Chronic HCV infection occurs in 60% to 80% of IDUs.[280] Current guidelines for the treatment of HCV state that recent or active injection drug use should not be viewed as a contraindication to treatment. Response rates to treatment are comparable to rates reported in non-IDUs, even with ongoing drug use, especially in multidisciplinary programs that incorporate treatment for addiction and directly observed therapy.[315] Despite a willingness to be treated, low uptake of HCV treatment among IDUs is reported.[312,316,317] Younger individuals appear to have better linkage to HCV care.[318] Patients coinfected with HIV and HCV are less likely to clear HCV viremia after infection and experience more rapid progression to HCV-related liver disease. Coinfected individuals should be prioritized for treatment, and response rates are comparable to rates reported for individuals with monoinfection.[319]

Hepatitis A

IDUs are also at risk for hepatitis A virus (HAV) infection. Although parenteral transmission of HAV has been reported in IDUs, other lifestyle factors are likely more important in explaining the increased risk for HAV in this population. Among IDUs in Baltimore, evidence of past HAV infection was not significantly associated with high-risk drug-using behaviors, but rather was associated with low annual income.[320] A more recent study of IDUs in Spain also found that socioeconomic factors, rather than injection drug use, were the main determinants of HAV infection risk.[321] Fulminant hepatitis caused by HAV in IDUs with chronic liver disease caused by HBV and HCV has been reported.[322,323] Nonimmune IDUs should receive the HAV vaccine. In settings where there is an ongoing HAV outbreak, people who use both injection and noninjection drugs should be offered vaccination even if their serostatus is unknown.

Hepatitis E

A study of IDUs in San Diego revealed an overall hepatitis E virus seroprevalence of 2.7%.[324] Older IDUs were more likely to be infected, but homelessness, incarceration, and high-risk sexual behavior were not associated with hepatitis E virus infection.

SPLENIC ABSCESS

Abscess of the spleen is a major complication of injection drug use. The splenic arteries are end arteries; any occlusion leads to ischemia or infarction. The ischemic or infarcted areas are highly susceptible to infection and serve as a nidus for abscess formation in the event of bacteremia. Trauma, including blunt trauma, also may lead to splenic injury and is an antecedent condition in some IDUs who develop splenic abscess.[325] Cocaine-associated splenic infarction with secondary bacterial infection has also been reported.[326] Endocarditis is the most common underlying infection in IDUs with splenic abscess,[325,327] although splenic involvement also may result from spread of local infection directly to the splenic artery or extension of an adjacent process with erosion and thrombosis of the splenic artery.[328]

Splenic lesions may be multiple and small or solitary, occasionally becoming large.[325,327,328] Lesions within the spleen are most often found in the upper pole (53.1%). Lower-pole lesions (21.9%) and midspleen lesions (15.6%) are found less often.[328] Staphylococci and streptococci are the organisms most often implicated; however, gram-negative bacilli and anaerobes are isolated in approximately 25% and 5% of cases, respectively.[328] IDUs who lick their needles are susceptible to splenic abscesses caused by mouth anaerobes, in particular, *Fusobacterium* spp.[329] *M. tuberculosis* has been reported as a cause of splenic abscess in IDUs who are infected with HIV.[330] Bacteremia is common in patients with splenic abscess, and usually the same organism is cultured from the blood and from the splenic cavity. However, IDUs have a tendency to have multiple infected sites that contain different organisms. Therefore isolation of an organism from the blood is not assurance that the same organism will be found in the spleen.[327]

Clinical Manifestations

The signs and symptoms of splenic abscess may be vague or overshadowed by underlying endocarditis. Almost all patients have fever and some degree of abdominal pain or discomfort.[325,327,328] Pleuritic chest pain is common.[325,327,328] Left shoulder pain has also been described. Abdominal tenderness, which is frequently confined to the left upper quadrant, is found in approximately 50% of patients.[325,327,328] Splenomegaly may be present, but a splenic rub is unusual [325] Abnormalities within the thorax, including left lower lobe lung infiltrate and pleural effusion, are detected in two-thirds of cases. The differential diagnosis includes subphrenic abscess, pulmonary empyema, perinephric abscess, and bland splenic infarct. The possibility of splenic abscess must always be excluded in IDUs with IE who fail to clear their bacteremia or remain persistently febrile despite negative blood cultures. There are no characteristic laboratory abnormalities, although an extremely high leukocyte count has been correlated with a poor prognosis.[328] The chest radiograph may reveal an elevated hemidiaphragm, infiltrate, or a pleural effusion; however, abdominal radiography is seldom useful. The most reliable diagnostic tests are ultrasound and CT of the abdomen.[325] MRI is also useful in characterizing a splenic pathologic process.[331]

