

chapter
96**Practice Points**

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a. Management of candiduria in the intensive care unit

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Introduction

Candiduria can be defined as the presence of greater than 10^5 fungal cfu/ml urine, though as little as 10^3 cfu/ml can result in disease in certain 'at-risk' groups. The prevalence of candiduria varies between 6.5% and 20% amongst hospitalized patients and presents a dilemma to clinicians, who must decide if the finding represents colonization alone or is a feature of invasive fungal infection. Probably only 3–4% of cases of candiduria lead to candidemia, but 10% of all cases of candidemia are associated with a prior episode of candiduria. Indeed, studies based in the intensive care unit (ICU) have shown that candiduria can be associated with a rise in mortality from 19% to 50%.

Pathogenesis

Candiduria can arise in several ways: simple contamination of specimens at the time of procurement can account for many such cases, hence the need for a confirmatory second specimen. Colonization of the urinary tract may occur in the catheterized patient. Local infection of both the lower urinary tract (cystitis, urethritis) and upper tract (pyelonephritis) with *Candida* spp. is encouraged by urological instrumentation, in particular catheterization. Other factors predisposing to such infections include ongoing broad-spectrum antibiotic therapy, diabetes mellitus, renal insufficiency and anatomic anomalies of the urinary tract. Finally, patients with disseminated candidiasis may seed the urinary tract from bloodstream spread (Table 96a.1).

Microbiology

The majority (50–70%) of *Candida* isolates from urine in the ICU are *C. albicans*, which is sensitive to fluconazole. Indeed, provided that patients have not previously been exposed to fluconazole, it is reasonable to assume that any germ tube-positive yeast will be sensitive to fluconazole. However, increasing numbers of yeasts other than *C. albicans* occur in the ICU setting and the prevalence varies between units. In particular, *C. tropicalis* and *C. glabrata* account for 10–20% of such isolates, the latter species being notable for its resistance to azole drugs.

Clinical features

Candiduria alone does not cause symptoms; local infection can cause classic cystitis or urethritis and pyelonephritis may lead to flank pain. Patients who have candiduria as a feature of disseminated candidiasis may have evidence of systemic candidal disease, which should be assiduously checked for: clinical features include sepsis, fever, lesions of the optic fundi, skin lesions and hepatosplenomegaly.

Investigations

From Table 96a.1, it is clear that a repeat fresh urine sample must be sent to the microbiology laboratory to confirm candiduria. Microscopy for the presence of white blood cells may be useful in differentiating colonization from urinary tract infection, but the finding can be nonspecific in a catheterized patient; the presence of granular casts containing hyphae is a rare finding which would confirm true renal infection. If the patient has not been catheterized or had

ETIOLOGY OF CANDIDURIA AND LABORATORY INVESTIGATION	
Source of candiduria	Laboratory investigations
Inadvertent contamination	Repeat sample: clear
Colonization of lower tract	No WBCs in urine, patient well
Infection of lower tract	WBCs in urine Ultrasound if not instrumented Screen for diabetes, renal disease
Infection of upper tract	WBCs + casts in urine Ultrasound Screen for diabetes, renal disease
Disseminated <i>Candida</i> infection	Blood cultures/other sterile site: positive for <i>Candida</i> CXR, abdominal ultrasound High CRP

Table 96a.1 Etiology of candiduria and laboratory investigation.

MANAGEMENT OF CANDIDURIA IN THE ICU		
Suspected cause of candiduria	Action	Additional considerations
Contamination	None	–
Colonization	No antifungal Remove/replace catheter Stop antibacterials if possible	If patient is at risk of infection, e.g. neutropenia or undergoing urological procedure, fluconazole 200mg/day for 7–14 days
Lower UTI	Fluconazole 200mg/day for 7–14 days if <i>C. albicans</i>	
Upper UTI	Fluconazole 6mg/kg/day for 2–6 weeks if <i>C. albicans</i>	Surgical drainage may be needed. Amphotericin B if patient unstable or if non- <i>albicans</i>
Disseminated infection likely	Fluconazole 6–12mg/kg/day (if <i>C. albicans</i>) or amphotericin B 0.7–1.0mg/kg/day, depending on severity, for at least 2–6 weeks	If dissemination confirmed: follow up for at least 3–6 months after discharge from ICU in case of distant seeding Use of lipid formulations of amphotericin B necessitates doses of 3–5mg/kg/day

Table 96a.2 Management of candiduria in the ICU.

urological instrumentation recently, it is prudent to screen for diabetes mellitus and renal insufficiency by biochemical testing, and anatomic anomalies using ultrasound. Ultrasound of the renal tract can also demonstrate the presence of fungal balls in patients who have persistent candiduria. Simple tests to screen for the possibility of disseminated candidiasis would include a chest X-ray, abdominal ultrasound, C-reactive protein, cultures of other potentially infected sites (e.g. tracheal aspirate or bronchial lavage, bile, surgical drains, intravascular line tips) and blood cultures.

Management

The modern management of candiduria in the ICU setting is determined by the likely source of fungi (see Table 96a.2). It is clear that colonization can be treated by simply replacing the urinary catheter or, better, permanent removal. In all cases, rational reduction in the spectrum of antibacterial agents administered to patients will help eliminate fungal colonization and infection. These simple measures allow up to 40% of patients with candiduria to clear fungi from the urine. True infection of the urinary tract should be treated with a definitive course of an antifungal, usually fluconazole, in addition to catheter removal or exchange. Fluconazole can be administered intravenously in the ICU or via the nasogastric tube in the oral form, if the patient's gastrointestinal system is functioning. Infection with germ tube-negative *Candida* spp. (other than *C. albicans*) may require intravenous amphotericin B. There is no clear case for local intermittent or continuous bladder irrigation with amphotericin B; the procedure necessitates instrumentation of the urinary tract which might otherwise be unnecessary. Furthermore, although local irriga-

tion with amphotericin B can achieve prompt clearance of funguria, the effect is short-lived compared with clearance rates achieved by fluconazole.

Finally, the candiduric patient who may have invasive fungal infection warrants more aggressive antifungal therapy. This must be based on careful assessment of combined clinical and laboratory findings. If *C. albicans* is isolated and the patient is stable, it is reasonable to treat with high-dose fluconazole for 2–6 weeks (400–800mg/day for a 70kg adult). However, if the same patient is clinically unstable or if the isolate is non-*albicans*, it would be prudent to treat with amphotericin B, as indicated in Table 96a.2. The appropriate duration of therapy in this setting is unclear and must be determined according to the individual clinical situation and response to therapy.

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b. Management of fever that relapses and remits

Nicholas Price

The patient who has recurrent febrile episodes commonly presents a particularly difficult diagnostic challenge. In addition to the classic criteria for fever of unknown origin (FUO; Chapter 82), Knockaert *et al.* have defined 'recurrent' FUO as repeated febrile episodes with fever-free intervals of at least 2 weeks. The number of relapses or overall duration was not specified but, in practice, the clinical course is typically protracted. One limitation of this definition is that several important infectious diseases that are characteristically associated

with a recurrent fever pattern are excluded. However, a clear definition and strict adherence to defining criteria are helpful because they focus the diagnostic approach and are essential for meaningful comparative studies.

