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L Diseases of Unknown Etiology

297 Kawasaki Disease

Jane C. Burns

SHORT VIEW SUMMARY

Definition
- Kawasaki disease (KD) is an acute, self-limited pediatric vasculitis that is the most common cause of acquired heart disease in children. Coronary artery aneurysms develop in 25% of untreated patients.

Epidemiology
- KD affects children of all ethnicities worldwide. Children of Asian and African-American descent are disproportionately affected. There is no evidence for person-to-person transmission. Temporospatial clustering of cases has been observed.

Etiology
- The cause of KD is unknown. According to the current paradigm, KD is triggered in genetically susceptible children after exposure to a widely dispersed agent.

Diagnosis
- The diagnosis is established by fulfillment of four of five clinical criteria in a child with fever and no other apparent cause. Clinical criteria include bilateral conjunctival injection; a polymorphous rash; oropharyngeal changes including erythematous, fissured lips, erythematous oropharynx without discrete lesions, and strawberry tongue; extremity changes including edema of the dorsa of the hands and feet, palm and sole erythema, and periungual desquamation during the convalescent phase; and a cervical lymph node mass measuring at least 1.5 cm. Coronary artery abnormalities are detected by transthoracic echocardiography.

Therapy
- High-dose intravenous immune globulin (IVIG) (2 g/kg) plus aspirin is the standard therapy for KD. If administered within the first 10 days after fever onset, the incidence of coronary artery aneurysms is reduced from 25% to 5%. A subset of patients (10%–20%) may be relatively resistant to IVIG and require additional antiinflammatory therapy.

Prevention
- There is no known intervention that can prevent KD.

Kawasaki disease (KD) is a self-limited vasculitis of infants and children that is now the most common cause of acquired heart disease in developed countries.[1,2] Although the disease was first described by Tomisaku Kawasaki in Japan in 1967, the cause remains elusive decades later. The current paradigm is that an environmental agent triggers a severe immune response in genetically susceptible children. Historical evidence suggests that KD was newly emergent in Japan in the 1950s and 1960s.[3] However, in the West, cases of infantile periarteritis nodosa, a fatal vasculitis of infants that is histologically indistinguishable from fatal KD, were reported in the 19th and early 20th centuries.[4,5]

EPIDEMIOLOGY

Although KD has been reported from all inhabited continents, the disease is most prevalent in Japan, where 1% of Japanese children develop the disease by age 10 years.[6] For every 100,000 children younger than 5 years of age, the incidence of KD ranges from 308 in Japan to 20 to 30 in the continental United States.[7–9] The incidence of KD among Japanese living in Hawaii is similar to rates in Japan, thus pointing to an important influence of host genetics on disease susceptibility.[10] In the United States, both Asians and African Americans are overrepresented among patients with KD.[11] The male-to-female ratio is 1.5:1, and 85% of patients with KD are younger than 5 years of age.

KD occurs with a distinct seasonality in the Northern Hemisphere with increased cases in winter and spring and midsummer and a nadir in the fall.[12] Temporospatial clustering of cases has also been documented, but person-to-person spread has not been observed.[8] Seasonality of KD cases has been linked to tropospheric wind currents from central Asia, although whether the association is causal has not been determined.[13,14]

ETIOLOGY

Despite 3 decades of investigation, the cause of KD remains unknown. Current understanding of the immune response that downregulates the acute inflammation through interleukin-10 suggests a response to a classic antigen that is protective against future exposure in most patients.[15,16] Previous theories postulating a response to a superantigen have been largely abandoned. One line of investigation suggests infection with a novel RNA virus that enters through the upper respiratory tract.[17] Analysis of coronary arteries obtained at autopsy has revealed upregulated expression of genes related to antigen presentation, myeloid dendritic cell function, and induction of type I interferons.[18] These findings were confirmed by immunohistochemistry and outline the complexity of the immune response in the arterial wall.[19]

CLINICAL MANIFESTATIONS

KD is recognized by a constellation of clinical signs and supportive laboratory data in the absence of other identifiable cause (Table 297.1). KD can mimic other rash/fever syndromes of children, and cases may be missed or misdiagnosed without a diagnostic test. Not all patients manifest the classic four of five criteria, and clinical presentation may be more subtle in infants younger than 6 months of age.[20] Clinicians must have a high index of suspicion for KD in any child presenting with the triad of fever lasting at least 5 days, rash, and bilateral conjunctival injection with sparing of the limbus and without exudate. Fever is essentially invariant, and no one particular pattern is characteristic. The fever is often high (>39°C [102.2°F]) and accompanied by extreme irritability. Description of each of the classic clinical signs follows.

TABLE 297.1 Diagnostic Criteria for Kawasaki Disease

A. Fever of at least 4 days' duration[a]
B. Presence of at least four of the following five conditions[b]
   1. Bilateral conjunctival injection
   2. Changes in lips and oral mucosa
      a. Dry, red, fissured lips
      b. "Strawberry tongue"
      c. Oropharyngeal erythema
   3. Changes in extremities
      a. Erythema of palms and soles
      b. Edema of hands and feet
      c. Periungual desquamation
   4. Polymorphous rash
   5. Cervical lymph node >1.5 cm
C. Illness not explained by other known disease processes

[a]Diagnosis may be made earlier in the course of fever by experienced clinicians.
[b]Kawasaki disease may be diagnosed in patients with fever and with fewer than four of five criteria in the presence of coronary artery abnormalities.

Exanthem

The exanthem of KD can take many different forms and is often polymorphous in the same patient. In its maculopapular presentation on the trunk and extremities, it can be easily confused with a drug reaction because many of these patients have been treated with antibiotics for erroneous diagnoses. Another common form of the rash is raised papules coalescing into plaques. This may be associated with target-like lesions with central clearing and can be confused with erythema multiforme. A pure erythroderma with no palpable component as in staphylococcal toxin–mediated disease is not associated with KD. Similarly, a confluent, fine maculopapular ("sandpaper") rash extending onto the face as in scarlet fever is unlikely and should prompt consideration of scarlet fever. A fine micropustular eruption on the buttocks, thighs, and extensor surfaces can sometimes be seen and is perhaps pathognomonic of KD.[21] Accentuation of the rash with confluent erythema in the groin that peels during the acute, febrile phase is seen in up to 50% of patients.[22,23] The histology of the exanthema is nonspecific and includes marked edema of dermal papillae, focal intercellular edema of the basal cell layer, and very slight perivascular infiltration of mononuclear cells in the papillary dermis, with dilation of small vessels.[24] Thus, skin biopsy is helpful only in excluding other diagnoses.

In the subacute phase, patients may develop an acute flare or first episode of eczema or psoriasis.[25] The lesions associated with both these rashes may be extremely severe and require aggressive, specific therapy in consultation with a pediatric dermatologist. The psoriasis may manifest as the pustular form with severe lesions on the cheeks.[26]

Conjunctival Injection

Prominent dilated vessels within the bulbar conjunctivae without edema or infiltration of inflammatory cells on conjunctival biopsy is the hallmark of KD (Fig. 297.1).[27,28] The lack of edema in the conjunctiva allows the limbus to be easily seen, giving the appearance of a white halo around the iris. The lack of edema and exudate are important features in distinguishing KD from other acute infections associated with fever and conjunctivitis, most notably adenovirus, enterovirus, and measles infection. The presence of exudative conjunctivitis should prompt a search for a different diagnosis.[29] Careful slit-lamp examination within the first week after fever onset reveals mild anterior uveitis with a cellular infiltrate in most patients.[30] Keratitis is less often seen, and photophobia is usually mild or absent. Uveitis usually resolves without treatment and without subsequent scarring.

Oropharyngeal Changes

Erythema of the lips with fissuring and erythema of the posterior pharynx without tonsillar exudate or discrete intraoral lesions are the most common mucocutaneous findings in acute KD. Sloughing of the filiform papillae of the tongue, leaving a glossy red surface punctuated by the fungiform papillae, creates the classic "strawberry tongue" appearance associated with both KD and streptococcal and staphylococcal toxin-mediated diseases (Fig. 297.2). The presence of a true strawberry tongue essentially eliminates common viral infections in the differential diagnosis of a patient because these agents are not associated with this pattern of injury. The presence of exudative pharyngitis or discrete intraoral lesions should prompt search for an alternative diagnosis.[29]

FIG. 297.1 Bilateral conjunctival injection with perilimbal sparing and without exudate. *(From the KD Foundation [www.kdfoundation.org].)*

FIG. 297.2 Dry, erythematous, fissured lips with "strawberry" tongue. The filiform papillae that give the tongue its characteristic gray appearance have sloughed off, leaving a denuded, red surface. The prominent fungiform papillae appear as the "seeds of the strawberry." *(From the KD Foundation [www.kdfoundation.org].)*

FIG. 297.3 Symmetrical, diffuse vasodilation of the soles of the feet with associated edema. *(From the KD Foundation [www.kdfoundation.org].)*

Peripheral Extremity Changes

Edema of the dorsa of the hands and feet with or without erythema of the palms and soles often develops after several days of fever (Fig. 297.3). The fusiform swelling of the digits accompanied by swelling and purple discoloration of the proximal interphalangeal joints is a classic finding. The painful arthritis may limit the use of the hands, and

the swelling of the feet often discourages ambulation. The vasodilation of the palms and soles is distinct from the exanthem on the rest of body and is a diffuse, blanching erythema that may be fluctuating.

Cervical Lymphadenopathy

Cervical lymphadenopathy is the least reliable feature and is seen in only 30% to 50% of patients. It is most commonly unilateral, and inflammation in the sternocleidomastoid muscle often limits rotation of the head. The cervical mass should be at least 1.5 cm in diameter to qualify for this criterion.[29] Studies have shown that correct diagnosis of KD is often delayed in patients who initially present with the cervical mass and fever (node-first presentation of KD), and bacterial lymphadenitis is diagnosed in these patients.[31] The appearance of the rash can further delay diagnosis when it is misinterpreted as a drug eruption, prompting a change in antibiotics.[32] In distinguishing node-first KD from bacterial lymphadenitis, helpful features include a higher erythrocyte sedimentation rate, C-reactive protein level, absolute band count, ultrasound or computed tomography that demonstrates clusters of nodes (rather than one dominant node), and retropharyngeal edema. Histopathology of the nodes reveals sinus expansion and paracortical zone enlargement, sometimes in the presence of subcapsular necrosis.[33] However, these findings are nonspecific, and the diagnosis of KD cannot be confirmed by lymph node biopsy.

