxacin 400mg IV bd (adults); 10mg/kg-15mg/kg IV bd (children) for 14 days; change to oral treatment when appropriate
- Check levels of gentamicin or streptomycin if used

See also

- Emergency contacts, personal protective equipment, pre and post exposure prophylaxis, infection control, biological incident action guide, microbiological testing, picture gallery

Venezuelan equine encephalitis (VEE)

Think of Venezuelan equine encephalitis

In any **previously healthy patient** with:

- Febrile illness and history of travel in endemic area in the two weeks before onset, *and/or*
- Viral meningitis or encephalitis, *or a*
- Cluster of cases of flu-like illness with encephalitis/neurological symptoms in a small proportion of the cases
- **In the UK, a single confirmed case with no history of recent travel or of occupational risk suggests deliberate release**

Key facts

- Caused by a mosquito-borne alphavirus
- Zoonosis (disease that affects animals and humans) spread by mosquitoes between rodents, bats and birds, and, in outbreaks, horses, mules and donkeys
- Does not occur in UK but common in central and northern parts of S America, also occurs in Mexico and southern USA; natural epidemics in humans are usually preceded by disease in horses
- Naturally acquired human infection usually the result of bite of infected mosquito, but can also follow breathing in the virus in the laboratory
- Occupational risks: outdoor work in an endemic area; work with the organism in a laboratory
- Human-mosquito-human spread has probably occurred in some epidemics, but direct person to person spread is not thought to occur
- Incubation period 1-6 days

Symptoms and signs

Mild or moderate VEE infection

- Fever
- Flu-like illness
- Backache, myalgia, malaise
- Headache
- Mild photophobia
- Sore throat
- Nausea, vomiting, diarrhoea
- Normal neurological exam
- Symptoms last 2-5 days, followed by complete recovery over next 1-2 weeks

Severe VEE infection

- May be more common in children (in natural outbreaks, 4-5% of children but 1-2% of adults)
- Abrupt onset
- High fever (38-40°C), chills, sweats
- Severe backache and myalgia, leg muscles tender
- Severe headache
- Neck stiffness
- Photophobia
- Nausea, vomiting, diarrhoea
- Confusion, sleepiness, altered mental state
- Convulsions, ataxia, paralysis, coma
- 20% fatality rate; neurological sequelae in survivors

Management

- If diagnosis suspected, discuss with senior emergency medicine clinician and consultant microbiologist/ID physician; if diagnosis confirmed, or cluster of suspect cases, alert local Health Protection Team
- Very low risk of person to person spread: use STANDARD precautions
- Exclude malaria (blood film for malarial parasites)
- Diagnosis clinical, confirmed by virus isolation/serology: 10mls clotted blood for serology (and further sample at least 14 days post onset); throat swab in virus transport medium; CSF if lumbar puncture performed
- CSF: increased pressure, raised lymphocytes, mildly elevated protein
- FBC: low WCC & lymphopaenia, and sometimes thrombocytopaenia early in disease; LFTs: mildly raised AST, LDH; CXR: normal
- If insect vectors (mosquitoes) are present, prevent any biting the patient (insecticides, insecticide-treated bed nets, screening)
- Treatment is supportive:
 - Mild/moderate cases: analgesia and antipyretics; correct/maintain fluid balance as needed
 - Severe cases may need intensive supportive care: fluid balance, nutrition, ventilation, anticonvulsants, treatment of secondary infection, and long term follow up

See also

- Emergency contacts, personal protective equipment, post-exposure prophylaxis, infection control, biological incident action guide, microbiological testing

Viral haemorrhagic fevers (VHF)

Think of viral haemorrhagic fever

In any **previously healthy patient** with:

- Fever of unknown origin and recent travel to endemic area or with flushed swollen face/haemorrhage
- **A single confirmed case in the UK, even if from endemic area, should be investigated to exclude deliberate release**