Causes

Infections, malignancy and multisystem inflammatory diseases are responsible for 60–70% of cases of classic FUO. If recurrent FUO is

CAUSES OF RECURRENT FEVER OF UNKNOWN ORIGIN
Infectious diseases
Focal bacterial infection (e.g. chronic prostatitis, subacute cholangitis) Q fever endocarditis (<i>Coxiella burnetii</i>) Rat-bite fever (<i>Spirillum minor</i> , <i>Streptobacillus moniliformis</i>) Relapsing fever (<i>Borrelia recurrentis</i> , <i>Borrelia duttoni</i>) Trypanosomiasis (<i>Trypanosoma gambiense</i> , <i>Trypanosoma rhodesiense</i>) Whipple's disease (<i>Tropheryma whippelii</i>) Yersiniosis (<i>Yersinia pseudotuberculosis</i> , <i>Yersinia enterocolitica</i>)
Multisystem diseases
Connective tissue diseases and vasculitides: Churg–Strauss disease Giant cell arteritis Polymyalgia rheumatica Mixed connective tissue disease Polyarteritis nodosa Systemic lupus erythematosus Wegener's granulomatosis
Rheumatologic diseases: Ankylosing spondylitis Relapsing polychondritis Rheumatoid disease Still's disease
Inflammatory diseases: Sarcoidosis
Neoplasia
Atrial myxoma Colonic carcinoma Lymphoma
Miscellaneous conditions
Castleman's disease Cholesterol embolism Crohn's disease Cyclic neutropenia Drug fever Extrinsic allergic alveolitis Factitious fever Familial Mediterranean fever , familial Hibernian fever Fume fever, hypersensitivity pneumonitis Gaucher's disease, Fabry's disease Hyper-IgD syndrome Hypertriglyceridemia (type IV) Mollaret's meningitis Seizures ('thermal epilepsy') Sweet's syndrome

Table 96b.1 causes of recurrent fever of unknown origin. The more common types are indicated in bold type. Adapted from Knockaert et al., 1993.

considered as a subset of classic FUO, these three causes account for only 20% of the cases; 50% go undiagnosed and a collection of diverse 'miscellaneous' conditions forms the largest subgroup (Fig. 14.6). Patients who have recurrent febrile episodes that persist for more than two years rarely have infections or malignant disorders.

Infectious causes

A silent focus of bacterial infection is the most common infectious cause that should be considered, rather than any of the limited number of specific infections listed (Table 96b.1). Other infections on the list of differential diagnoses that present with a relapsing and remitting fever pattern, which may not fulfill the stringent criteria for



Fig. 96b.1 Characteristic evanescent rash of Still's disease.

recurrent FUO, include malaria, brucellosis, secondary syphilis, tuberculosis, trench fever (caused by *Bartonella quintana*), filariasis and visceral leishmaniasis. However, it is important to note that malaria does not always produce the classic 'quartan' or 'tertian' fever patterns since parasites may mature asynchronously.

Neoplastic causes

Many malignancies can cause FUO; however, those listed (Table 96b.1) have been specifically reported as causing recurrent FUO.

Multisystem disease

All vasculitides or connective tissue diseases can flare up suddenly and remit spontaneously, producing a recurrent fever. Still's disease is a seronegative arthritis of unknown etiology; it is essentially a diagnosis of exclusion. The diagnosis should be strongly suspected in a young adult who has the classic triad of high fever above 104°F (40°C), evanescent rash (Fig. 96b.1) and arthritis (particularly if pharyngitis is also reported).

Miscellaneous causes

Familial Mediterranean fever is a clinical diagnosis characterized by recurrent polyserositis but a molecular diagnosis may also be established by identifying mutations of the pyrin gene (*MEFV*), located on the short arm of chromosome 16. Similar to familial Mediterranean fever, 'hyper-IgD syndrome' is an autosomal recessive inherited disorder that has been described in European families and was recently linked to a locus on chromosome 12. Patients characteristically have elevated IgD levels, and cervical lymphadenopathy and abdominal pain are prominent clinical features. Tumor necrosis factor (TNF)-receptor-associated periodic syndrome (TRAPS) is another rare hereditary condition, first described in a large Irish family and originally called familial Hibernian fever. Affected individuals are thought to be unable to neutralize TNF because serum levels of soluble type 1 TNF receptor are typically low. Inheritance is autosomal dominant and common features are localized myalgia and conjunctivitis.

Crohn's disease is an important cause of recurrent FUO and may present with weight loss, fever and anemia without any gastrointestinal symptoms. Castleman's disease (angiofollicular lymph node hyperplasia) may present with focal mediastinal or generalized lymphadenopathy. The localized type occurs in young adults and is curable by surgery. The generalized form affects older patients, has a less benign prognosis and may undergo malignant transformation. Sweet's syndrome is characterized by a painful neutrophilic dermatosis and is

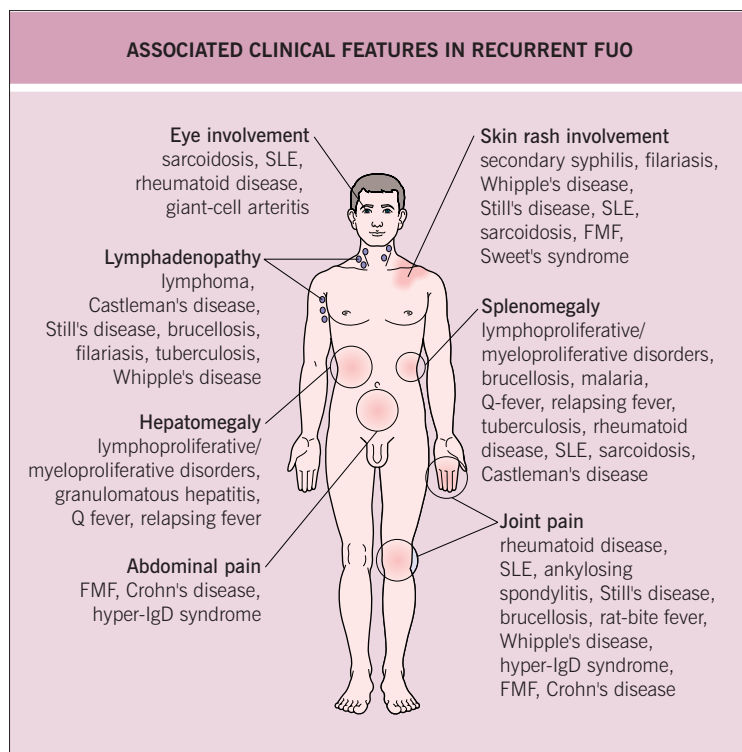


Fig. 96b.2 Clinical features associated with recurrent fever of unknown origin. SLE, systemic lupus erythematosus; FMF, familial Mediterranean fever.

associated with joint pains and malignancy. Very rarely, epileptic seizures may produce periodic febrile confusion.

'Idiopathic granulomatosis' and 'granulomatous hepatitis' should not be readily accepted as final diagnoses because it is likely that they encompass a variety of different underlying conditions, which may be revealed during careful long-term follow-up.

Clinical assessment

As for any FUO, a detailed history and thorough clinical examination are paramount and repeated assessments are often necessary. Associated clinical features are illustrated in Figure 96b.2. In general, the pattern of the fever is seldom of diagnostic value but a notable exception is cyclic neutropenia, which has a classical 'periodic' fever pattern that reoccurs predictably after every 21 days. In addition, high fevers recurring at fixed intervals of 2–8 weeks are characteristic of the rare 'PFAPA' (*periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome*) that has recently been described in children.

Hereditary causes of recurrent FUO almost always present before 20 years of age, and febrile attacks start in the first year of life in hyper-IgD syndrome. In addition, a detailed family history and inquiry about racial background is particularly important in the evaluation of these inherited conditions. A thorough travel history should be obtained and in the tropical traveler the risk of disease transmission by insect vectors should be assessed by asking about visits to game parks, accommodation (camping, downmarket hotels, log cabins) and protective measures such as bed nets. A bite from a tsetse fly (vector in African trypanosomiasis) is often memorably painful and leaves an indurated lesion for days. In contrast, the bite in tick-borne relapsing fever is characteristically painless (Chapter 145). Specific enquiry should also be made about consumption of unpasteurized milk (a cause of brucellosis), occupational exposure (e.g. fume fever), animal contact (e.g. rat-bite fever, Q fever, psittacosis), previous medical conditions (e.g. episodes of cholecystitis) and drug treatment (especially if taken intermittently). Repeated attacks of fever may also represent a relapse of a pre-existing infection, particularly if

treatment fails or is discontinued. Treatment compliance or antimicrobial resistance may therefore need to be addressed.