Associated Clinical Features

Nonspecific respiratory, gastrointestinal, and rheumatologic complaints can be associated with KD and often cloud the diagnosis (Table 297.2). In a study of associated symptoms in the first 10 days after fever onset in 198 patients with KD, irritability was reported in 98 (50%), vomiting in 88 (44%), cough in 55 (28%), diarrhea in 52 (26%), rhinorrhea in 37 (19%), abdominal pain in 35 (18%), and joint pain (arthralgia or arthritis) in 29 (15%). One or more gastrointestinal symptoms (vomiting, diarrhea, or abdominal pain) were present in 120 patients (61%), and 69 patients (35%) had at least one respiratory symptom.[34]

The most important associated clinical feature of KD is myocarditis, which is present in virtually all patients. Overt signs of congestive heart failure are rare, but biopsy-proven myocardial inflammation is universal.[35,36] Diastolic dysfunction may be apparent clinically with a gallop rhythm on cardiac examination. Although coronary artery aneurysms are the most severe complication of KD, signs of myocardial ischemia during the acute phase of the illness are rare. A presentation with shock has been described and is most commonly associated with peripheral vascular dilation (warm shock) with or without compromise in ventricular function.[37,38] Other inflammatory complications of KD may include hoarseness,[39] sensorineural hearing loss,[40] aseptic meningitis,[41] anterior uveitis,[28] cranial nerve palsies,[42,43] arthritis, urethritis, pancreatitis, and hydrops of the gallbladder.

Arthritis

Both large and small joint arthritis have been described in the acute and subacute stages of KD. Small joint arthritis frequently involves the proximal interphalangeal joints of the hands and can be extremely painful. The original series describing arthritis associated with KD found small joint arthritis in 15% of patients and axial arthropathy in 35%.[44] In a more recent series, the prevalence of arthritis was 7.5% (31 of 414 patients). In the 31 children with arthritis, 55% had oligoarticular involvement, and 45% had polyarticular involvement.[45] Limited magnetic resonance imaging studies suggest a nonerosive synovitis that resolves with nonsteroidal antiinflammatory therapy.[46] Naproxen (Naprosyn) (15 mg/kg/day divided into two equal doses for 1 week) is usually effective therapy.

TABLE 297.2 Associated Features of Kawasaki Disease

Cardiac disease
Coronary artery aneurysms
Myocarditis
Pericarditis
Mitral or aortic regurgitation
Arrhythmias
Irritability
Arthralgia, arthritis
Aseptic meningitis
Urethritis with sterile pyuria
Hepatitis
Hydrops of the gallbladder
Pancreatitis
Pneumonitis
Anterior uveitis
Sensorineural hearing loss
Peripheral ischemia

Gastrointestinal Features

Noncalculous cholecystitis or hydrops of the gallbladder with or without bilirubinuria and elevated levels of γ-glutamyltransferase is seen in up to 20% of patients with KD.[47–49] This unusual feature is also associated with streptococcal infection and toxin-mediated disease, thus complicating the differential diagnosis.

Acute pancreatitis can also be associated with the acute phase of the illness.[50] Prominent complaints of abdominal pain should prompt laboratory testing for elevated levels of serum lipase and amylase. Inflammation can rarely lead to common bile duct stenosis.[51] Successful treatment of pancreatitis associated with KD with a single infusion of infliximab (anti–tumor necrosis factor agent) has been reported.[52]

DIAGNOSIS

The laboratory evaluation of patients with suspected KD should include markers of inflammation and tests to exclude other competing diagnoses (see Table 297.2). The acute phase is associated with an elevated white blood cell count with neutrophil predominance and elevated acute-phase reactants including fibrinogen, α_1-antitrypsin, C-reactive protein, C3, C4, and haptoglobin. The platelet count usually rises during the second week after illness onset, whereas the acute-phase reactants normalize over 4 to 6 weeks after treatment.[53]

The American Heart Association has established criteria for the diagnosis of complete and incomplete KD.[54] The diagnosis of KD may be made on or before the fifth day of fever in the presence of four of the five classic criteria or in the presence of fewer criteria with a coronary artery Z-score (internal diameter of the left anterior descending artery or right coronary artery expressed as standard deviation units from the mean normalized for body surface area) greater than or equal to 2.5. Diagnosis may be made in patients who present with fewer than four of the five classic criteria according to the American Heart Association algorithm, which was validated in a retrospective study to identify greater than 97% of patients at risk for developing coronary artery aneurysms (Fig. 297.4).[55] A computer-based decision support tool is being tested to aid in the diagnosis of KD.[56] Until the etiologic agent of KD is established, both underdiagnosis and overdiagnosis will continue.

DIFFERENTIAL DIAGNOSIS

KD is most commonly confused with viral infections associated with rash and conjunctivitis, including infections caused by adenovirus, enterovirus, measles, and parvovirus (Table 297.3). In KD, the lack of tearing or conjunctival exudate may be helpful in differentiating it from these common viral infections. Laboratory testing for these specific agents, coupled with the standard laboratory evaluation for KD, is usually sufficient to differentiate KD from these other infections.[56] However, sensitive methods such as polymerase chain reaction assays may detect viruses that are present concomitant with KD.[57] Such results must be interpreted cautiously, and given the seriousness of the potential sequelae of this vasculitis, treatment with intravenous immune globulin (IVIG) may be warranted in patients for whom the diagnosis is unclear. Bacterial toxin–mediated disease caused by staphylococci and streptococci should also be considered in the differential diagnosis. Bilateral conjunctival injection is specifically not a feature of scarlet fever, and this physical finding may be helpful in distinguishing this form of streptococcal infection from KD. In patients presenting with the triad of fever, conjunctival injection, and rash, leptospirosis and tularemia may also be considered. Noninfectious conditions that can be confused with KD include systemic drug reactions such as Stevens-Johnson syndrome and systemic-onset juvenile idiopathic arthritis.[58]

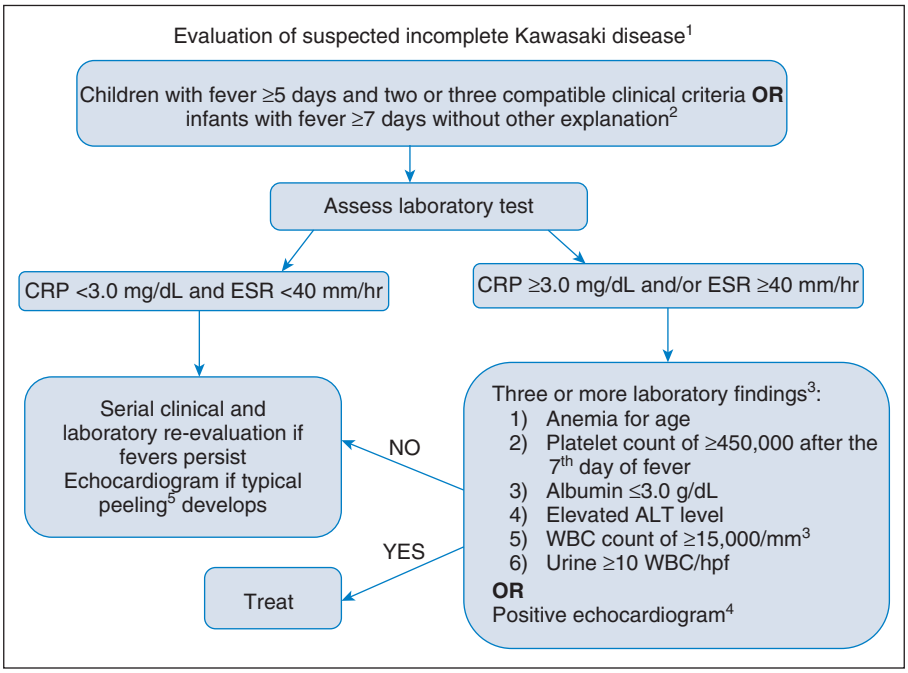

FIG. 297.4 Evaluation of suspected incomplete Kawasaki disease (KD). [1]In the absence of a gold standard for diagnosis, this algorithm cannot be evidence-based, but rather represents the informed opinion of the expert committee of the American Heart Association. Consultation with an expert should be sought anytime assistance is needed. [2]Infants ≤6 months old on day ≥7 of fever without other explanation should undergo laboratory testing and, if evidence of systemic inflammation is found, an echocardiogram, even in the absence of clinical criteria. Patient characteristics suggesting KD are listed in Table 297.1. Characteristics suggesting diseases other than KD include exudative conjunctivitis, exudative pharyngitis, discrete intraoral lesions, bullous or vesicular rash, or generalized adenopathy. Consider alternative diagnoses (see Table 297.3). [3]Supplemental laboratory criteria include albumin ≤3.0 g/dL, anemia for age, elevation of alanine aminotransferase level, platelets after 7 days ≥450,000/mm^3, white blood cell count ≥15,000/mm^3, and urine ≥10 white blood cells/high-power field. Can treat before performing echocardiogram. [4]Echocardiogram is considered positive for purposes of this algorithm if any of three conditions are met: Z-score of left anterior descending artery or right coronary artery ≥2.5; coronary arteries meet Japanese Ministry of Health criteria for aneurysms; or three or more other suggestive features exist, including perivascular brightness, lack of tapering, decreased left ventricular function, mitral regurgitation, pericardial effusion, or Z-scores in left anterior descending artery or right coronary artery of 2 to 2.5. If echocardiogram is positive, treatment should be given to children within 10 days of fever onset and to children beyond day 10 with clinical and laboratory signs (C-reactive protein, erythrocyte sedimentation rate) of ongoing inflammation. [5]Typical peeling begins under nail bed of fingers and then toes. *ALT,* Alanine aminotransferase; *CRP,* C-reactive protein; *ESR,* erythrocyte sedimentation rate; *hpf,* high-power field; *WBC,* white blood cell. *(From McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association.* Circulation. *2017;135:e927-e999.)*

TABLE 297.3 Differential Diagnosis of Kawasaki Disease

Infections
Adenovirus infection
Enterovirus infection
Measles
Scarlet fever
Staphylococcal or streptococcal toxic shock syndrome
Rocky Mountain spotted fever
Parvovirus B19 infection
Leptospirosis
Other Conditions
Rheumatic fever
Stevens-Johnson syndrome
Systemic-onset juvenile idiopathic arthritis
Polyarteritis nodosa
Reactive arthritis
Drug reaction

PATHOLOGY

KD is a systemic vasculitis that primarily affects medium-sized, extraparenchymal musculoelastic arteries with a predilection for the coronary arteries. Myofibroblast infiltration with secretion of proinflammatory cytokines, matrix metalloproteinases, and elastases destroys the structural integrity of the vessel wall and can result in aneurysm formation.[59] Three linked vasculopathic processes characterize the acute and chronic pathologic changes in the vessel wall and include an acute, self-limited necrotizing arteritis, a subacute or chronic vasculitis, and luminal myofibroblastic proliferation.[60]