Key facts

- Caused by viruses from four different families: arenaviruses, filoviruses, bunyaviruses, and flaviviruses
- VHFs include Lassa fever, Junin (Argentinean haemorrhagic fever), Machupo (Bolivian haemorrhagic fever), Guanarito (Venezuelan haemorrhagic fever), Congo-Crimean haemorrhagic fever (CCHF), Rift Valley fever, Ebola, Marburg, yellow fever and dengue viruses, and others
- All are zoonoses (diseases that affect animals and humans): distribution of natural disease is governed by the geographic distribution and ecology of the animal reservoir
- VHFs do NOT occur naturally in UK; imported cases are rare (< one a year)
- Route of infection varies: mosquito bite (dengue, yellow fever, Rift Valley fever); tick bite (CCHF); inhalation of dust contaminated with infected rodent droppings/urine (Lassa fever, hantaviruses); needlestick or direct contact of infected blood or body fluids with eyes, nose or mouth (Lassa, CCHF, Ebola, Marburg); most are infectious by aerosol in the laboratory, but no evidence of naturally occurring airborne spread
- For Lassa, Ebola, Marburg and CCHF, **HIGH RISK** of person to person spread and nosocomial infection (spread within health care settings to other patients and/or health care workers) by percutaneous or mucocutaneous exposure to blood or body fluids from febrile symptomatic patients; afebrile, asymptomatic contacts are not infectious
- Incubation periods disease-specific, vary from 1 day - 21 days
- Illnesses range from mild to life threatening, but all VHFs have a febrile prodrome (fever, headache, malaise, myalgia, nausea, vomiting, prostration) of up to 7 days, followed by signs of vascular involvement. In the second week of illness, cases tend either to recover or to deteriorate rapidly
- Differential diagnosis includes: malaria, typhoid, shigella, meningococcal sepsis, leptospirosis, other causes of DIC

Symptoms and signs

Lassa fever	Ebola/Marburg	Congo Crimean HF
<i>Incubation period 3-21 days</i> <ul style="list-style-type: none">• West Africa (Nigeria, Sierra Leone, Guinea, Liberia)• Naturally occurring cases may have stayed in rural endemic areas/seen rodents, though direct contact with rodent not necessary for infection• Slow onset of febrile prodrome• Severe prostration• Sore throat, reddened eyes• Facial oedema, retrosternal pain• Vomiting and diarrhoea• Bleeding in severe cases in second week• Pleural effusion, ascites, encephalopathy• Many cases mild – mortality in outbreaks higher in pregnant women; nerve deafness in 1/3 survivors	<i>Incubation period 2-21 days</i> <ul style="list-style-type: none">• Tropical rain forest areas in Africa (cases in Ivory Coast, Gabon, Congo, DRC, Sudan, Angola)• Reservoir unknown, but in some outbreaks initial cases associated with killing and eating primates• Abrupt onset of febrile prodrome• Severe prostration• Diarrhoea (sometimes bloody), vomiting, dehydration, shock• Maculopapular rash days 3-8• Bleeding• Hiccups• Sleepiness, delirium, coma, restlessness, hepatomegaly, multi-organ failure• Mortality in outbreaks 30%-90%	<i>Incubation period 1-12 days</i> <ul style="list-style-type: none">• Crimea, Balkans, Africa, C & S Asia• Tick bite usual source in naturally occurring cases• Abrupt onset of febrile prodrome• Vomiting, diarrhoea, abdominal pain• Sore throat, reddened eyes• Sleepiness, lethargy• Facial oedema• Petechial rash, palatal petechiae• Bleeding in 75% cases, begins on day 4 or 5• Hepatomegaly; CNS signs (neck stiffness, agitation, coma) in 20%• Mortality in outbreaks 30%-50%

Management

- If you suspect VHF, discuss with senior emergency medicine clinician, and **IMMEDIATELY ISOLATE** patient in single room, close the door, and restrict entry to essential personnel. Admitting doctor to remain with patient, provide reassurance and any immediately necessary supportive care
- Enforce STANDARD and AIRBORNE infection control precautions
- **IMMEDIATELY** arrange URGENT assessment by ID physician and consultant microbiologist/ICD who will categorise case according to risk and arrange admission to High Security Infectious Disease Unit if needed; for further details of risk categorisation and case investigation and management, see ACDP guidance (can be found via www.hpa.org.uk); alert local Health Protection Team
- Minimise investigation until VHF confirmed or excluded. Diagnosis of VHF is made by antigen detection/serology: 10ml clotted blood (obtained by staff experienced in phlebotomy), further sample at least 14 days post onset, but seek advice from ID physician and await risk categorisation before obtaining any samples from the patient. Blood film +ve for malaria parasites may not exclude diagnosis of VHF; do NOT take fingerprick sample or make direct blood smear for malaria parasites – laboratory will do this using blood from EDTA sample)
- Treatment mainly supportive: analgesia, sedation, oxygen, minimise invasive procedures, avoid antiplatelet drugs (including aspirin) and IM injections, correct and maintain fluid balance, correct coagulopathy, treat secondary infection
- Ribavirin effective in Lassa fever and Congo-Crimean haemorrhagic fever but not for Marburg, Ebola, or flaviviruses:
 - For adults, initial dose ribavirin 30mg/kg IV, then 15mg/kg IV tds for 4 days, then 7.5mg/kg IV tds for 6 days; or
 - Oral treatment: ribavirin 2g orally (loading dose), then 1g orally qds for 4 days, then 0.5g orally tds for 6 days; total treatment 10 days

See also

- Emergency contacts, personal protective equipment, post-exposure prophylaxis, infection control, microbiological testing, biological incident action guide, picture gallery