Investigations

The investigative work up is the same as for classic FUO (Chapter 82). Because the range of potential underlying causes is so diverse, no comprehensive diagnostic algorithms exist.

Hematologic indices occasionally provide useful clues but are not always reliable (e.g. eosinophilia may indicate lymphoma, Churg–Strauss disease, drug reaction or parasitic infection). In addition to malaria, the causative organisms in relapsing fever and trypanosomiasis may be visualized on a thick blood film taken during a febrile episode. A moderately elevated acute phase response is not remarkable in itself, although it does exclude factitious fever. However, in some conditions, inflammatory indices are exceptionally high: an erythrocyte sedimentation rate above 100mm/h is seen in drug fever, malignancy, giant-cell arteritis and Still's disease. Serum ferritin is nonspecifically elevated in inflammatory conditions, but extremely high levels (>1000mg/l) are also typical in Still's disease and a raised serum angiotensin converting enzyme may indicate a granulomatous disorder. Although there may be a polyclonal increase in immunoglobulins, hyper-IgD syndrome is diagnosed by characteristic clinical findings and continuously high IgD levels (>100U/ml). Serologic and immunologic tests should be done as appropriate but, as in classic FUO, they are often unrewarding unless these are suspected to yield significant results beforehand.

Radioisotope-labeled white cell imaging may be useful in identifying occult foci of infection but often does not contribute more than computed tomography scanning of abdomen/ pelvis and chest. Magnetic resonance imaging is valuable when bone infection is suspected. There should be a low threshold for investigating the gastrointestinal tract (e.g. by endoscopy, small bowel transit study or barium enema) in order to look for inflammatory bowel disease and malignancy. In an elderly patient who has a very elevated erythrocyte sedimentation rate, temporal artery biopsy may be useful diagnostically where there is no prior localizing information.

General approach

Because the cause of recurrent FUO is generally not life threatening, if no clues are provided by diagnostic tests, a 'watch-and-wait' strategy can often be adopted. Periodic outpatient assessment is likely to reveal significant pathology in time and many of the undiagnosed cases may resolve spontaneously. It is useful to ask patients to record their own temperature using a digital thermometer and to keep a symptom diary. In order to make a more valuable clinical assessment it is often helpful to ask patients to come up to the hospital immediately when they become unwell or pyrexial.

In general, empiric trials of antibiotic or anti-inflammatory therapy as diagnostic tests are inadvisable. However, if empiric treatment is felt to be absolutely necessary, a full course should be prescribed so that complications arising from inadequate therapy are avoided. In the future, genetic studies will probably identify other rare causes of recurrent FUO that persist and are presently undiagnosed.

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c. Infections associated with near drowning

It is thought that about 100 million North Americans use the marine environment for recreation each year. This leads to an estimated 8000 deaths from drowning per annum in the USA and at least 150,000 deaths worldwide. The epidemiology of 'near drowning' is less well known and estimates vary between two and 20 times the deaths from drowning. Drowning implies death due to cerebral hypoxia as a result of immersion in water. In the majority of cases water is aspirated into pulmonary air spaces. This produces a variety of pathologies depending on whether fresh or sea water is inhaled, but the end result is alveolar dysfunction, causing venous blood to be shunted into the systemic circulation past underventilated alveoli to cause hypoxemia. In a minority of cases hypoxemia can result from apnea caused by several different mechanisms. Although 'near drowning' by definition means that the victim survives the initial hypoxic insult, a number of complications may then ensue, including pulmonary edema, convulsions and infective problems such as pneumonia or sepsis.

Pathogenesis

The majority of people who have near drowning episodes have aspirated either sea water or fresh water. The resulting lung damage produces inflammation and edema, which damage alveolar defense mechanisms and enhance the risk of infection. The relatively anaerobic conditions may also favor infection. Infecting organisms may include those already colonizing the lungs or upper airways, which have been carried distally with the aspiration and have then taken advantage of improved conditions for growth. Alternatively, organisms in the aspirated water may give rise to infective problems. Finally, an ill patient who has lung damage may be admitted to hospital (and to an intensive care unit) and therefore be exposed to all the risks of nosocomial pneumonia.

Microbiology

The literature on the microbiology of near drowning consists mainly of single case reports rather than large-scale reviews but some common themes do emerge. Organisms that have been implicated are shown in Table 96c.1, and these can be divided into those that are characteristically associated with pneumonia (either community-acquired or nosocomial) and those that are more specifically associated with immersion incidents. Gram-negative organisms predominate in the aquatic environment (both sea water and fresh water) but anaerobic organisms and *Staphylococcus* spp. can also be found. There may be some organisms that are more likely depending on whether immersion took place in sea water or fresh water and depending on whether the water was clean or contaminated. Certain organisms may be more common in particular geographic areas. For example, one might anticipate exposure to *Burkholderia pseudomallei* following a near-drowning episode in the paddy fields of South East Asia (Chapter 175).

Several cases of infection with *Aeromonas* spp. exist in the literature and these are associated with a high proportion of positive blood cultures and a high mortality. Fungal infections can also cause problems and there are reports of *Aspergillus* pneumonia and disseminated aspergillosis after immersion incidents. *Pseudallescheria boydii* is also reported. Infection is commonly polymicrobial.

Clinical features

The clinical features of infection after near drowning are similar to those seen when the particular infection arises from more conventional causes and depend on the site of infection. The main complication is pneumonia (as might be predicted from the portal of entry) but there is often an associated bacteremia, which may produce clinical features of sepsis. There have also been case reports of meningitis after near drowning.

MICRO-ORGANISMS IMPLICATED IN PNEUMONIA OR SEPSIS AFTER NEAR DROWNING

Conventional respiratory pathogens (including atypical organisms and those associated with nosocomial pneumonias)

Staphylococcus aureus
Haemophilus influenzae
Streptococcus pneumoniae
Escherichia coli
Pseudomonas spp.
Moraxella spp.
Klebsiella spp.
Legionella spp.

Pathogens specifically related to immersion

Aeromonas spp.
Pseudomonas putrefaciens
Francisella philomiragia
Chromobacterium violaceum
Burkholderia pseudomallei
Vibrio spp.
Pseudallescheria boydii
Aspergillus spp.

Table 96c.1 Micro-organisms implicated in pneumonia or sepsis after near drowning.

Noninfective pulmonary edema is a common complication of near drowning and can progress to full adult respiratory distress syndrome. Pulmonary edema can be difficult to distinguish clinically and radiographically from pneumonia. In one series of 125 near drowning episodes, the incidence of pulmonary edema was 43% whereas the incidence of pneumonia was 14.7%. These figures are sensitive to changes in case definition, and clearly many patients who initially have pulmonary edema may subsequently go on to develop pneumonia, which tends to be a later complication.

Most patients who have pneumonia have fever (although recognition of this may be confounded if there is any residual hypothermia from the immersion). They may have clinical features of pulmonary consolidation or edema, or both.

Investigations

Near-drowning victims should have a chest radiograph on admission and this may well be clear or show nonspecific shadowing. They should also have a full blood count and arterial blood gas analysis. It is unlikely that an asymptomatic patient who has normal arterial blood gases and chest radiograph will develop any pulmonary complications. Leukocytosis is usual in patients who have pneumonia but is not specific for infection.

Pulmonary secretions must be examined microbiologically; these may include expectorated sputum or tracheal aspirates in intubated patients. There may be pus cells in the samples and it is common to find infecting micro-organisms by stain and by subsequent culture. Blood cultures must always be taken because there is a high rate of bacteremia. Empyema may develop later in the natural history, necessitating pleural aspiration.