Therapy

Splenectomy remains the preferred treatment of splenic abscess. Although randomized controlled trials are not possible, there are an increasing number of reports of successful management using either ultrasound-guided or CT-guided percutaneous drainage.[332–334] Percutaneous drainage can serve as a bridge to surgery in patients who are critically ill. Splenectomy continues to be preferred in patients who must undergo valve replacement for the management of IE. Removal of the spleen may be difficult if it adheres to adjacent structures; removal or partial resection of these organs may be required.[325,326,329] Laparoscopic splenectomy for splenic abscess has been reported, but experience with this modality remains limited.[335,336]

Complications of splenic abscess include spontaneous rupture, which can be so subtle in some cases that the patient has no signs of generalized peritonitis or purulence in the abdominal cavity.[325] Other manifestations include recurrent bacteremia and intestinal obstruction.[328] Although associated with significant morbidity and mortality, splenic abscess detected early and treated promptly has a good prognosis.

CENTRAL NERVOUS SYSTEM INFECTIONS

IDUs may present with a variety of CNS manifestations that may or may not be infectious in origin. The differential diagnosis is extensive and frequently difficult. Complications related to the injection of illicit drugs include coma caused by overdose or intoxication, postanoxic encephalopathy, delirium, and acute confusion states. Seizures, cerebral edema, and dementia may result from noninfectious as well as infectious causes. Hemorrhage and infarction may be secondary to infection or compromise of the neurovascular system. Parkinsonism is most often the result of drug effects but has been reported in infection.[337] The etiology of these disorders may be obscure, necessitating a thorough workup to exclude an infectious cause. Infections of the CNS may be local or secondary to an infectious process elsewhere. When infection is the primary problem, focal findings and fever are usually present. When present, focal findings suggest the possibility of a mass lesion requiring immediate surgical intervention. Therefore an IDU with neurologic findings requires a differential diagnosis that includes both infectious and noninfectious causes and an effort to differentiate between a local process and a complication of a distant primary infection.

Risk Factors

CNS manifestations are more common in IDUs than in non-IDUs and are found in 45% to 58% of IDUs with endocarditis.[338] In one study of IDUs with left-sided IE, CNS complications were found in 52% of patients with mitral valve infection but in only 28% of patients with aortic valve disease.[202] Other investigators found a greater incidence in aortic valve disease, especially when *S. aureus* was involved and the patients had congestive heart failure.[339] Endocarditis, particularly when caused by *S. aureus* or *S. pneumoniae,*[213,340] is the most common cause of CNS disease in IDUs, and it accounts for the most serious complications including brain abscess, meningitis, encephalopathy, and hemorrhage from ruptured mycotic aneurysms.[150,341] Mycotic aneurysms may manifest as a progressive focal neurologic deficit resulting from expansion of the aneurysm or as an acute subarachnoid or intracerebral

hemorrhage.[342] Before rupture, patients may complain of severe localized headache, which should prompt immediate evaluation. CT angiography and MRA can detect aneurysms that are greater than 5 mm in size; the sensitivity of MRA is slightly higher (94% vs. 86%).[343] For smaller aneurysms the sensitivity of CT angiography and MRA is far less (35% and 57%, respectively).[343] If a strong suspicion remains, a negative study should be followed by four-vessel cerebral angiography, which remains the definitive test. Even with a negative test result, if symptoms persist, repeated angiography may reveal lesions that were not detected previously.