The necrotizing arteritis that occurs during the first 2 weeks after onset of fever is characterized by infiltration with neutrophils from the lumen of the vessel. Myocarditis is universal at this stage and can progress to fibrosis and scarring in the later stages.[35] During the subacute phase, which may begin within the first 2 weeks after fever onset, there is an infiltration of lymphocytes, plasma cells, and eosinophils from the adventitial vasa vasorum that progresses toward the lumen. Aneurysms of the coronary arteries with or without thrombosis can occur. Immunohistochemistry shows a predominance of CD8$^+$ T cells and macrophages infiltrating the vessel wall with secretion of matrix metalloproteinases during this stage.[61,62] Infiltration of immunoglobulin A–secreting plasma cells is also noted.[63]

A different vasculopathic process involves a progressive, asynchronous intraluminal stenosis mediated by myofibroblasts. This process is associated with intimal thickening, remodeling of aneurysms, thrombotic occlusion, and stenosis in the medium-sized arteries.[60]

GENETICS

Evidence for a genetic component to KD susceptibility includes the increased incidence among Japanese children and among children of Japanese descent residing outside Japan, the occurrence of KD within extended pedigrees, the increased incidence of a history of KD in the parents of a patient with KD, and the increased incidence among siblings of an index case.[10,64,65] Twin studies have yielded conflicting results, and numbers of monozygotic twins concordant for KD are

small, owing in part to the rarity of monozygotic twins in the Japanese population.[66] Family linkage studies and genome-wide association studies have implicated single nucleotide polymorphisms in the transforming growth factor-β and calcineurin-NFAT (nuclear factor of activated T cells) pathways as well as variants in the Fcγ receptor genes.[67–73] Whole-genome sequencing of a family with two affected siblings revealed compound heterozygous mutations in TLR6.[70] Clearly the genetics of KD susceptibility is multifactorial, and further studies will be needed to capture this complexity. Whether additional genetic determinants predispose to aneurysm formation is currently under study.

THERAPY

The standard therapy for KD is infusion of IVIG (2 g/kg) in combination with aspirin. If administered within the first 10 days after fever onset, this regimen reduces the risk for coronary artery aneurysms from 25% to 5%.[74] Although this regimen rapidly reduces markers of inflammation, fever, and clinical signs in most patients, 10% to 20% of patients will have persistent or recrudescent fever at least 36 hours after the end of the IVIG infusion and are classified as IVIG resistant. Different strategies are used to treat this subset of patients, including a second infusion of IVIG, infliximab, and methylprednisolone.[75–78] However, the requirement for a large sample size and associated costs of a prospective, randomized clinical trial have prevented the generation of evidence-based guidelines for treatment of IVIG-resistant patients. At the present time, a comparative effectiveness clinical trial (KIDCARE) is randomly assigning IVIG-resistant subjects with KD to receive either a second IVIG infusion (2 g/kg) or infliximab (10 mg/kg) (Kawasaki Disease Comparative Effectiveness Trial [KIDCARE]; ClinicalTrials.gov Identifier: NCT03065244; https://clinicaltrials.gov/ct2/show/NCT03065244).[79]

In an attempt to prevent IVIG resistance, investigators have tested different strategies for intensification of initial therapy in three different randomized, placebo-controlled clinical trials. The addition of single-dose intravenous methylprednisolone to standard therapy did not reduce IVIG resistance or median coronary artery Z-score.[78] However, standard therapy with the addition of intravenous followed by oral methylprednisolone for up to 4 weeks in Japanese patients selected by a scoring system to be at increased risk for IVIG resistance resulted in a significant decrease in both treatment failures and coronary artery Z-score in the corticosteroid-treated group.[80] The validated scoring system for Japanese patients has had low sensitivity when applied to patients with KD of other ethnic backgrounds, and attempts to create alternative scoring systems have failed.[81,82] In the third clinical trial, the addition of infliximab (5 mg/kg) to standard therapy resulted in a more rapid decrease in inflammatory markers, fever, and coronary artery Z-scores but did not prevent IVIG resistance.[83]

Therapy for patients with highly resistant KD may include steroids, cyclosporine, low-dose methotrexate, plasmapheresis, and cytotoxic agents such as cyclophosphamide. There are no evidence-based recommendations to guide therapy in this subset of patients with KD.

CARDIOVASCULAR INVOLVEMENT

In his initial description of KD, Kawasaki was unaware of the cardiovascular complications and described KD as a benign, self-limited illness with no sequelae. In 1970, after a survey commissioned by the Japanese Ministry of Health, it became clear that KD could cause coronary artery aneurysms and lead to myocardial infarction and death.[1] Coronary artery aneurysms develop in 25% of untreated children, although the lesions may remain silent until adulthood, when sudden thrombosis can lead to myocardial infarction and death.[84] Transthoracic echocardiography is the method of choice for measuring the internal diameter of the proximal coronary arteries in children, and detailed guidelines are available for the method and timing of these studies during the acute and subacute illness.[54] Arteries with a Z-score less than 2.0 are considered normal. In patients treated within the first 10 days after fever onset, 20% to 30% will have transiently dilated arteries, whereas 5% to 7% will develop permanent damage to the coronary artery wall with aneurysm formation. Although most of these aneurysms will remodel over time, the vessel wall is never again normal, and the risk for subsequent stenosis and thrombosis is still being defined.[85]

Patients with aneurysms require lifelong follow-up regardless of internal dimension or subsequent remodeling. Acute therapy may include aspirin at antiplatelet doses with or without clopidogrel for small to medium-sized aneurysms (Z-score <10). Patients with larger aneurysms (>8 mm or Z-score ≥10) require systemic anticoagulation to prevent thrombosis and may be treated with low-molecular-weight heparin or warfarin.[86]

LONG-TERM OUTCOME

Patients with large coronary aneurysms after KD are at high risk for subsequent cardiovascular events and will require lifelong surveillance by cardiologists knowledgeable about management issues in this patient population.[87,88] Patients with regressed aneurysms after KD remain at increased risk for thrombosis and other adverse outcomes and should be followed closely. Whether KD is associated with accelerated development of atherosclerosis remains controversial, but the vasculopathy of KD appears to be distinct from that of atherosclerosis.[89]

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The complete reference list is available online at Expert Consult.

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Special Problems

IV

A Nosocomial Infections

298 Infection Prevention and Control in the Health Care Setting

Tara N. Palmore

SHORT VIEW SUMMARY

- Infection-prevention and infection-control programs aim to reduce the risk of health care–associated infections in institutions that care for an increasingly vulnerable, elderly, and often immunosuppressed patient population. The goal is to make the hospital a safe place for patients and staff.
- Health care epidemiologists use an expanding repertoire of evidence-based techniques and technology to identify and mitigate risks from an ever-changing array of invasive devices and procedures. Hand hygiene remains the staple infection-prevention measure; although hospitals have attempted many methods for improving adherence, an improving array of electronic compliance monitoring systems may increasingly perform that function.
- The built environment of the hospital is a well-documented reservoir for pathogens that can infect susceptible patients. Environmental disinfection depends on manual cleaning with effective disinfectant solutions. Microbial killing on surfaces can be augmented with use of adjunctive ultraviolet C light, which reduced acquisition of nosocomial pathogens in a randomized trial, or with hydrogen peroxide vapor or mist. Hospital water systems can harbor *Legionella* or other waterborne pathogens and must be managed attentively in order to minimize the risk to patients. Engineering, including tailored air handling, is used to help protect patients from airborne pathogens such as *Mycobacterium tuberculosis* and mold spores.
- Multidrug-resistant organisms are an evolving challenge for infection-control personnel, who must monitor and attempt to control the spread of resistant organisms within the institution, including emerging pathogens such as *Candida auris*. Newer, more rapid tools for surveillance aid in decisions to isolate carriers. Old measures have found new evidence; in a randomized trial chlorhexidine baths reduced transmission of methicillin-resistant *Staphylococcus aureus* and in other studies prevented central line–associated bloodstream infections. Because antimicrobial stewardship, dealt with in Chapter 51, can affect antimicrobial resistance, some hospitals assign this responsibility to hospital infection-control staff.
- Outbreak investigation involves increasingly sophisticated tools, such as microbial genome sequencing, to confirm clonality. Shoe-leather epidemiology remains a critical means of collecting exposure data that can be combined with genomic data to elucidate routes of transmission. Emergence and rapid global spread of new pathogens requires hospital epidemiologists to be nimble. The 2014–15 Ebola outbreak required rapid initiation of drastically new screening and isolation measures in hospitals, despite the low risk of identifying an Ebola-infected patient in any given facility.
- Collaboration of infection-control and occupational medicine staff helps reduce risk of occupational exposures and infection. Plans need to be in place for immediate management of exposures to varicella and bloodborne pathogens. Rapid investigation of health care personnel and patient exposures to these communicable pathogens allows prompt initiation of postexposure prophylaxis. Preexposure immunization of health care personnel to influenza and other vaccine-preventable diseases makes the hospital a safer place for both staff and patients.

Hospital infection control traces its roots to the mid-19th century, when medical and scientific investigators noted the preventive benefits of hand hygiene, surgical antisepsis, and hospital hygiene. These measures remain at the core of infection prevention, with an expanding base of scientific research to guide their application in the setting of increasingly complex medical care and increasing antibiotic resistance.

Infection-prevention programs are charged with a mission that involves conducting surveillance; implementing isolation; investigating and rapidly intervening in suspected nosocomial transmission; educating health care personnel, patients, and visitors; reporting infections to public health authorities; participating in antimicrobial stewardship; and working with occupational health specialists to anticipate and avert

preventable exposures and infections and to manage those that occur despite those efforts.[1] This chapter aims to address important aspects of some of these infection-prevention and infection-control activities. Antimicrobial stewardship is discussed separately, in Chapter 51.

PATHOGEN TRANSMISSION IN THE HOSPITAL

Bacterial pathogens of epidemiologic significance typically inhabit specific niches on or in the human body, or in the hospital environment, that can serve as reservoirs for transmission. Patients' skin, intestinal, and respiratory microbiota are distorted within a few days in the hospital, and their flora in turn colonize their inanimate environment within the hospital.[2] Patients' flora can also be deranged by antibiotic therapy or chemotherapy, lowering resistance to colonization with antibiotic-resistant nosocomial pathogens.[3]

Patients who are colonized with resistant bacteria serve as accidental reservoirs for spread to other patients. Colonization pressure, the proportion of patients in a given ward who are carriers, is an independent risk factor for transmission of resistant bacteria.[4,5] Most nosocomial pathogens are thought to be transmitted from person to person on the hands of health care personnel, from contaminated surfaces in the hospital environment, or from contaminated patient care equipment. Hand hygiene and correct disinfection of equipment and hospital surfaces are thus important means of preventing spread.