Management

Patients who have survived a near drowning episode require emergency evaluation to determine whether they are at risk of subsequent delayed complications. If they are asymptomatic, with no abnormalities on physical examination and with a normal chest

radiograph, arterial blood gases and full blood count, they can be safely discharged because they are at low risk of pulmonary problems. However, any abnormality on this initial evaluation should prompt hospital admission for observation. The level of monitoring required depends on the clinical status and may include serial arterial blood gas analysis or oxygen saturation monitoring, serial full blood counts and chest radiographs in addition to frequent clinical evaluation.

If hypoxemia is present, supplemental oxygen should be given. If this does not correct the situation, it may be necessary to admit the patient to an intensive care unit for further respiratory support.

In common with many other intensive care situations, there used to be a widespread practice of administering glucocorticoids to patients who had undergone aspiration. There has never been evidence of benefit in near-drowning incidents and this practice is not recommended.

Antibiotics

Prophylactic antibiotics have been shown of no benefit in at least one study and their use is not recommended. However, there should be a low threshold for instituting antimicrobial therapy if there is any suspicion of developing pneumonia or sepsis (Table 96c.2). Features giving rise to concern include deteriorating arterial blood gases, new infiltrates on chest radiograph, hemodynamic disturbance or the development of fever or leukocytosis. It is likely that antibiotics will have to commence before any microbiologic information is available from the laboratory (although initial Gram stains may be helpful). Therefore, broad-spectrum empiric cover with good pulmonary penetration is indicated.

Numerous antibiotics have been used, including aminoglycosides, monobactams, carbapenems, cephalosporins and extended-spectrum penicillins (with and without β -lactamase inhibitors). There are no large-scale trials to guide rational therapy. I suggest the use of clindamycin, which has good penetration and will provide good Gram-positive cover as well as treating anaerobic infection. This should be combined with ciprofloxacin to cover the Gram-negative organisms and also provide some cover against *Legionella* spp. Other reasonable combinations would be ticarcillin–clavulanate with gentamicin and ceftazidime with metronidazole, although neither of these two regimens offers cover against *Legionella* spp. Clearly the

ANTIBIOTIC REGIMENS FOR PNEUMONIA AND SEPSIS ASSOCIATED WITH NEAR DROWNING	
Dose for average adult patient	
Clindamycin	900mg q8h
Ciprofloxacin	400mg q12h
Ticarcillin–clavulanate	3g q6h
Gentamicin	5mg/kg/day
Ceftazidime	2g q8h
Metronidazole	500mg q8h

All these antibiotics are administered intravenously.

Table 96c.2 Antibiotic regimens for pneumonia and sepsis associated with near drowning.

initial regimen may need to be modified in the light of subsequent information from the microbiology laboratory, but it is important to remember that polymicrobial infection is common. If there is no adequate response, it may be necessary to consider the use of antifungal treatment.

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d. Initial management of a suspected outbreak of smallpox

Andrew W Artenstein

Introduction

Smallpox, the human disease caused by infection with variola virus, was a worldwide scourge for thousands of years, recognized from the inception of recorded history. The disease accounted for more deaths than any other epidemic disease in history, and its impact on the course of human civilizations has been extensive and well documented. Following an intensive campaign from 1966–1977 by the World Health Organization (WHO), smallpox was certified as ‘eradicated’ from the world in 1980, although viral stocks were officially deposited in the former Soviet Union and at the CDC in Atlanta. There have been persistent concerns about the availability of these stocks outside of their presumed secure internment.

The clinical occurrence of even a single case of smallpox would be pathognomonic for bioterrorism because natural disease no longer

occurs and there is no known animal reservoir for the virus. The intentional re-introduction of variola virus would be an international public health crisis of massive proportions for the following reasons:

- case fatality rates were historically 25–30%;
- the virus is efficiently transmitted person to person among close contacts in an amplified fashion, with the potential for air-borne transmission over longer distances;
- most of the world’s population are susceptible hosts, either because vaccination against smallpox ceased in most areas more than two decades ago or because of waning of previous vaccine-induced immunity; and
- vaccine supply is currently limited and there are no antivirals proven to be effective against this pathogen.

Clinical features

After an average incubation period of 10–12 days, a 2- or 3-day prodromal illness ensues characterized by the abrupt onset of high fevers, chills, malaise, prostration, headache, backache and vomiting. The temperature defervesces concurrent with the appearance of enanthema involving the oral mucous membranes and, a day later, by a macular rash that begins on the face and extremities and becomes papular over a 1-2-day period and subsequently vesicular over an

additional 1–2 days, rapidly becoming generalized. All the lesions are generally present by day four of the eruption and evolve into umbilicated pustules over the next few days. The rash is typically centrifugal, not only in onset, but it remains denser peripherally than centrally (Fig. 96d.2) and involves the palms and soles (Fig. 96d.1). Additionally, the lesions are typically synchronous (i.e. at similar stages of evolution and appearance). This distribution and appearance help to distinguish ordinary-type smallpox (*variola major*) from other eruptive illnesses (see Table 6.3, Chapter 6).



Fig. 96d.1 Typical centrifugal distribution of the rash in smallpox. From Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. Smallpox and its eradication. Geneva: World Health Organization; 1988. Reproduced with permission of the World Health Organization



Fig. 96d.2 Smallpox lesions on the sole, day 14 of the eruption. From Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. Smallpox and its eradication. Geneva: World Health Organization; 1988. Reproduced with permission of the World Health Organization

The vesicles and pustules of smallpox are described as ‘shotty’, almost nodular, epidermal lesions. By the second week of the rash the lesions begin to crust and the scabs begin to separate, a process that is complete by day 21. The period of infectiousness extends from the onset of the enanthema to the complete separation of all scabs, although most transmission occurs during the first 7–10 days of illness, when virus is replicating to high titers in the oropharynx.

Variola major, ‘ordinary’ type of smallpox, traditionally accounted for nearly 90% of cases; the remaining cases during epidemics were generally distributed among a few different forms of the disease. ‘Modified’ type is a milder form more commonly noted in previously vaccinated individuals and less likely to be fatal. The malignant or ‘flat’ type of smallpox is characterized by the slow progression of flattened vesicular lesions that coalesce and is associated with death in the vast majority of cases. Historically, hemorrhagic smallpox accounted for less than 3% of cases but was associated with rapid progression to death in nearly 100%. Although pregnant women appear especially vulnerable to this form, it is likely that other forms of immune suppression may predispose to it. Both malignant and hemorrhagic smallpox pose difficult diagnostic dilemmas.

Diagnosis

The possible diagnosis of smallpox is suggested by clinical features and mandates the immediate institution of isolation procedures with contact and air-borne precautions and prompt notification of public health officials. The public health authorities will be essential in orchestrating an effective community-wide response to a smallpox outbreak. This will necessitate:

- coordination between hospitals and emergency personnel;
- prompt dissemination of vital health information for the public; and
- cooperation with military and law enforcement official investigations.

Epidemiologic information will be helpful in secondary cases or once a known outbreak is underway; however, early cases presenting before a bioterrorism event is recognized may be missed unless clinicians consider the diagnosis.

Recently immunized health care providers adhering to air-borne and contact precautions should obtain blood, aspirates from vesicular or pustular fluid and scrapings of crusts and skin lesions. This will generally require collaboration with public health officials because these specimens must be processed by designated laboratory facilities with high-level containment capabilities. Diagnostic assays for variola virus include electron microscopy, immunohistochemical analysis of viral antigens, or polymerase chain reaction for viral genetic sequences. Confirmation is obtained by viral isolation on chorioallantoic membranes.

Management

The initial management of a suspected case of smallpox involves immediate institution of appropriate infection control precautions, contact tracing, strategic deployment of pre- and post-exposure vaccine, and possibly the use of antiviral agents. A patient who has suspected smallpox must be placed in a negative-pressure respiratory isolation room. Contact and air-borne precautions are necessary; most transmission occurs between close contacts but in selected circumstances the virus is capable of longer distance dissemination via aerosol suspension. Standard N-95 masks (95% efficiency, small particle, filter masks used for prevention of tuberculosis transmission) are widely available and useful to prevent transmission to health care workers.