Cerebral Mycotic Aneurysm

The optimal management of cerebral mycotic aneurysms remains undefined. In some cases, lesions resolve completely or decrease in size with antibiotic treatment alone. In other cases the lesion may enlarge, or new aneurysms may appear. Surgery is important for control of ruptured aneurysms of peripheral arteries or when an intracranial location or masslike lesion occurs. Some researchers recommend serial angiograms to assess the progress of aneurysms; others call for aggressive surgical management, especially if the lesion is accessible. When the patient's condition precludes surgery, an endovascular procedure for embolization of the lesion may be advised.[344,345] Introducing a coil into the affected vessel is a frequent alternative to surgical removal or clipping; however, in the case of aneurysms in IDUs the lesions are often peripheral and in very small vessels. The size of the involved vessel often precludes the introduction of a coil, and the fragility of the lesion carries a risk of perforation should a coil be attempted. There is always a risk of causing a catastrophic neurologic injury when attempting occlusion of the vessel with a coil or embolization of these vessels, especially if doing so obliterates blood flow to a critical area. In lesions that were adjacent to eloquent cortex, Chalouhi and colleagues used superselective imaging (sodium amobarbital injected into a target vessel with the patient awake to determine the safety of vascular sacrifice) before a definitive procedure to eradicate mycotic aneurysms in a series of patients who were not considered surgical candidates.[346] Once satisfied there would be no significant deficit, they had excellent results after introducing a coil and injecting Onyx 18/34. The presence of multiple aneurysms may make a surgical approach impossible. In some of these cases, patients do well with antimicrobial treatment, but each case must be treated individually.[347] Whether surgical or endovascular management of ruptured mycotic aneurysms is optimal has not been defined. Some experts advocate for endovascular management with surgery reserved for easily accessible lesions, lesions associated with large parenchymal hematoma, lesions in young patients, and lesions involving eloquent territory of the brain.[348] Regardless of the treatment chosen, close angiographic follow-up is recommended.

Focal abnormalities also result from septic emboli (which frequently result in transient focal neurologic deficits) and multiple cerebral abscesses. These lesions tend to resolve in 1 to 2 weeks with appropriate antibiotic therapy.[150] IDUs also commonly develop a diffuse encephalopathy that may be due to bacteremia or injected toxins.

Brain Abscess and Subdural Empyema

Localized CNS infection in IDUs is confined primarily to brain abscess and subdural empyema. Pyogenic bacteria usually cause brain abscess; *Nocardia* has also been reported. Fungi, including *Aspergillus* spp., *Chaetomium strumarium, Candida* spp., and mucormycosis, have also been reported. Isolated cerebral mucormycosis in IDUs is rarely associated with HIV infection and manifests as focal cerebritis or abscess. In contrast to the more extensive aggressive process observed in immunocompromised hosts, in IDUs there seems to be a predilection for involvement of the basal ganglia.[349] Cerebral mucormycosis in IDUs is not caused by spread from sinuses. It appears the organism is either a contaminant in the illicit drugs or enters the bloodstream from an infected injection site, finding its way to areas of the brain predisposed by earlier drug-induced injury. The patient usually presents with signs and symptoms of a mass lesion. The differential diagnosis of such lesions includes toxoplasmosis, lymphoma, TB, and cryptococcosis. Isolated involvement of the basal ganglia is uncommon in toxoplasmosis and lymphoma. Radiologic contrast enhancement may or may not be seen in patients with mucormycosis and therefore lends little to the diagnosis. Biopsy of the lesion is required to establish the diagnosis; failure to do so is associated with a very high mortality rate.[350] Remarkably the outcome of this disease is very good, with survival in most cases after prolonged amphotericin B therapy and excision of as much of the infected tissue as possible.

The clinical signs and symptoms of brain abscesses in IDUs are the same as in non-IDUs and depend on the size and location of the lesion within the brain. They usually result from infected cerebral emboli in patients with mitral or aortic valve endocarditis.[150,183,202,341] Rarely, emboli travel through or originate in the pulmonary circulation. Alternatively, pathogens may seed the brain after an inadvertent injection into the arterial system during an attempted jugular vein injection. Tuberculous brain abscesses may also be seen, particularly in IDUs who are coinfected with HIV. The lesions are typically solitary, multiloculated, and contrast enhancing. They must be distinguished from lesions due to *Toxoplasma,* which usually causes multiple lesions that are not multiloculated, and lymphoma, which can be necrotic with multiple loculations but is more often located near an ependymal surface.[351] IDUs with HIV infection who have characteristic lesions may be treated empirically for toxoplasmosis, but failure to respond within 2 weeks should prompt a biopsy, which will lead to the correct diagnosis. Subdural empyema is also seen in IDUs and may be secondary to direct extension from a local infectious process or complicated bacteremia.

Meningitis

Meningitis in IDUs is most often secondary to endocarditis[341] and is usually due to *S. aureus* or *S. pneumoniae.*[338] However, abnormal CSF findings are common in patients with CNS complications of endocarditis. Findings in patients with meningitis include purulent CSF with a neutrophilic pleocytosis and elevated protein level, with normal or decreased glucose level. Hemorrhagic CSF may also be found. A pattern consistent with aseptic meningitis is seen in 25% of cases; normal CSF is seen in only 30%.[338] Positive CSF cultures are seen in a minority of patients, most of whom have *S. aureus* infection and purulent CSF.