Hand Hygiene

Hand hygiene is a critical infection-control measure[6,7] yet one of the most challenging to follow consistently. The World Health Organization's "Five Moments for Hand Hygiene" is a simple representation of transitions in patient care at which hand hygiene should be done in order to prevent cross-transmission: before touching a patient, before clean or aseptic procedures, after body fluid exposure or risk, after touching a patient, and after touching patient surroundings.[6] Monitoring hand hygiene compliance is required of hospitals in many countries. Despite evidence that hand hygiene prevents nosocomial infections,[8] adherence remains as low as 40% to 60%.[9,10]

Researchers have attempted to understand the basis for inadequate hand hygiene compliance in order to identify opportunities for improvement. A study found that full compliance with World Health Organization guidelines would cost each intensive care unit (ICU) nurse 58 to 70 minutes spent on hand hygiene per patient during a 12-hour day shift.[11] The report illustrates the tension between patient care workload and commitment of time to meticulous hand hygiene. Studies aimed at improving hand hygiene compliance have focused on improving compliance monitoring and addressing behavioral and psychological barriers to consistent hand hygiene. One hospital system addressed both goals by broadening compliance monitoring to all frontline health care personnel, producing more robust monitoring data, engaging staff more deeply in the effort, and perhaps instilling an interest in improving hand hygiene.[12] Many studies have explored ways to improve hand hygiene and (perhaps more challenging) sustain the improvement. Some reports describe engagement of patients in the effort. Electronic hand hygiene monitoring systems hold promise, but results from early-generation systems have been mixed,[13,14] demonstrating that the technology cannot yet accurately measure adherence to a simple manual task. As treatment options for some classes of multidrug-resistant bacteria diminish, hand hygiene remains the single most important intervention to limit morbidity and mortality due to these organisms. Achieving better hand hygiene compliance is a major goal of infection-control programs.

Disinfection and Sterilization (See Chapter 299)

Disinfection and sterilization of patient care equipment are a fundamental aspect of infection prevention in a hospital. The Spaulding classification for disinfection and sterilization is outlined in Table 298.1. Patients and health care personnel generally take for granted that medical instruments used for invasive procedures are appropriately disinfected or sterilized and represent the least of the patient's risk for postprocedure complications. Yet hospital disinfection and sterilization programs present many opportunities for errors and mishaps. For example, disinfection or sterilization can fail if visible organic or inorganic material is not first cleaned from instruments, reagents are expired and have lost potency, or biologic indicators are not used properly. Sizeable clonal outbreaks of multidrug-resistant bacteria in recent years have brought to light the frailties of high-level disinfection procedures for gastrointestinal endoscopes, particularly those used for biliary procedures. Some large outbreaks were traced to endoscopes that retained infectious material even after cleaning and disinfection according to published guidelines.[15,16]

Environmental Cleaning and Disinfection

Environmental cleaning in the health care environment is aimed at removing visible soiling, and disinfection is aimed at reducing the burden of microorganisms on surfaces in the health care setting.[17,18] A patient who occupies a room that has been vacated by a person infected or colonized with *Clostridioides difficile* (formerly *Clostridium difficile),* vancomycin-resistant enterococci (VRE), or methicillin-resistant *Staphylococcus aureus* (MRSA) has elevated risk of developing *C. difficile* infection or becoming colonized with the respective organism.[19–22] In a separate transmission scenario, health care personnel can transfer viable organisms through contact with surfaces in the patient room, even if they do not touch the patient, and, in the absence of proper hand hygiene, carry them outside the room to the common hospital environment from which they can be spread to other patients.[17,18] This chain of transmission can be mitigated by meticulous hand hygiene and thorough disinfection of the patient care environment, but neither activity is performed with consistently high quality in many hospitals.[23,24]

Methods of Environmental Cleaning and Disinfection

Liquid chemicals used for environmental cleaning are also low-level disinfectants, and, if applied correctly, can serve both purposes. Environmental cleaning and disinfection focus on surfaces that are repeatedly soiled, such as bathrooms and surfaces that are "high touch." Even floors should be considered as potential sources of transmission to patients; guidelines recommend use of disinfectant floor cleaners in

TABLE 298.1 Indications for Sterilization, High-Level Disinfection, and Low-Level Disinfection

TECHNIQUE	DESCRIPTION	INDICATION
Sterilization	Elimination of all microbial life, including spores,[a] using pressurized steam, gas, or liquid chemicals	Critical medical and surgical devices and instruments that enter normally sterile tissue or the vascular system or through which blood or other sterile body fluids flow
High-level disinfection	Elimination of all microbial life, except bacterial spores, using liquid chemicals	Semicritical patient care equipment (e.g., gastrointestinal endoscopes, bronchoscopes, respiratory therapy equipment) that touches either mucous membranes or nonintact skin
Low-level disinfection	Removal of most microorganisms, except bacterial spores, using liquid chemicals	Noncritical patient-care surfaces (e.g., bed rails, over-the-bed table) and equipment (e.g., blood pressure cuff) that touch intact skin.

[a]Standard sterilization techniques are not considered sufficient to destroy prions.
Data from Rutala WA, Weber DJ; Healthcare, Infection Control Practices Advisory Committee (HICPAC). Guideline for Disinfection and Sterilization in Healthcare Facilities. *Atlanta: Centers for Disease Control and Prevention; 2008.*

wards with high endemic rates of multidrug-resistant organisms (MDROs).[25,26] Cleaning solutions that contain quaternary ammonium compounds are relatively ineffective at killing *C. difficile* spores and inactivating nonenveloped viruses such as norovirus. Hydrogen peroxide and bleach solutions have activity against these pathogens, in addition to standard viruses and vegetative bacteria, and may be preferable for routine environmental cleaning and disinfection.[27]

C. difficile spores and MDROs, particularly those that are hardy (e.g., resist desiccation, tolerate a range of temperatures) such as VRE, *Acinetobacter baumannii,* and *Candida auris,* contaminate the environment in the rooms of patients who are colonized with these bacteria.[28] Several techniques developed to enhance environmental disinfection have been tested in clinical trials, most notably machines emitting hydrogen peroxide and ultraviolet light.

Hydrogen peroxide vapor treatment requires rooms, or entire wards, to be sealed, disconnected from air handling systems, and then filled with vapor at a concentration that is monitored and adjusted throughout the treatment. The treatment, which must be administered by specially trained technicians, inactivates heavy concentrations of vegetative bacteria and spores, even in the presence of proteinaceous material.[29] Its potent inactivation of viruses made it the decontamination method of choice in Europe, the United Kingdom, and the United States during the 2014–15 Ebola virus outbreak (see later). Another form of hydrogen peroxide, an aerosolized mist, is aimed more directly on targets of disinfection and has less impact on microbial contamination in vitro.[30,31]

Ultraviolet light–emitting devices for environmental disinfection use low-pressure mercury vapor lamps to emit germicidal ultraviolet C (UV-C) wavelengths or use pulsed xenon-generating broad-spectrum ultraviolet light that includes UV-C wavelengths. Prospective clinical trials have evaluated the ability of hydrogen peroxide vapor and UV-C disinfection, as adjuncts to terminal room cleaning, to reduce the risk that newly admitted patients would acquire MDROs from prior room occupants.[32] A single-center, prospective cohort study found that standard terminal room cleaning followed by hydrogen peroxide vapor treatment reduced the risk of MDRO acquisition by more than 60% compared with standard cleaning.[32] A large cluster-randomized crossover trial compared four arms (standard cleaning, standard cleaning followed by UV-C, bleach cleaning, and bleach cleaning followed by UV-C), and found that the addition of UV-C to standard cleaning reduced subsequent acquisition of pathogens by 30%.[33] Oddly, standard cleaning followed by UV-C had a greater impact than bleach cleaning followed by UV-C, and the addition of UV-C to bleach cleaning had no impact on acquisition of *C. difficile* infection. Clinical outcome data from these trials suggest that these adjunctive modalities do reduce nosocomial transmission of pathogens above and beyond what is accomplished with manual cleaning. Ultraviolet devices can be used by trained housekeeping staff, and may be worthwhile for targeted use if financially feasible.

Water Management

Hospital water safety is a priority and a challenge for health care epidemiologists, hospital safety officers, and facility engineers. As with other health care–associated infections, waterborne infections can cause significant morbidity and mortality, and some are preventable. Pathogens such as *Legionella* and nontuberculous mycobacteria can colonize the central pipes or outlets of potable water distribution systems in hospitals, and other gram-negative bacteria reside in biofilms near the points of use. Because so many outbreaks of nosocomial waterborne infections are preventable,[34] hospitals are required to have proactive water management programs.

Although municipal and hospital tap water is not expected to be free of potential pathogens, municipal water is tested routinely to ensure safe levels of important pathogens such as coliform bacteria. Contaminated municipal water can cause outbreaks that affect immunocompromised patients in health care settings,[35] but contamination of hospital water usually occurs within the plumbing of the health care facility.[36] Waterborne bacteria that would not affect community dwellers or even the majority of hospitalized patients may infect the most highly vulnerable because of underlying diseases, immunosuppression, and the presence of invasive devices that provide a route of entry, bypassing the normal defenses.

Transmission of Waterborne Pathogens

Waterborne pathogens can be transmitted to patients via aerosols, such as through a shower or room humidifier,[37–40] cooling tower,[41] or aspiration while drinking water. Recent outbreaks of deep-seated nontuberculous mycobacterial infections among cardiac surgery patients around the globe were traced to heater-cooler units that aerosolized the bacteria from contaminated water tanks in the direction of the surgical field.[42] Some waterborne bacteria may be transmitted indirectly from hands[43] or objects that had contact with contaminated water, such as bath supplies and linens[44] or by means of tap water used inappropriately for respiratory care of ventilated patents[45,46] or rinsing of respiratory therapy or endoscopic equipment in tap water.[47,48] As in most nosocomial infections, the precise route of transmission is often unknown, even when the link to a water source is apparent.[49]

Biofilms in Hospital Plumbing

Biofilms in the pipes and outlets of water distribution systems provide the environment for growth of *Legionella,* mycobacteria, *Pseudomonas*, *Sphingomonas,* and other waterborne organisms. Eliminating bacteria that dwell in biofilms is difficult because they are somewhat impervious to disinfectants.[50,51] Stagnation of water, due to pipe design or low flow, creates optimal conditions for biofilm formation and colonization. Certain water pipe formations, such as dead legs and long horizontal runs of pipe,[52,53] contribute to stagnation and are discouraged in hospital construction guidelines. Many older facilities have convoluted plumbing that has, over time, developed low-flow zones and may be more vulnerable to water system colonization with *Legionella,* mycobacteria, and others. Cooling towers have been implicated in nosocomial and community outbreaks.[41,54] Biofilms can also form at the points of use; electronic eye faucets,[55–58] aerators, ice machines, decorative fountains,[52,59] and other items that are at the interface between water and patients can become colonized and have been implicated in nosocomial transmission.