If the number of suspected smallpox cases in an institution exceeds the number of negative-pressure rooms, cohorting may be necessary.

In extraordinary circumstances portable high-efficiency particulate air filtration units with ultraviolet lights should be used. Overflow of patients in a massive outbreak will require coordination and assistance with the public health authorities.

Access to suspected smallpox cases should be limited. Clothing, linens and equipment in contact with the patient are considered to be contaminated and must be autoclaved or incinerated after use. Diagnostic specimens and body fluids must be collected and handled using rigorous biosafety precautions under the guidance of proper public health authorities.

Pre-exposure vaccination using live vaccinia virus is highly effective in inducing immunity against smallpox. Immunity after primary vaccination appears to wane after 5–10 years, a phenomenon also noted historically in those having experienced natural infection. There is, however, immunologic evidence that multiply revaccinated individuals maintain immunity for more than 30 years. In the event of confirmed or a highly suspected case(s) of smallpox, pre-exposure vaccination of healthcare and laboratory workers within an institution would be indicated.

Post-exposure immunization, using the ring vaccination and containment strategy, has shown proven effectiveness in controlling the spread of infection. Based on this strategy, persons exposed to an aerosol release of agent, those with face-to-face or household contact with an infected individual, or those caring for infected individuals should receive smallpox vaccine. Vaccination within 4 days of exposure may attenuate disease course, prevent death or prevent disease altogether.

Smallpox vaccination is generally contraindicated in immunocompromised individuals, pregnant women and those with eczema or other exfoliative skin disorders due to the high potential for complications. Additionally, vaccination is relatively contraindicated in close personal contacts of those in these risk groups. In the event of mass casualties related to bioterrorism the risks would need to be weighed against the potential benefits of vaccinating high-risk groups.

A number of serious complications have been described in association with smallpox vaccine. These include:

- postvaccinial encephalitis, a rare and potentially fatal neurologic syndrome;
- progressive vaccinia, a frequently fatal complication in immunocompromised recipients;
- generalized vaccinia, usually self-limited in primary vaccines;
- eczema vaccinatum, a severe dissemination of the vaccine virus in patients with active or previous eczema; and
- accidental infection, involving either auto-inoculation of virus from the skin lesion or transmission via close contact to household members.

A large, national survey reported at the end of the vaccine era in the USA noted 1254 complications and one fatality per million primary vaccines in 1968. These rates would likely be higher today given the increased prevalence of immunocompromising conditions and eczema. Vaccinia immune globulin (VIG), a preparation of pooled antibodies from hyperimmune individuals, is available in limited supply and may be beneficial in the management of selected vaccine complications.

Specific treatment of patients with smallpox involves:

- supportive care;
- the administration of fluids;
- adequate nutrition; and
- possibly systemic antimicrobial agents to treat secondary bacterial infections that may occur with the disruption in skin or mucosal integrity.

Recent data have demonstrated that cidofovir, currently licensed for the treatment of cytomegalovirus infections in humans, protects animals from lethal aerosol challenges with related orthopoxviruses. Despite the absence of direct efficacy data in humans, the

use of this agent to treat smallpox should be considered an experimental option. VIG has no proven efficacy in the management of smallpox.

Conclusion

The initial management of a suspected outbreak of smallpox involves controlling the spread of the infection among susceptible hosts. Central to this is the early recognition of disease, followed by the expeditious institution of isolation procedures and the rapid deployment of contact tracing with ring vaccination. The general approach of integrating clinical observations, epidemiologic investigation, preventive actions and treatment strategies in the management of an outbreak is applicable to a wide variety of pathogens.

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e. Prophylactic antibiotics for animal bites

Patricia Cristofaro

Annually one to two million patients with animal bites are treated by US physicians; one out of every two people will be bitten in his lifetime. Wound infection is the most common complication. Other less frequent infectious complications include tenosynovitis, septic arthritis and osteomyelitis. Even more serious problems such as sepsis, meningitis, peritonitis and endophthalmitis result from severe penetrating and crushing injuries. Could any of these sequelae be prevented by prophylactic antibiotics and if so, who should receive them, under what circumstances and which antibiotics? This practice point will discuss the use of prophylactic antibiotics in patients who have sustained cat, dog or human bites.

Given an accurate estimate of the potential for infection for each unique wound, one could calculate a risk: benefit ratio taking into account antibiotic toxicity/cost and setting a limit to treat when the risk of infection is $>x\%$. Such precise data are not available. However, much experiential data and a number of prospective and randomized clinical studies as well as retrospective analyses have attempted to refine the concept of appropriate antibiotic use. Unfortunately, the use of antibiotics to prevent bite wound infection is so ingrained in current medical practice that this aspect of therapy could not be randomized. Wound decontamination, debridement and closure are also variables of clinical care that cannot be adequately controlled. Nonetheless, the following opinions represent a reasonable consensus of current information and practice.

Antibiotic prophylaxis is considered reasonable if the risk of infection is 5–10%. Dog bite wounds carry reported infection rates from 1.6% to 30%; cat bite wounds 15.6–50%; and human bite wounds 10–20% (although these infections may be quite severe due to location and microbiology). For comparison, simple lacerations seen in the emergency room carry an infection rate of 4.5–15.1%. Toxicity outside of frank allergy is unlikely to be significant from a 3–5 day course of oral antibiotics. That stated, how can these wounds be stratified so that those most likely to be problematic receive anticipatory treatment?

Type and depth of wounds, extent of contamination, proximity to tendon, joints and bones or prosthetic joints, potential for functional loss, especially of the dominant hand, or disfigurement are all variables that must be considered. Immunocompromised states of the

host by diabetes, renal or vascular insufficiency, cirrhosis, collagen vascular disease or its therapy, transplant-associated immunosuppression, age and frailty as well as the potential for the complications of sepsis such as infectious endocarditis of a prosthetic valve are all complicating factors. Obstruction of lymphatic or venous drainage of the involved body part predisposes to infection. In the absence of statistical data, clinical judgment would tend toward use of prophylactic antibiotics in these circumstances.

A 3–5 day course of antibiotics is now recommended for each of the following conditions:

- wounds seen less than 8 hours after infliction that are moderate or severe, with crush injury or edema,
- those that might involve bones or joints,
- hand wounds,
- cat bites,
- punctures, especially near a joint,
- wounds adjacent to a prosthetic joint
- wounds in those with co-morbid conditions which predispose them to serious infections.

Treatment of wounds in these situations should decrease the rate of wound infection from 15–20% down to approximately 5%. Wounds that are seen after 24 hours and are not infected are not likely to become infected.

Which antibiotics should be used? Cultures of the uninfected bite wound are likely to yield the mouth flora of the offending animal but are not predictive of which organism or organisms will cause infection, if any. Antibiotics are chosen on epidemiological grounds. All bites deemed appropriate for therapy must be covered for *Staphylococcus aureus* and streptococcal species. Cat and dog bites must be covered for *Pasteurella multocida* (cats > dogs); human bites require coverage for *Eikenella corrodens*. Oral Gram-negative rods and anaerobes must also be considered.

Amoxicillin-clavulanate (875/125mg orally q12h) is the treatment of choice for both human and animal bites as it covers *E. corrodens* and most other major pathogens. For penicillin-allergic patients the choice is problematic. No single available agent is effective against all potential pathogens and a combination of agents must be used. Clindamycin plus trimethoprim-sulfa-methoxazole or clindamycin

TYPES OF WOUNDS FOR WHICH ANTIBIOTIC PROPHYLAXIS SHOULD BE CONSIDERED (HIGH RISK)	
Location	Hand, wrist or foot Scalp or face in infants Possibly involving bones or joints Near a prosthetic joint
Type of wound	Puncture (impossible to irrigate) Tissue crushing that cannot be debrided Edema less than 8 hours after infliction
Species	Domestic cat Human hand bite wounds

Table 96e.1 Types of wounds for which antibiotic prophylaxis should be considered (high risk).