Spinal Epidural Abscess

A spinal epidural abscess should be considered in any IDU presenting with spinal ache or back pain, especially if focal neurologic signs are present. Occasionally, blunt trauma may predispose an area of the spine to infection after an episode of transient bacteremia.[352] In Kentucky, legislation was passed in 2012 that increased control of prescription narcotics, and there was a subsequent ninefold increase in the diagnosis of spinal abscess strongly associated with drug abuse by 2014.[353] It appears IDUs had become dependent on narcotics obtained without prescription as a response to the new law. In western Massachusetts in the decade between 2005 and 2015 there was a 3.3-fold increase in spinal epidural abscess from 2.5 to 8.0 per 10,000 admissions.[354]

Patients tend to have a prolonged, several-month symptomatic course. Alternatively the disease can advance rapidly leading to permanent neurologic damage. Typically the disease progresses from focal vertebral pain to root pain, neurologic deficits (motor or sensory), and, finally, paralysis. The classic triad of fever, back pain, and neurologic deficit is seen in a minority of patients and cannot be relied on to initiate a diagnostic workup. The most reliable finding to aid in diagnosis of an IDU with epidural abscess may be back pain alone.[355] The thoracic or lumbar spine is most often involved, although cervical spine lesions are also seen and may be more common among IDUs than non-IDUs.[146] Initial laboratory results, including white blood cell count, are frequently not helpful.[355] Contrast-enhanced MRI or CT is usually sufficient to identify the lesion. Multiple levels of involvement in the cord, frequently in noncontiguous areas, may occur, emphasizing the necessity of carefully imaging the cord before any intervention so as not to overlook infected material that needs to be addressed. In a more recent series, blood cultures were positive in almost two-thirds of cases.[354] *S. aureus* is the most common cause, but other gram-positive and gram-negative organisms have been reported, occasionally in combination with other organisms. *M. tuberculosis* also causes spinal epidural abscess, and it too may be found in combination with other organisms,[356] making careful definition of the microbial etiology imperative. Occasionally, difficult-to-culture organisms are responsible; laboratories should be advised that special techniques may be necessary when original cultures

are negative.[357] The pathophysiology is usually directly spread to the epidural space from adjacent disk or vertebral body infection or hematogenous dissemination from a distant focus of infection, frequently endocarditis.

In most cases, immediate drainage relieves symptoms; although once a chronic condition ensues, there may be nothing but granulation tissue, requiring multiple-level laminectomy to relieve pressure on the spinal cord. Controversy remains regarding the benefits of surgical versus medical management. In most series, there is a higher risk of failure among patients treated conservatively, and some authors have found best results if surgery is performed in the first 24 hours.[358] If surgery is delayed, careful observation is required, and surgery should be undertaken at the first sign of neurologic deficit. Further delay usually results in permanent neurologic deficit.[355,359]

Intramedullary spinal cord abscess has been reported in IDUs with symptoms resembling those of an epidural abscess.[360,361] This condition is extremely rare. Early surgical drainage accompanied by systemic antibiotics is required to increase the likelihood of a favorable outcome.[362]

Tetanus and Wound Botulism

Toxin-mediated diseases, specifically wound botulism and tetanus, are being seen with increasing frequency among IDUs and must be considered in IDUs who have neurologic symptoms. Epidemics of both tetanus and wound botulism have occurred in California,[363,364] and cases are likely to be found elsewhere. A patient with tetanus is likely to be a long-time IDU who has poor venous access and multiple skin lesions caused by failed attempts at intravenous injections or by skin popping. These lesions become colonized by multiple pathogens including *Clostridium* spp. In the proper anaerobic environment, toxin is generated and produces disease.[365] Among the patients from California who had tetanus, 89% were Hispanic Americans, which may be explained by a study finding that only 58% of Mexican Americans had protective levels of antibody to tetanus toxoid compared with 73% of non-Hispanic whites.[364] In a more recent report of tetanus surveillance in the United States, IDUs, particularly those of Hispanic ethnicity, remained an important risk group.[366] Skin popping probably accounts for the higher mortality rate due to tetanus in IDUs than in non-IDUs. One proposed reason is that because of the number and severity of skin lesions in addicts, there is greater opportunity for large amounts of toxin to be produced. In addition, an addict presenting with the typical symptoms of tetanus may be believed to be manifesting the effects of illicit drug toxicity, overdose, or drug withdrawal.[367,368] In view of the risk for tetanus associated with injection drug use, it is worthwhile to consider giving a tetanus booster to any IDU who is being treated for any other condition who has not been immunized recently.