Legionnaires' Disease

Legionnaires' disease, a potentially severe pneumonia caused by *Legionella* species, is an important health care–associated infection. *Legionella pneumophila,* the species responsible for the vast majority of infections, is one of the most dreaded nosocomial waterborne pathogens. The mortality rate of hospital-acquired legionnaires' disease is approximately 32%, more than three times higher than that of community-acquired infection, likely because of the underlying comorbidities of hospitalized patients.[60] Although most legionnaires' disease is acquired in the community, approximately 33% of outbreaks occur in health care facilities, accounting for 85% of deaths due to legionnaires' disease outbreaks.[61] As described elsewhere (see Chapter 232), the most immunologically vulnerable patients in the hospital and those with advanced age and chronic lung disease are at highest risk for nosocomial legionnaires' disease.

Legionella experts are divided regarding proper primary prevention of nosocomial *Legionella* outbreaks and whether hospital water should be cultured prospectively for *Legionella* spp. The Centers for Disease Control and Prevention (CDC) recommends close clinical surveillance for *Legionella* infection and a low threshold for investigation when a suspected nosocomial case occurs.[62] Other sources, including published guidelines in much of Europe, recommend routine sampling and testing of hospital water even when no nosocomial infections have occurred. Most would agree with testing water regularly for the presence of *Legionella* after an outbreak has already occurred, for secondary prevention.

Disinfection of Hospital Water

Water circulating in health care facilities should have adequate concentrations of disinfectant at the point of use. Although most municipal water may be adequately chlorinated, free chlorine, the component of total chlorine that has antimicrobial activity, can dissipate as water travels through the water distribution system, leaving low residual levels at the patient room faucet.[63] If hospital chlorine measurements are performed at a central location, the concentrations that directly affect patient safety will not be apparent. Supplemental disinfection systems add chlorine (in the form of sodium hypochlorite, or bleach), monochloramine, chlorine dioxide, ozone, or copper-silver ions to the water supply. Even

when seemingly optimal supplemental disinfection is used, clinicians must be vigilant for breakthrough contamination, which generally manifests earliest as infections among the most immunocompromised or critically ill patients.[64]

Wastewater Plumbing Contamination

A more recently recognized aqueous threat to hospitalized patients is contamination of sink drains and other drains in rooms of patients with MDROs. Although the drains are not in direct contact with patients, experimental studies have demonstrated the dispersal of organisms from the sink drain when water from the faucet splashes back from the drain or its sieve.[65] Resistant organisms may also disseminate in an aerosol when hospital toilets are flushed.[66] In one quasiexperimental study, addition of a lid to ICU hoppers (toilet-like waste disposal fixtures) and biofilm-inhibiting devices to sink drains reduced by half the nosocomial acquisition of carbapenemase-producing organisms.[67]

Air Handling

Hospital ventilation is a critical feature of the building infrastructure that must be engineered to meet a range of infection-control requirements in different areas of the hospital. Notable issues include negative pressure isolation rooms for patients who have suspected or confirmed airborne infections; positive pressure protective environment rooms for patients who are undergoing treatment for leukemia or stem cell transplantation; and laminar flow in operating rooms.

Air Handling for Airborne Infections

Patients infected with airborne infections, such as tuberculosis, measles, and chickenpox, cough or exhale pathogens in tiny droplets that travel and remain viable in air currents, and can infect susceptible persons who are in the path of airflow from the affected patient. Health care personnel and other patients outside the room of a patient with an airborne infection may be exposed when the door is opened, and such exposures have been documented in health care outbreaks.[68,69] Therefore, hospitalized patients who have suspected or known airborne infection should be housed in airborne isolation rooms—private rooms that have monitored negative airflow with respect to the anteroom or hallway, and 6 to 12 air changes per hour, with the exhausted air filtered through a high-efficiency particulate air (HEPA) filter or released to the outside.[70] Negative airflow draws infectious particles toward the patient and prevents their dispersal out of the room when the door is opened.

Air Handling to Prevent Nosocomial Mold Infections

Patients who have prolonged neutropenia during treatment of leukemia, stem cell transplantation, and some immunotherapies are highly vulnerable to nosocomial mold infections (see Chapter 306). Mold spores, which are as small as 2 to 4 μM, are ubiquitous and easily disseminate in the hospital via air currents, dust, and other particulate matter. Protective isolation rooms are equipped with HEPA-filtered air intake, use positive pressure airflow with at least 12 air changes per hour to repel air currents that carry mold spores, and have seams and cracks sealed to prevent incursion of mold spores through tiny breaches in the envelope of the room.[71] When vulnerable patients leave their rooms and their wards for tests or procedures, they are usually entering areas of the hospital that do not have special environmental precautions, and where they may be exposed to mold spores. Directional airflow and HEPA filtration are also used to minimize escape of fungal spores from construction sites within the hospital. Exposure to construction is a well-described risk factor for invasive mold infections among neutropenic patients, and planned engineering measures, in addition to traffic control and other dust containment measures, can significantly reduce the mold spore content of air near an indoor construction zone.[72–74] Neutropenic patients who leave their rooms are advised to don surgical masks, which offer little protection against mold spores, or less commonly N95 respirators, which have not been tested for protection against mold infections.

Air Handling in the Operating Room

Operating rooms require fresh, filtered air in order to prevent surgical site infections. Operating rooms should have positive pressure airflow with respect to the surrounding rooms and hallway, with at least 20 filtered air changes per hour, including fresh (outside) air. Airflow can be laminar or directional within the room, such that it enters at the ceiling and exhausts near the floor. Operating room air must be maintained at a moderate range of humidity, 20% to 60%, in order to minimize risk of both static electricity (low humidity) and conditions that promote microbial growth (high humidity).[75]

Air Quality

Routine air samples for fungal culture are not recommended. Air samples may be collected as part of an investigation of a suspected cluster or outbreak of nosocomial mold infections. Even then, they are rarely helpful because there is not a clear correlation between air sample mold growth and risk to patients.[76,77] In addition, mold outbreaks among immunocompromised patients are typically polyclonal, and air samples often capture different species or strains than those that are relevant in the outbreak. Use of enhanced clinical monitoring and surveillance for possible nosocomial mold infections is recommended in order to detect possible acquisition from the hospital environment.[71] An exception is the required microbiologic air sampling that must be conducted in hospital pharmacies and clean-room laboratories in which medications or cell products are prepared for intravenous infusion. In such facilities, routine air sampling is a required part of an environmental monitoring program to ensure sterility of parenteral solutions.

TRANSMISSION-BASED INFECTION-CONTROL PRECAUTIONS

Colonization

Colonization refers to the peaceable presence of bacteria or fungi on or in a person, including organisms that are part of the normal human microbiota. Patients develop infection if the organisms with which they are colonized subsequently invade, stimulate a symptomatic immune response, or both. Colonized patients can serve as silent reservoirs for transmission. The routes by which pathogens are thought to spread determine the isolation precautions used to limit their transmission.[78] In a more conservative approach, patient isolation is implemented not only when a patient has a confirmed communicable infection or colonization, but also when a transmissible pathogen is suspected, in order to prevent transmission during the diagnostic interval. Such empirical isolation is used until the results of testing confirm or refute the need for ongoing isolation.

Organisms Transmitted by Contact

Most epidemiologically important bacteria, including MDROs and many viruses, are spread directly by means of person-to-person contact, or indirectly via contact with contaminated patient care equipment or surfaces. Intestinal pathogens (e.g., *C. difficile, Salmonella, Shigella, Escherichia coli,* norovirus, astrovirus, and adenovirus 40/41) are shed in high concentrations, and therefore are highly transmissible, when patients are symptomatic. Of note, some are also transmissible when shed by asymptomatic persons.[79,80] Contact precautions with use of barriers such as gowns and gloves are intended to interrupt transmission of MDROs and other pathogens, although their effectiveness can be undermined by contaminated equipment such as stethoscopes or portable radiography film cartridges that are not properly disinfected.

Despite established recommendations to use contact isolation to care for patients who are colonized or infected with MDROs,[78] the measures are controversial in part because of a paucity of evidence to support their use. In a cluster-randomized trial by Harris and colleagues, ICUs were randomized to universal gowns and gloves for all patient care or contact precautions for standard indications.[81] Universal contact precautions reduced acquisition of MRSA but not VRE, demonstrating that barrier precautions do not thwart all the nosocomial routes by which patients become colonized. Implementation of universal gowning and gloving may be a useful measure during an ICU-based outbreak.

Organisms Transmitted by Droplet

Pathogens that infect or colonize the upper respiratory tract, such as respiratory viruses, staphylococci, *Bordetella pertussis,* and group A streptococci, can spread via droplet routes. These pathogens are shed

from the upper respiratory tract in droplets that are typically greater than 5 μM in size and fall within 1 to 2 meters of the patient. Pathogens within those droplets can spread to health care personnel when they land on mucous membranes or may be transmitted indirectly via hands or fomites. Thus a face mask and gloves are components of droplet isolation.[78]

Organisms Transmitted by the Airborne Route

Infections known to spread via the airborne route include tuberculosis, varicella, and measles. Pathogens that are shed in droplet nuclei, which are viable particles 2 to 5 μM in size, can remain airborne for prolonged periods, traveling in air currents. Isolation rooms for airborne infections were described earlier. The room door must remain closed in order for these measures to contain infectious particles, and an anteroom provides an additional layer of protection between the patient room and the hallway. Health care personnel wear fitted particulate respirators, referred to as N95 respirators because they filter 95% of airborne particles, or powered air-purifying respirators that draw air into a hood through a HEPA filter and provide better protection.[82]

Organisms Transmitted by Aerosol

Some pathogens may be shed by forceful coughing, sneezing, or vomiting, in aerosols that include droplets of varying sizes, some of which may travel farther than 2 meters before falling as a result of gravity. Aerosols are thought to play a role in spread of influenza, among other pathogens.[83,84] Aerosol-producing procedures, such as endotracheal intubation, bronchoscopy, sputum induction, and pentamidine administration, merit use of respirators to protect health care personnel from the temporarily airborne particles.[70]

DEVICE-RELATED INFECTIONS

Invasive procedures and indwelling devices, often essential to providing lifesaving supportive care, can serve as portals of entry for pathogens. Each major category of device has distinct, evidence-based preventive measures that can reduce the associated risk of infection.