TYPES OF PATIENTS FOR WHOM PROPHYLAXIS SHOULD BE CONSIDERED (HIGH RISK)
Diabetic Renal insufficiency Vascular insufficiency Cirrhotic Asplenic Taking immunosuppressive drugs Age <2 or >50 Drainage impairment to affected extremity (venous or lymphatic) Valvular heart disease Transplant

Table 96e.2 Types of patients for whom prophylaxis should be considered (high risk).

plus ciprofloxacin should provide adequate coverage in most situations. If erythromycin alone is used, the patient will require closer follow-up. The first dose of antibiotic should be given parenterally if feasible, in order to ensure adequate tissue levels. Duration of therapy should be 3–5 days if the wound remains uninfected.

CHOICE OF AGENTS	
Allergy to PCN	Preferred prophylactic antibiotic regimen
No	Amoxicillin-clavulanate 875/125mg po bid
Yes	Clindamycin 600mg po tid plus ciprofloxacin 500mg po bid (adults only) or Clindamycin plus TMP/Sulfa (adults or children) If feasible first dose may be given parenterally

Table 96e.3 Choice of agents.

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f. Management of a health care worker exposed to tuberculosis

E Jane Carter

Tuberculosis (TB) has been a recognized hazard for health care workers (HCW) since the discovery of the contagious nature of TB over a century ago. Patients with active pulmonary tuberculosis – both unsuspected and diagnosed – continue to be a risk to HCWs. Transmission of TB to HCWs has been documented in a variety of health care settings, most commonly in general medical wards but also in operating rooms, autopsy rooms, ICUs, renal transplant units and outpatient HIV clinics. The most common methods by which occupational exposure to TB occurs are either by exposure to the unsuspected case where effective chemotherapy for TB has not had the opportunity to reduce contagion risk or by failure of environmental controls, such as inadequate ventilation or lack of protective masks, to block transmission in identified cases with active TB. In developed countries the former risk is greater while in resource-poor countries, the latter risk often predominates. In low incidence regions of the world where TB is uncommon, the constant vigilance required to consider and actively pursue the diagnosis of TB has lessened over time.

This increases the risk that an unsuspected case of TB will go unrecognized and expose HCWs to the possible risk of infection.

Typical case

A 40-year-old US-born patient with insulin-dependent diabetes and chronic renal failure is referred for persistent cough. One year earlier, she was diagnosed with asthma. Treatment with asthma medications resulted in disappearance of her symptoms. Six months later she developed increasing cough, unresponsive to intensification of her asthma regimen. A chest radiograph revealed a right mid-lung field cavity with surrounding infiltration. An outpatient bronchoscopy was performed without specific TB precautions. One day post bronchoscopy the patient experienced fever and dyspnea. She was admitted following a 10-hour wait in the emergency room (ER). Later on the day of admission, her bronchoscopy smear was reported as 4+ acid-fast bacilli (AFB) smear positive. Expecterated sputum was also 4+ AFB positive. Exposed HCWs included the admission clerks, the

bronchoscopy nursing staff, the recovery room staff and the ER staff (nursing, physicians, respiratory therapy, maintenance and transport personnel).

Diagnosis/management options

Mycobacterium tuberculosis is spread through the air as droplet nuclei by a source case that aerosolizes the organism generally through cough, sneezing and respiration. The organism may stay suspended – and thus transmissible – in the air for as long as 6 hours. Exposure occurs to all individuals who share the air space with the source case and this exposure risk is delineated by history.

This case was not suspected so appropriate hospital infection control methods – placement in an isolation room, masking of individuals entering the room – were not performed. This is the most common clinical setting for HCW exposure. Risk of infection from exposure varies widely and is determined by multiple factors: contagiousness of the source case, time spent in the infected air space by the susceptible HCW, proximity to the index case, ventilation of the contaminated air space and the immune status of the susceptible host (Table 96f.1). Although a large number of individuals were exposed in this instance, their respective risks of actual infection are not equivalent.

The first step in evaluating the HCWs' exposure risk is to evaluate the source case. How contagious is the patient? This evaluation is based on the expectorated sputum. In this instance, the source case was very infectious, with heavily positive smears. In addition, the source case was coughing; cough is an effective aerosolization method. For a proportion of the HCWs exposed, the issue was not just cough but rather a cough-inducing procedure – bronchoscopy. Although it is standard in the US to mask HCWs for a bronchoscopy, masks are generally removed immediately following the procedure. HCWs remain in the room in which the patient is recovered. Patients are most contagious in the hours after the bronchoscopy due to increased cough provoked by residual congestion following instillation of fluid in the form of lavage or washings.

The next step in evaluating the HCWs' exposure risk is to evaluate the time of exposure in the infected air space. The longer the time spent in the infected air space, the greater the risk of infection. Thus, the nurse who spent 45 minutes in the room will be at more risk than the dietary aide who was present for a few minutes only. Analysis of exposure time as well as the intensity of exposure leads to the development of a hierarchy of urgency in performing the subsequent evaluations.

The only test presently available for TB infection is the tuberculin skin test or purified protein derivative (PPD). In many countries, health care facilities are required to have TB screening programs in place. Therefore, HCWs should know their PPD status. Tuberculin skin testing is offered to exposed individuals to assess TB infection. Not every exposed HCW needs to be tested simultaneously; those

with the most exposure – as determined by time exposed and/or presence at cough-inducing procedures – should undergo testing first.

It takes 2–10 weeks after infection for the tuberculin skin test to turn positive. Thus, the first or immediate test is to determine if the HCW has been infected by another, possibly unsuspected, exposure since last testing. Prior receipt of BCG immunization by the HCW can complicate the interpretation of the PPD. In general, BCG vaccination in childhood does not affect the interpretation of the PPD in adults but the receipt of multiple BCG immunizations may cause positive PPDs and in these situations the risks and benefits of treatment for possible recent infection should be considered on an individual basis. Further discussion about BCG and its impact on PPDs is found in Chapter 000. The follow-up skin test 10–12 weeks after this exposure tracks it as the cause of resultant infection.

Circles of exposure, based on length of time and intensity of exposure, are performed until the percentage of positive skin tests within the circle meets the incidence of positive skin tests in the community at large. Thus if, in the circle of 2-hour exposure, there are no positive skin tests then it is reasonable to expect that individuals who were exposed to the source case for less than 2 hours are not at risk. If 25% of the individuals in the 2-hour circle show evidence of infection based on a positive skin test than further testing of individuals with lesser exposure must be initiated, e.g. those exposed for 1 hour only (Fig. 96f.1).

HCWs with latent TB infection (LTBI) should be evaluated for TB disease with a chest radiograph and a physical examination. Signs or symptoms of active TB or chest radiographic abnormalities are pursued. For those with a normal chest radiograph and no TB symptoms, treatment of LTBI should be offered. The first 2 years after TB infection is the highest risk period for development of disease; therefore, the risk: benefit ratio of treatment of LTBI is always in favor of treatment in a new infection. There are three LTBI treatment regimens approved in the United States: isoniazid for 6–9 months (9 months is the preferred length of therapy), rifampin/pyrazinamide for 2 months (60 doses) or rifampin for 4 months. The ultra-short course regimen of rifampin/pyrazinamide has been associated with 17 deaths due to hepatitis since its approval; patient selection for this regimen must involve screening for hepatitis risk and active blood surveillance throughout therapy. The choice of rifampin alone is not based on any clinical trial data, only expert opinion. Susceptibility testing of the source case must be checked to verify susceptibility to the drugs being used to treat contacts.

The rifampin or rifampin/pyrazinamide regimen is recommended when the index case is known to harbor an INH-resistant strain of *M. tuberculosis*. The treatment options are much more limited in the event of exposure to multidrug-resistant (MDR) TB. MDR-TB is increasingly prevalent in eastern European countries and some regions of Asia and Africa. Latent infection with TB from INH and rifampin-resistant strains is generally managed with empirical chemoprevention therapies that include pyrazinamide with ethambutol or a fluoroquinolone such as levofloxacin or ofloxacin. None of these regimens have been shown to be clearly efficacious in controlled clinical trials.

Questions arise regarding recommendations for the immunocompromised HCW due to HIV infection or other medical problems. HIV-infected HCWs exposed to TB should be approached in the same manner as a young child. HIV-infected individuals, like children, may develop disease in an accelerated fashion so they should be quickly evaluated for active disease. If no disease is noted, primary prophylaxis is instituted until the issue of TB infection is determined. LTBI therapy is initiated even before any skin testing results can be obtained and is continued until both (baseline and follow-up) PPDs can be performed. If the HIV-infected HCW is in a circle in which the

RISK OF INFECTION TO HCW ONCE EXPOSED TO TUBERCULOSIS	
Directly related to	Inversely related to
Contagion status of source case	Ventilation of the infected air space
Effectiveness in aerosolizing the organism (e.g. bronchoscopy vs random cough)	Time since institution of chemotherapy for the source case
Time spent in the infected air space	Distance between HCW and index case
Immune status of the exposed individual	Efficiency of room ventilation and efficiency of face mask

Table 96f.1 Risk of infection to HCW once exposed to tuberculosis.

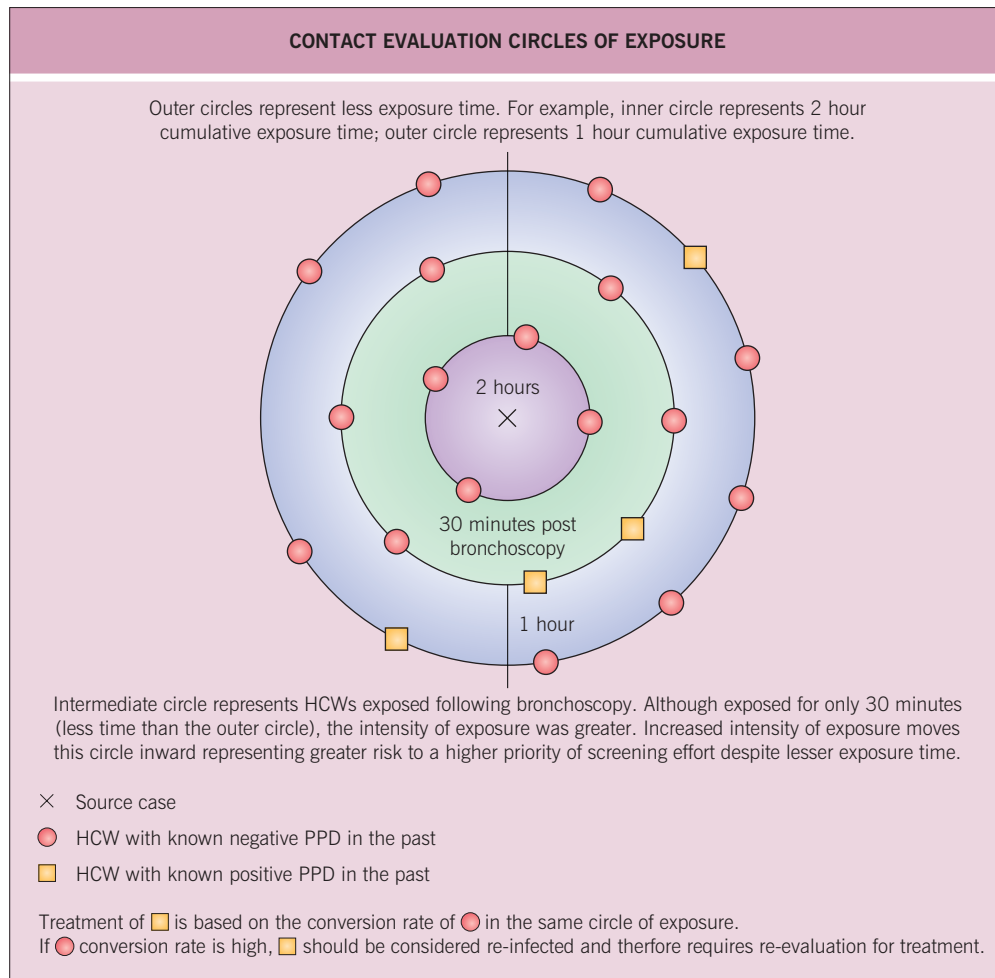


Fig. 96f.1 Contact evaluation: circles of exposure. Circles are constructed based on length of time of exposure and intensity of exposure. The innermost circle represents the highest risk; individuals in this circle are the first priority for screening. Circles of risk are constructed with each having less exposure – and thus less risk – until the PPD conversion rate in a circle is equivalent to the prevalence of LTBI in the local population.

conversion rate of PPDs is high, consideration should be given to completion of INH therapy regardless of skin test results. If the contact evaluation is performed solely in the context of the work environment, knowledge of the medical conditions of the HCW may not be known; therefore, clear instructions regarding risk should be conveyed to the HCW for discussion with a personal physician in a confidential setting.

If a HCW is known to be PPD positive prior to exposure, treatment decisions are based on the prevalence of TB infection that occurs in the circle of exposure to which that HCW belongs. If the previously infected HCW is in a circle of exposure where the conversion rate is high, the HCW should be considered as reinfected and evaluation for retreatment pursued. If the rate of conversion is low, no further evaluation of the previously positive HCW need be performed.

Following completion of LTBI therapy, no further evaluation need be done. Surveillance chest radiographs for treated – or for untreated – individuals with LTBI are of low yield. Individuals should be counseled regarding the signs and symptoms of active TB; only symptom-driven chest radiographs should be considered.

HCWs cannot be barred from work for failure to participate in programs of screening or for refusing LTBI treatment. Only individuals with contagious TB can be barred from the workplace.

Conclusion

Health care workers are at risk for occupational exposure to TB, especially in low incidence areas where the awareness and necessary active surveillance for TB are difficult to maintain. Risk of exposure is related primarily to the unsuspected case of TB. Risk of infection is based on contagiousness of the source case, extent and length of exposure to the index case and immune status of the HCW. Skin test

screening for exposure is based on a circle of contact approach; circles are determined by length and intensity of contact. Treatment of LTBI, if it occurs, should be offered and is effective in protecting against the development of TB disease.

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g. Management of a health care worker with chickenpox and the subsequent infection control problem

Katherine N Ward

Definition of the problem

Chickenpox (varicella) is caused by primary infection with varicella-zoster virus (VZV). After primary infection, the virus remains latent in sensory ganglia for life. Shingles (herpes-zoster) occurs when VZV reactivates.

In children the complications of chickenpox are sepsis, cerebellar ataxia and, rarely, encephalitis whereas in adults, especially pregnant women and those who smoke, the most common complication is pneumonia which may be fulminating. Neonates and the immunocompromised are at risk of severe disseminated disease. Varicella in pregnancy during the first two trimesters carries a small risk (probably <1%) of congenital varicella syndrome, which is characterized by one or more of the following: microcephaly, microphthalmia, mental retardation, chorioretinitis, Horner's syndrome, limb hypoplasia, contractures and skin scarring.

Chickenpox is very contagious and up to 90% of susceptible household contacts will develop the disease. Transmission is person to person by direct contact, droplet or air-borne spread of vesicle fluid or respiratory secretions. The usual incubation period for varicella is 14–16 days (range 10–21) and the infectious period about a week, i.e. from 2 days before the rash appears until the vesicles dry up. In shingles, VZV is shed from vesicle fluid but not respiratory secretions and is thus less transmissible, especially if covered by clothing. Virus transmission to antibody-negative contacts causing varicella occurs from the day of onset of the zoster rash until crusting of vesicles. In disseminated zoster the patient is infectious for longer, i.e. from 2 days before onset of rash. Finally, contagiousness may be prolonged in the immunocompromised with either varicella or zoster because of continuing virus replication.