Ventilator-Associated Pneumonia (See Chapter 301)

Ventilator-associated pneumonia (VAP) is a largely preventable complication of mechanical ventilation in the ICU. Although the incidence of VAP varies by definition,[85] VAP is diagnosed in approximately 10% of ventilated patients,[86] leading to prolonged length of ICU stay, greater duration of mechanical ventilation, and an attributable mortality of about 13%.[87]

Measures to Prevent Ventilator-Associated Pneumonia

Avoiding intubation is the most obvious method of preventing VAP and may be feasible in some clinical scenarios with use of noninvasive positive pressure ventilation. In patients who are already intubated, national consensus guidelines recommend minimizing sedation, conducting spontaneous awakening trials, and assessing patients' readiness for extubation daily in an effort to reduce the duration of mechanical ventilation.[88] In addition, patients should have the head of the bed elevated to 30 to 45 degrees to reduce reflux of gastric contents and should undergo regular subglottic secretion suctioning to avoid pooling of secretions above the endotracheal tube cuff.[88]

Additional methods to prevent VAP that are less uniformly accepted include oral care with antiseptics and silver-coated endotracheal tubes.[88] A Cochrane review evaluated 18 randomized controlled trials of oral hygiene care, including those employing chlorhexidine mouthwash or gel, and concluded that oral hygiene, compared with placebo or usual care, reduced the risk of VAP from 25% to 19% but had no impact on mortality, ventilation days, or duration of ICU stay.[89] A meta-analysis of randomized trials comparing chlorhexidine oral care with placebo concluded that use of chlorhexidine prevented nosocomial pneumonia in cardiac surgery patients but did not prevent VAP or significantly affect mortality, duration of ventilation, or ICU length of stay in other ventilated patients.[90] Another meta-analysis reviewed randomized controlled clinical trials of silver-coated endotracheal tubes compared with noncoated tubes. Although the tubes led to a significant reduction in VAP rates in one well-designed trial,[91] the Cochrane review authors concluded that overall evidence that the tubes prevent VAP or have other beneficial clinical impact is weak.[92]

Selective Oral and Digestive Decontamination

Selective oral decontamination and selective digestive decontamination use antibiotic combinations to reduce the microbial burden in the oral cavity and gastrointestinal tract, respectively, and have shown promising results in clinical trials conducted in Europe. Selective oral and digestive decontamination reduced mortality by 3.5% and 2.9%, respectively, in a cluster-randomized trial of 13 ICUs in the Netherlands.[93] The concern that they could increase antibiotic resistance has not been borne out conclusively by clinical trial data. Studies conducted in ICU settings with low prevalence of multidrug resistance showed low impact on prevalence of resistance.[93–95] The practices have not been widely adopted in the United States in part because of unresolved concerns about antimicrobial stewardship, *C. difficile* infection, and long-term exacerbation of antimicrobial resistance, and the paucity of data on comparative effectiveness of these and other strategies for preventing VAP.[96]

Ventilator-Associated Events

A recent development in the surveillance and measurement of ventilator-associated complications in the United States is the use of ventilator-associated events, an umbrella category that developed owing to the ambiguity of VAP definitions and the difficulty of differentiating infectious and noninfectious conditions in complex intubated patients. Among ventilator-associated events, a minority of events have been classified as infections.[97] Because this surveillance definition is relatively new, there are not yet evidence-based estimates on the overall preventability of ventilator-associated events.

"Bundled" Ventilator-Associated Pneumonia Prevention Strategies

Although most of the individual prevention strategies discussed earlier have an evidence base for their use, they are often implemented in various combinations as VAP-prevention bundles, in an effort to amplify effect and ensure consistency. The prototypical VAP bundle was published by the Institute for Healthcare Improvement, which recommends the following collective interventions: head-of-bed elevation, daily sedative interruption and daily assessment of readiness to extubate, peptic ulcer prophylaxis, deep vein thrombosis prophylaxis, and daily oral care with chlorhexidine.[98] Bundles have been controversial in part because, despite comprising individual evidence-based elements, the composite interventions are inadequately studied in clinical trials to determine their overall effect on patient outcomes. Whether prevention methods are introduced individually or as bundles, educating and engaging the multidisciplinary ICU staff are essential to implementing and improving compliance with VAP-prevention measures and decreasing the burden of VAP on mechanically ventilated patients.[88,99]

Central Venous Catheter–Associated Infections (See Chapter 300)

Central venous catheters (CVCs) are often essential to the care of hospitalized patients. Their use is associated with complications, including bloodstream infections introduced by contamination of the foreign material that is penetrating the skin and residing in a large vein. Patients who develop catheter-associated bloodstream infections have increased length of stay and approximately triple the risk of in-hospital death.[100] Although evidence-based measures and concerted efforts have led to a 50% reduction in catheter-associated bloodstream infections across the United States since 2008,[101] they remain an important health care–associated infection that requires continual efforts toward prevention.

Preventive Measures for Catheter Insertion

Prevention of catheter-associated bloodstream infections begins with evidence-based preventive strategies during catheter insertion, including checklists providing reminders of appropriate insertion practices, nursing observation of insertion procedures, hand hygiene, all-inclusive catheter kits, maximum sterile barrier precautions for the operator and for the patient, and chlorhexidine-alcohol antiseptic skin preparation.[102]

Catheter placement into the femoral or internal jugular vein poses an increased risk of infection.[103] Infections related to infection-prevention breaches during catheter insertion typically manifest within 5 days of insertion.[104] Studies using antiseptic- or antibiotic-impregnated catheters have shown variable benefits for catheter-associated bloodstream infection prevention and have not identified the ideal antiseptic agent or antibiotic combination.[105–109]

Preventive Measures for Catheter Maintenance

Although measures related to CVC insertion significantly reduce infection rates,[110,111] practices related to maintenance of the catheters are also vital to preventing infections.[102,112] Evidence-based measures include nurse-to-patient ratios of at least 1 to 2, scrubbing of the catheter hub with disinfectants each time it is accessed, and cleansing of catheter sites with chlorhexidine-based antiseptic every 5 to 7 days along with dressing changes, or sooner if soiled.[102] Disinfectant caps and chlorhexidine-impregnated dressings have been shown to reduce catheter colonization and catheter-associated bloodstream infection rates.[113,114] Disruption of catheter dressings poses risk for infection,[103] but the impact of that accidental occurrence may be mitigated by the vigilance that is possible with a high nurse-to-patient ratio. The longer a CVC remains in place, the greater the risk of infection[102]; however, routine line changes based on time since insertion are not recommended.[115] Once the catheter has been inserted, the medical team must make efforts to reduce the number of catheter-days for each patient by reviewing the indications for maintenance of the catheter daily on rounds, with a goal of removing the device as soon as possible.

Chlorhexidine Gluconate Daily Baths

Daily rinses with 2% chlorhexidine gluconate are an effective preventive public health measure in the ICU. The antiseptic solution is applied on each patient from jaw to toes and left on to dry, leaving residual antimicrobial that reduces, for approximately a day, skin colonization with some antibiotic-resistant organisms, including MRSA, VRE, and possibly carbapenemase-producing Enterobacteriaceae.[116–118] Chlorhexidine baths can replace or follow regular showers or baths. Occlusive dressings, the perineum, and the 6 inches of lines, tubes, and drains closest to the skin can all be wiped with 2% chlorhexidine as part of the daily baths in order to minimize skin recontamination.[119] Because of strong (although not unanimous[120]) evidence from clinical trials demonstrating reduced rates of catheter-associated bloodstream infections, chlorhexidine daily baths have become standard of care in ICUs.[102] Few studies have been conducted outside the ICU, and existing studies of chlorhexidine baths in other hospital wards have shown mixed results for catheter-associated bloodstream infections rates, but very rare adverse effects.[121–123]

"Bundled" Catheter-Associated Bloodstream Infection–Prevention Strategies

As with other device-related infections, catheter-associated bloodstream infection–prevention measures, many of which have been tested individually in clinical trials, are often collected into bundles for insertion[110] and maintenance.[124] A systematic review and meta-analysis evaluating the effectiveness of insertion and maintenance bundles to prevent central line–associated bloodstream infections across adult, pediatric, and neonatal ICUs found that implementation resulted in a 60% decrease in such infections.[125,126] Evidence-based preventive measures that are recommended are clearly effective, assuming that they are implemented with sustained effort.

Catheter-Associated Urinary Tract Infections (See Chapter 302)

Catheter-associated urinary tract infections are among the most common health care–associated infections,[127,128] confounding efforts to limit antimicrobial use, prolonging hospital stay, and contributing cumulatively to nosocomial morbidity and mortality.[129] Risk factors for catheter-associated urinary tract infections were established long ago and include duration of catheterization, female sex, critical illness, and older age.[130–132]

Measures to Prevent Catheter-Associated Urinary Tract Infections

Avoiding catheter placement and limiting the duration of each patient's catheterization are key preventive measures because they reduce the days at risk of infection.[130,133] Current guidelines have outlined appropriate indications for placement of indwelling catheters, including acute urinary retention or obstruction, urinary incontinence in the presence of perineal or sacral wounds, precise monitoring of urine output, improved comfort for end-of-life care, and perioperative management of selected surgical procedures (e.g., urologic procedures or surgeries with long duration or need for intraoperative urinary monitoring).[129,134] Daily reevaluation of indications for urinary catheters identifies unnecessary catheter use and significantly reduces catheter use, duration of catheter use, and the rate of catheter-associated urinary tract infections.[135,136] Use of alternatives to indwelling catheters, such as condom catheters and intermittent straight catheterization, also reduces risk of urinary tract infection.[128] Other strategies that prevent catheter-associated urinary tract infections include education, sterile and atraumatic insertion, and maintenance of a sterile, closed drainage system.[128,137]

A national program implementing these measures demonstrated a one-third reduction in catheter-associated urinary tract infection rates outside ICUs, and no change in infection rates in ICUs.[128] One possible reason for the lack of progress is a plateau in catheter use within ICUs.[128] In addition, urine cultures are often reflexively collected during the course of evaluations for fever; positive cultures may meet the CDC criteria for catheter-associated urinary tract infections, but these fevers are often found to have plausible alternative explanations.[138] Treatment of asymptomatic bacteriuria is a major driver of overdiagnosis and overtreatment of catheter-associated urinary tract infections. A reduction in kneejerk culturing of urine combined with evidence-based preventive measures can result in fewer infections and improved patient outcomes.[139]

SURVEILLANCE

Hospital epidemiologists conduct two forms of surveillance for nosocomial infection: passive surveillance and active surveillance. Passive surveillance (known simply as "surveillance") involves collection of existing clinical data in order to track rates of infection or colonization, and to detect unusual infections or clusters that merit further investigation (discussed subsequently). Active microbial surveillance ("active surveillance") is testing specifically to screen patients for colonization with epidemiologically significant organisms.

Active Microbial Surveillance

Identification and isolation of colonized patients are standard measures to reduce the risk of transmission from otherwise silent reservoirs. The knowledge that a patient is colonized with an antibiotic-resistant organism provides an opportunity to interrupt nosocomial spread from that patient by using isolation precautions or, in limited circumstances, decolonization. Health care facilities transferring patients must notify receiving facilities of a patient's colonization status in order to prevent nosocomial spread within the institution accepting the transfer.[78]

Although targeted screening and isolation have been highly effective in some clinical settings,[140–143] various ICU-based strategies have shown no significant reduction in acquisition of resistant organisms in cluster-randomized clinical trials.[144,145] Screening tests have imperfect sensitivity, likely owing to variations in prevalence of the target organism in the screened population, variations in specimen collection, and the limits of detection of molecular and culture-based assays.

Widespread implementation of microbial screening and isolation is highly resource intensive and often does not show clear benefit in single centers that have low endemic rates of resistant organisms.[146] Universal screening for MRSA, implemented in 150 Veterans Affairs hospitals in combination with other measures, reduced MRSA infections by more than 40% among nearly 2 million admissions.[147] Using a centralized infection-control program involving active surveillance and isolation in all health care facilities (including long-term care facilities), the government of Israel, combatting a nationwide nosocomial outbreak of carbapenemase-producing Enterobacteriaceae, achieved sustained declines in transmission.[148] As gram-negative bacterial resistance rises in prevalence with limited treatment options, screening patients on transfer

TABLE 298.2 Sites for Microbial Surveillance to Detect Colonization With Select Multidrug-Resistant Organisms

RESISTANT ORGANISM	HIGHEST-YIELD SITES
Methicillin-resistant *Staphylococcus aureus*	Anterior nares[187]
Vancomycin-resistant *Enterococcus faecium/faecalis*	Rectal/perirectal[188]
Multidrug-resistant *Acinetobacter baumannii*	Groin and throat[189,190]
Multidrug-resistant Enterobacteriaceae	Rectal/perirectal[189]
Candida auris	Groin and axillae[28]

from other health care facilities and those who have been hospitalized in the past 6 months abroad for carbapenem-resistant gram-negative organisms has become a stronger imperative than screening for MRSA, for which there are usually multiple treatment options (Table 298.2).

Decolonization and Skin Antisepsis

Decolonization aims to eliminate carriage of potential pathogens in order to reduce the patient's risk of developing invasive infections and transmitting those pathogens to others. Despite clinical trials of decolonization for a number of nosocomial pathogens, the strongest evidence exists for *S. aureus* decolonization.[149]

Although no-rinse 2% chlorhexidine gluconate daily baths reduce skin colonization with a range of gram-positive and gram-negative nosocomial organisms, the treatments have shown more convincing benefit for preventing gram-positive infections than gram-negative infections. Some, but not all, clinical trials of their use in ICUs have demonstrated reduced rates of MRSA and VRE acquisition.[120,121,150,151] Data from single-center studies suggest a possible effect on infection with and transmission of *A. baumannii*.[152,153]

Management of Nosocomial Transmission of Multidrug-Resistant Organisms

When a nosocomial outbreak is suspected, hospital epidemiologists simultaneously escalate infection-control measures and initiate an investigation. Outbreak-control measures may involve isolating and cohorting infected or exposed patients and encouraging heightened adherence to hand hygiene, disinfection of equipment, enhanced environmental cleaning and disinfection, and other rigorous interventions. The use of dedicated adherence monitors may help ensure appropriate infection-control behaviors among health care staff, patients, and visitors.[154,155]

Outbreak investigations generally involve identifying cases, determining uniformity or clonality of the infecting pathogen, cataloguing detailed exposure histories to identify possible sources of infection or routes of transmission, and conducting surveillance to identify additional patients who are colonized or have subclinical infection. Surveillance should target the highest-risk patients first. Because of low sensitivity of surveillance swabs, variable intervals between exposure and detectable colonization, and the possibility of ongoing transmission, surveillance should be conducted repeatedly on at-risk populations.[156] If colonized or infected patients are identified in multiple wards, signaling a broader at-risk patient population, a surveillance sweep of the entire inpatient population, or large sections thereof, could identify isolated colonized outliers who could serve as reservoirs for new phases of transmission.[155]

Typing of Isolates

Spread of epidemiologically significant pathogens in a health care facility may manifest initially as an increase in clinical infections or an increase in positive results of surveillance tests (cultures or polymerase chain reaction [PCR] assays). Epidemiologic data are used to identify potential sources and routes of transmission, and molecular or genomic testing can determine relatedness of isolates. When clusters are detected via PCR testing, infection-control personnel may need to collect additional specimens for culture, in order to have isolates for comparison.

Older typing methods used for decades in health care epidemiology and public health include bacteriophage typing, ribotyping, and pulsed-field gel electrophoresis. Pulsed-field gel electrophoresis, in which bacterial DNA fragments are separated by size through electrical pulses, and repetitive extragenic palindromic PCR (rep-PCR), which compares the pattern of repetitive DNA sequences, remain in use. The techniques have quickly become outdated with the advent of fast and inexpensive microbial genome sequencing that can compare strains with high resolution to detect minor differences.

Genome sequencing provides information at a level of detail and precision previously unattainable with other typing methods. Hospital epidemiologists can use the unambiguous results of sequencing combined with epidemiologic data to elucidate an outbreak. Sequencing has become rapid and inexpensive, with bioinformatic expertise a limiting factor in its widespread adoption as a typing method.

Surveillance and Public Health Reporting

Infection-control departments conduct surveillance for incident infections, syndromes, and colonization, focusing on the most critical patient populations and the most concerning pathogens.[1] Surveillance results are used to detect clusters and trends that may require intervention, and to track the success of performance improvement initiatives, such as introduction of checklists for indwelling urinary catheters or new environmental cleaning procedures.

US states and territories publish criteria for reporting communicable diseases. Hospitals and laboratories must report these conditions to local health departments for the purposes of public health surveillance. In many states, nosocomial outbreaks must also be reported to public health departments. Highly contagious conditions, such as measles, or clusters of infection, such as legionnaires' disease or Shiga toxin–producing *E. coli,* may trigger urgent public health investigations.

A majority of US states and territories require hospitals to report data on nosocomial infections to the CDC's National Healthcare Safety Network. In 2008, Centers for Medicare and Medicaid Services instituted nonpayment of health care–associated conditions, including infections, as an incentive for hospitals to implement preventive measures; the policy has been associated with an 11% reduction in targeted health care–associated conditions.[157] The specter of nonreimbursement has further complicated the role of the hospital epidemiologist.

OUTBREAK INVESTIGATION

Investigation of outbreaks and exposures to prevent spread of a communicable disease is an integral part of hospital infection control. Outbreaks are detected through surveillance, notification by the microbiology laboratory, and reports from alert clinicians, among other sources. A cluster of infections, or even one case of a high-concern infection (such as chickenpox or nosocomial legionnaires' disease) may prompt an investigation. The goals of investigation are to identify the source of the outbreak and inform strategies for control.

Special Situation: Varicella-Zoster Virus Exposure Investigation

When a diagnosis of primary varicella-zoster virus (VZV) infection (chickenpox) or disseminated zoster is confirmed, the investigation is divided into two parallel lines of inquiry: the patient-related epidemiologic investigation, and the staff-related epidemiologic investigation. Because of the urgency of administering passive immunoglobulin and antiviral prophylaxis to exposed, susceptible, immunocompromised persons, the initial focus of the investigation is on patients.

Management of Exposed Patients

An in-hospital "travel history" is first obtained from the index case. Departmental records from any area in the patient's travels should be examined. Other patients documented to be in an area at the same time as the index patient should be included in the roster of patients at risk. The second component of the patient-related investigation is the rapid identification of exposed patients at high risk for severe complications of primary VZV infection, including pediatric, oncology, and transplant patients who are hospitalized as well as those who are outpatients. Interviewing pediatrics, oncology, and transplant

staff in addition to the staff along the index patient's travel route may yield additional contacts or other crucial information that was not documented.

Once the population at risk has been identified, the immunologic status of all patients on the list is assessed. If a patient is found to be potentially immunosuppressed, the patient, patient's family, and medical staff are questioned regarding the potential exposure and prior history of chickenpox or varicella immunization. Immunosuppressed patients who were potentially exposed and have a negative or an equivocal history of VZV infection have baseline serologies ordered, and prophylactic acyclovir and VariZIG are administered. VariZIG can be given up to 10 days after exposure.[158]

Exposure and VZV histories are obtained from immunocompetent patients after evaluation of immunocompromised patients. Exposed, susceptible immunocompetent patients have serologies drawn and, when possible, are discharged from the hospital. In general, those with negative exposure histories or positive histories of prior VZV infection need no further follow-up. In immunocompetent patients up to 120 hours from exposure, varicella vaccination should be considered as postexposure prophylaxis.

Exposed, susceptible, immunocompetent patients should be placed in strict isolation from 9 days after the first possible exposure until 21 days after the last possible exposure to the index patient. Exposed, susceptible, immunosuppressed patients (even those receiving VariZIG or prophylactic acyclovir) should be placed in strict isolation at the time the patient is identified as being at risk until at least 21 days after the last possible exposure. The incubation period in immunosuppressed patients can be shorter than 10 days, and, based on case reports, prolonged to 28 days in those who receive VariZIG.[159] Although there are no studies of acyclovir prophylaxis in immunocompromised patients, experts recommend that acyclovir be administered to exposed immunosuppressed patients prophylactically from days 3 to 22, or, if the patient has received VariZIG, days 3 to 28.[160–163]

Management of Exposed Personnel

After exposure and VZV histories have been taken from all potentially exposed staff, those who relate negative or equivocal histories of VZV infection should undergo serologic assessment of immunity. There are conflicting data on the reliability of a recalled history of chickenpox among health care personnel.[164,165] Even naturally immune, immunocompetent medical staff can rarely become reinfected with VZV.[166] Immunocompromised employees should be managed with the same sense of urgency that is used for immunosuppressed patients.