Nosocomially acquired varicella is increasingly recognized as a problem. Sources of VZV infection include patients, visitors, especially children, and staff. For susceptible contacts, significant exposure includes sharing a hospital room with an infectious patient or prolonged, direct, face-to-face contact with an infectious person; in each case the type of infection, whether varicella or zoster, and the timing and closeness of exposure must be assessed. A common problem is that of the susceptible health care worker, inadvertently exposed to either chickenpox or zoster, who subsequently develops varicella and may transmit VZV to other staff and patients, e.g. in the antenatal clinic or hematology ward, with consequent morbidity and mortality.

Typical case

A medical student, attached to the hematology unit of a university teaching hospital during his elective, telephones his educational supervisor on a Friday to say that he has developed chickenpox. The rash appeared the day before when he briefly visited the sickle cell anemia outpatient clinic but had felt unwell and returned to his lodgings in the student hostel. On the previous 2 days, i.e. Tuesday and Wednesday, he had been clerking patients on the bone marrow transplant unit. His supervisor contacts the medical school's general practitioner who visits the student later that day and confirms varicella, adding that the patient smokes 20 cigarettes a day. The practitioner also reports that the student did not recall having chickenpox as a child but 2 weeks previously was present when samples were taken from a patient for the diagnosis of shingles.

Diagnostic methods

For the purposes of hospital infection control and timely patient management, laboratory tests should give a rapid result, preferably on the same working day.

Varicella and zoster can be reliably diagnosed clinically. However, where there is doubt, for example if only a few vesicles are present, the diagnosis can be confirmed with the help of the laboratory. The relevant samples are vesicle fluid and cells scraped from the base of the lesion and useful rapid tests are immunofluorescence to detect VZV antigen in cells from the lesion, electron microscopy to detect a herpesvirus in vesicle fluid and PCR to detect VZV DNA in either sample. Tests for VZV IgM or IgG antibody are of little help in diagnosis, although they may sometimes be used to detect the absence of IgG antibody in the acute illness to confirm chickenpox or to exclude zoster.

As regards immunity to VZV, more than 90% of adults are immune although rates of immunity may be lower for adults raised in certain tropical or subtropical areas. A reliable history of varicella is a valid indicator because the rash is distinctive. In contrast, a negative history of varicella is not a reliable test of lack of immunity since the infection may not be recalled or may have been subclinical. Moreover, in the immunosuppressed a past history of varicella does not guarantee the presence of antibodies and hence immunity. Therefore antibody tests are often required to determine susceptibility to infection with VZV. The criteria for assay selection include sensitivity, specificity and the length of time required to obtain results. In particular, the test must be capable of detecting low levels of antibody such as may be found many years after primary infection with VZV. Thus, enzyme-linked immunosorbent assay or latex agglutination tests are appropriate whereas complement fixation tests are not sensitive enough. Assays that are too labor intensive or time consuming include indirect immunofluorescence and neutralization.

Management options

The medical student with varicella

Valaciclovir or high-dose oral aciclovir is indicated, especially in a smoker, and should be given within 24 hours of the onset of rash to reduce the duration and severity of the illness. The student should be warned of the risk of varicella pneumonia and asked to report any respiratory symptoms, in which case he should be admitted to the hospital's infectious diseases ward for assessment and treatment with high-dose intravenous aciclovir. He should not otherwise return to the hospital until all his vesicles are dry and if at all possible he should move to alternative accommodation away from the hostel, e.g. be collected by his parents and taken home. In any case his contacts should be known to be immune to VZV (either by history or antibody positive). Finally, the question as to how this susceptible student was allowed to visit a patient with shingles and help to collect samples for diagnosis should be reviewed. No doubt there was a policy in place that only staff known to be immune should be exposed to VZV but it is all too easy to overlook the occasional visitor such as this elective student.

Susceptibility of contacts

A list should be made of patients and staff in the clinic and on the ward who had significant exposure to the student whilst infectious. Possible contacts in the student hostel should also be investigated. The lists should state whether each individual has had chickenpox or not and whether anyone was pregnant or immunosuppressed. Blood should be taken for VZV antibody testing from persons with no

history of chickenpox and from all immunosuppressed patients so as to determine susceptibility. Those with antibody can be regarded as immune and reassured.

In the event it was found that the student had been in the sickle cell anemia clinic before any patients arrived but had spent 15 minutes having tea and biscuits in the company of the receptionist who has no history of chickenpox and no antibody to VZV.

In contrast, the student had spent all of the previous 2 days on the hematology ward where there were 16 inpatients, all of whom had received a bone marrow transplant for various hematological malignancies. He had been on a ward round and had also visited and taken a history from several of the patients. All 16 patients were tested for VZV antibody and two were found to be seronegative. The student had also been in the ward kitchen for some time with the pregnant ward cleaner, who was not a permanent member of staff but had been supplied by an agency. She had lived in Bangalore, India, for the first 15 years of her life, her English was poor and she gave an uncertain history of chickenpox. On antibody testing she was susceptible to varicella. Finally in the hostel, two students living in rooms on the same corridor as the student did not recall having chickenpox as children although both were in fact VZV seropositive and hence immune to varicella.

Management of susceptible health care workers

There were two susceptible health care workers, one of whom was pregnant and will be considered later. The other was the receptionist in the sickle cell anemia clinic who should be excluded from patient contact just before the incubation period for chickenpox has elapsed, i.e. 8–21 days after her exposure to VZV. This could either take the form of paid leave or, less realistically perhaps, reassignment to a location in the hospital well away from patients, such as the financial department. A less practical option is to screen daily for skin lesions, fever and systemic symptoms and exclude her from the clinic if she develops varicella. However, on some days of the week bone marrow transplant patients are reviewed in the clinic and this is therefore an especially high-risk strategy. Aciclovir prophylaxis is not recommended as it may not prevent varicella and may prolong the infectious period, but it might be appropriate if on enquiry the receptionist is a heavy smoker. Likewise, the use of human varicella-zoster immunoglobulin (VZIg) for prophylaxis is not an option as it does not necessarily prevent varicella and may prolong the incubation period for a week or more. (VZIg is prepared from pooled plasma from blood donors with a history of recent chickenpox or zoster or from those who on screening are found to have suitably high titers of VZV antibody and is usually reserved for neonates, pregnant women and the immunosuppressed.) Finally, if varicella develops valaciclovir or high-dose oral aciclovir is indicated.

Management of susceptible pregnant or immunosuppressed contacts

The pregnant ward cleaner and the two bone marrow transplant recipients should be given VZIg to prevent or modify varicella. During the likely infectious period, which may be longer than normal, the member of staff should be managed as described above except that aciclovir prophylaxis and treatment with valaciclovir are both contraindicated in pregnancy. As regards the two bone marrow transplant patients, they should be appropriately isolated, preferably on an infectious diseases unit, and only be cared for by immune staff. Both of these patients were receiving oral low-dose aciclovir to prevent herpes simplex virus infections but there are insufficient data to suggest that this could replace VZIg. If varicella develop high-dose intravenous aciclovir should be given.

Conclusion

The infection control measures described above may seem straightforward but in practice, tracing contacts of varicella and zoster and obtaining blood samples for VZV antibody testing is time consuming and expensive. Excluding potentially infectious health care workers from the hospital is also expensive as they must be replaced by agency staff. Moreover, contacts may be missed because people are unaware they have been in contact or ignorant of the risks. Secondary cases may then occur with further risk of transmission.

In summary, the control of varicella in hospitals will remain a considerable burden unless the pool of susceptibles is reduced. Fortunately varicella vaccine is now licensed in both the United States and the UK and vaccination of all health care workers identified as VZV antibody negative at the time of employment and before any possible exposure in hospital should become the preferred method for preventing nosocomial varicella outbreaks.

Further reading

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