Susceptible employees should be immunized within 3 to 5 days of exposure for postexposure prophylaxis; some may develop chickenpox, but the disease may have milder manifestations.[167] Susceptible staff, including those who have received postexposure prophylaxis, should be reassigned to a low-risk area or placed on administrative leave from 8 days after the first possible exposure until 21 days after the last possible exposure,[168,169] although some have advocated a more liberal approach.[170–172] Employees who develop primary VZV infection should not return to work until the last lesion is crusted over (usually 7 or 8 days after the appearance of the last lesion).

OCCUPATIONAL MEDICINE

Hospital epidemiology services work closely with occupational medicine programs to safeguard the health and safety of patients and staff.

Preexposure Screening

Hospital personnel who may have patient contact or work in patient care areas undergo preplacement screening before entry into the workplace, including personal communicable disease and immunization histories and the presence of underlying medical conditions that may place them at higher risk for occupational infection. Clinical personnel should undergo preexposure screening—with serologies in combination with documented vaccine history—for immunity to vaccine-preventable infections, including hepatitis B, measles, mumps, rubella, pertussis, and varicella.[173] Surgeons who are infected with bloodborne pathogens, namely hepatitis B, hepatitis C, or human immunodeficiency virus (HIV), can be managed according to published guidelines that consider providers' individual risk for transmission to patients.[174]

Health care personnel should also undergo preexployment screening for tuberculosis with two-step tuberculin skin testing or, if immunized in the past with bacillus Calmette-Guérin (BCG), an interferon-γ release assay (IGRA) such as T-SPOT.TB or QuantiFERON-TB Gold. The IGRAs do not cross-react with BCG, but they do cross-react with *Mycobacterium marinum, Mycobacterium szulgai,* and *Mycobacterium kansasii*.[175] Discordance between tuberculin skin test and IGRA results is common, and low-positive IGRA results frequently revert to negative when the test is repeated.[176] Health care personnel who have positive test results should be managed according to CDC guidelines.[70] Subsequent testing is part of a collaborative tuberculosis prevention program among the occupational health, hospital biosafety, and hospital epidemiology services. The frequency of testing for personnel in various job categories in a given facility is based on an institutional risk assessment that takes into consideration the hospital size, annual tuberculosis case load, history of tuberculosis transmission, and the prevalence of tuberculosis in the local community.[70] Other components of the tuberculosis-prevention program include medical evaluations for N95 respirator fit testing (mandated by the Occupational Safety and Health Administration), tuberculosis surveillance among patients and employees, and exposure management. When a patient is found to have previously unrecognized pulmonary tuberculosis, occupational health and hospital epidemiology staff launch a contact investigation to identify and gather exposed personnel for repeat testing to detect skin test or IGRA conversions.

Preexposure Immunizations

Preexposure screening and review of vaccine history provide an opportunity for catch-up and booster immunization against hepatitis B, measles, mumps, rubella, and pertussis. VZV-susceptible health care personnel should be strongly encouraged to be immunized with the VZV vaccine. Immunocompromised persons should not receive live vaccines, but some vaccines can be given to health care personnel who have contact with immunocompromised patients. The measles, mumps, and rubella vaccine has no reported secondary transmission from recipients.[177] The Oka strain of varicella-zoster, on the other hand, has rarely spread to contacts of vaccinees who developed postvaccination rashes; health care personnel who develop a rash should avoid patient contact until the rash has crusted or ceased to progress.[178]

Influenza Immunization

Influenza immunization of clinical staff is an important patient safety measure, particularly because many patients cannot mount effective immune responses after vaccination and are at high risk for complications if they develop influenza. National guidelines recommend that staff who have patient contact or work in patient care areas be required to undergo annual influenza immunization.[178,179] Most health care facilities offer clinical staff the inactivated influenza vaccine, although some allow (or offer) immunization with live-attenuated intranasal vaccine. Although no secondary transmission of the vaccine strain from health care personnel to patients has been reported, hospitals serving highly immunocompromised patients may choose to interdict the live-attenuated vaccine on the basis of rare documented cases.[180] Egg allergies, which have previously led to exemption of some health care personnel from immunization with egg-based vaccines, are no longer a barrier with the advent of recombinant influenza vaccines, which are more expensive than egg-based vaccines but are increasingly available.

Preventing Transmission of Respiratory Viruses to Patients

Because the inactivated influenza vaccine is 40% to 80% effective at preventing influenza infections among healthy persons, influenza viruses may still circulate among a fully immunized health care staff. Symptoms of mild influenza may be indistinguishable from those of other community respiratory viruses, such as parainfluenza, respiratory syncytial virus, and adenovirus, which can all cause severe, even life-threatening infection in vulnerable hosts, or from rhinovirus, which rarely causes severe illness. Health care personnel must therefore take personal measures to avoid transmitting their upper respiratory infections to patients, ideally remaining out of the workplace during the peak of illness and for at least 24 hours after a fever (in the absence of antipyretics) to minimize the risk of spread to patients or to other health care personnel. The

work ethic of many health care staff, especially medical trainees, may lead to "presenteeism," or coming to work despite illness; occupational medicine and infection-control staff must educate all personnel that doing so may directly harm patients. Donning a mask during patient care after return to work is a common practice when milder respiratory symptoms remain present. There are no clinical data to support this practice, but one experimental study found that surgical masks reduce exhaled influenza viral copies by more than 70%.[181] In combination with meticulous hand hygiene, surgical masks used while lower levels of virus are shed as the infection resolves may reduce the risk of transmission. Apart from respiratory symptoms, fever, diarrhea, and vomiting should prompt immediate removal from the workplace to avoid spread of communicable diseases.

Universal and Standard Precautions

Universal precautions are a basic set of occupational safety measures designed to prevent transmission of bloodborne pathogens (such as HIV, hepatitis B, and hepatitis C) in the health care workplace. Because patients may have undiagnosed infection with a bloodborne pathogen, all patient interactions and handling of patient specimens should be performed in a manner that prevents the transmission of bloodborne pathogens; these precautions are applied universally, disregarding perception of a patient's level of risk. Standard precautions encompass all aspects of universal precautions but apply to contact with additional body fluids that do not necessarily transmit bloodborne pathogens, such as urine, sputum, spinal fluid, and others. These precautions differ from isolation precautions, which are designed to contain known or suspected communicable diseases.

Postexposure Prophylaxis

Personnel who experience a potential blood or body fluid exposure should wash the wound or area of nonintact skin with soap and water or flush the exposed mucous membrane, and seek prompt evaluation by an occupational medicine specialist.[182] The risk for infection with a bloodborne pathogen following an exposure depends in part on the route of inoculation, inoculum size, exposure severity, and magnitude of viremia.[183] The occupational health provider will assess the route and extent of the exposure, the condition of the source patient (if known), and the employee's own underlying health conditions in making a decision about postexposure prophylaxis.[183]

The literature suggests that the average risk of HIV infection after a percutaneous exposure or mucous membrane exposure to HIV-infected blood is approximately 0.3% and 0.09%, respectively.[183] In contrast, the average risk of acquiring hepatitis C after a sharps or needlestick injury is approximately 1.8%.[184] In a nonimmune worker, serologic evidence of hepatitis B infection following parenteral exposure to blood from a hepatitis B surface antigen–positive and e antigen–positive patient develops in 37% to 62%, and clinical infection in 22% to 31%. The risk of transmission is lower if the source patient is e antigen negative.[184]

Postexposure prophylaxis for hepatitis B is discussed in Chapter 303. Occupational exposures to pathogens for which there is no recommended postexposure prophylaxis, such as hepatitis C, should nonetheless be documented and followed. Institutional surveillance for needlestick injuries and exposures is used to identify opportunities for performance improvement initiatives that can reduce the risk of these events.[182]

Management of Occupational Exposure to Human Immunodeficiency Virus

Occupational exposures that put health care personnel at risk for HIV infection are percutaneous injuries or mucous membrane or nonintact skin contact with blood or other body fluids that potentially contain infectious virus. Injuries that are deep, made by hollow-bore needles, or involve blood or other fluids containing high titers of virus increase risk of transmission.[185] Exposed personnel should be evaluated immediately or within hours of exposure and should be managed according to published guidelines for postexposure prophylaxis (Table 298.3). When the source patient's HIV status is unknown, prophylaxis should be started immediately if there is likely to be a delay in acquiring medical records or laboratory results.

TABLE 298.3 Treatment Regimens (Recommended Duration 28 Days)

RECOMMENDED REGIMEN	ALTERNATIVE REGIMENS
Raltegravir 400 mg twice daily or, if not pregnant,[a] dolutegravir 50 mg once daily *PLUS* Tenofovir 300 mg coformulated with emtricitabine 200 mg once daily	Tenofovir plus emtricitabine or tenofovir plus lamivudine *or* Zidovudine plus lamivudine or zidovudine plus emtricitabine *PLUS one of the following:* Raltegravir or, if not pregnant,[a] dolutegravir *or* Ritonavir-boosted protease inhibitor *or* Rilpivirine or etravirine

[a]Recent reports have raised concerns about neural tube defects potentially associated with use of dolutegravir during pregnancy.[191]
Data from references 183 and 192.

Postexposure Testing and Follow-Up

In addition to baseline HIV testing, serologic testing for a documented occupational HIV exposure is usually performed 6 weeks, 3 months, and 6 months after exposure. If a more sensitive fourth-generation combination antibody-antigen test is used, testing may conclude earlier and is typically performed 6 weeks and 4 months after exposure.[183] CDC guidelines recommend a prolonged HIV follow-up period (e.g., 12 months) for health care personnel who develop hepatitis C virus infection after an exposure to a source who is coinfected with hepatitis C virus and HIV.[183] Close medical follow-up is recommended during postexposure treatment with antiretroviral drugs in order to help manage side effects, encourage adherence, and provide support.[183]

EMERGING INFECTIOUS DISEASES

Hospitals must consider and plan for exceptional infectious diseases events, such as influenza pandemics and the emergence or reemergence of highly contagious diseases. As the 2003–04 severe acute respiratory syndrome epidemic, 2014–15 Ebola epidemic, and 2015 Middle East coronavirus outbreaks demonstrated vividly, the regularity of international travel allows importation of infectious agents to distant regions with secondary spread in health care facilities. Hospitals must be prepared for such possibilities, with procedures and infrastructure poised to contain severe infections that may be highly contagious. Patients infected with emerging pathogens do not typically present to health care with a diagnosis, and the transmission dynamics of the pathogen may be unknown, warranting enhanced infection-control measures for suspected cases. Clinicians can remain vigilant for possible cases, taking careful travel histories and maintaining awareness of current international infectious diseases epidemiology. The lessons of past epidemics have been codified into guidelines and training courses that can inform and steer the process of maintaining preparedness.

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The complete reference list is available online at Expert Consult.

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