Wound botulism in IDUs was first described in New York City in 1982. Subsequently, sporadic cases were reported from different locations. After 1990, a dramatic increase in the number of wound botulism cases occurred in California.[365] With rare exceptions, patients were IDUs who injected black tar heroin, a black, gummy form of the drug synthesized in Mexico and distributed widely throughout the western United States. Skin popping of black tar heroin was the major risk factor for acquisition of wound botulism. The greatest risk was seen among heavy users, but disease also occurred in occasional users with subcutaneous or intramuscular injection. The drug was most likely contaminated during the dilution process, when substances were added to the heroin to increase the amount of the product and thereby increase the seller's profits. Wound botulism results from colonization of wounds by *Clostridium botulinum* with subsequent toxin production. Initially patients experience blurred vision or diplopia, dysarthria, and dysphagia, followed by descending muscle weakness and respiratory failure. The symptoms are similar to those of botulism in non-IDUs except that gastrointestinal symptoms are absent. Also, in contrast to non-IDUs, who usually have a dietary history to suggest the diagnosis, in IDUs the organism can usually be recovered from wound cultures. Frequently, fever results from the associated wound infection. Serum assays for botulism toxin are rarely positive; administration of antitoxin, which is helpful only if given within the first 24 hours, must be done on the basis of a high index of suspicion, rather than after culture identification. In an IDU having characteristic signs and symptoms, a fever (which helps to distinguish from other forms of botulism) and an abscess, wound botulism should be strongly considered and treatment begun immediately with antitoxin and wound débridement.[369] The epidemic associated with black tar heroin use is ongoing, and recurrent cases are reported.[366]

OCULAR INFECTIONS

Endophthalmitis

Endophthalmitis is a common and serious complication of injection drug use.[370,371] Both fungal endophthalmitis and bacterial endophthalmitis are hematogenous in origin and frequently manifest as complications of IE. *Candida* is the most common fungal cause. Endophthalmitis may also occur as part of a disseminated syndrome involving eyes, bone, and skin in heroin users. Fungal endophthalmitis has been reported after injection of crack cocaine dissolved in lemon juice and after injection of diverted sublingual buprenorphine.[372,373] A report from New England of an increase in cases of fungal endophthalmitis associated with injection drug use (most commonly *Candida* spp.) suggests that the incidence may be increasing as a result of the new injection opioid epidemic.[374] Symptoms of endophthalmitis include blurred vision, pain, and decreased visual acuity. White exudative lesions are found in the choroid and retina, with vitreous haziness. Diagnosis requires a high index of suspicion, and because blood cultures are usually negative at the time of ocular symptoms, definitive diagnosis often involves vitreous sampling. The antifungal regimen that has been used most extensively for the treatment of *Candida* chorioretinitis is amphotericin B in combination with flucytosine; however, fluconazole or voriconazole is now recommended as first-line therapy for susceptible isolates with amphotericin reserved for azole-resistant isolates.[213] Echinocandins are not recommended. If extension into the vitreous humor has occurred (i.e., endophthalmitis), intravitreal amphotericin B or voriconazole with or without pars plana vitrectomy is recommended; the use of intraocular dexamethasone to treat inflammation associated with infection is controversial (see Chapter 114).[213,375]

Aspergillus spp. are the second most common cause of fungal endophthalmitis in IDUs. As with *Candida* spp., the pathogenesis reflects mycotic contamination of drug paraphernalia or of the heroin injected, rather than host immunosuppression. Physical findings and treatment are similar to those of *Candida* infection.

Bacterial endophthalmitis is less common, and the presentation is often acute with rapid progression of symptoms. Inflammation usually is present in the anterior and posterior chambers. In addition to pain, redness, and lid swelling, evidence of retinal vasculitis may be present. *S. aureus* is the organism most frequently isolated. A rapidly destructive form of endophthalmitis has been reported for *B. cereus,* which has been cultured from heroin and drug paraphernalia.[376] Bacterial endophthalmitis is treated primarily with intravitreal antimicrobial agents with or without vitrectomy, although the role of systemic antibiotics continues to be debated (see Chapter 114). In both mycotic and bacterial endophthalmitis, early diagnosis and intervention increase the chance of a favorable outcome. A case series of endophthalmitis in IDUs found that the prognosis for visual outcome was equally poor for both bacterial and fungal infections.[377] Whereas bacterial endophthalmitis is infrequent, ocular peripheral emboli are frequent complications of IE in IDUs. These include subconjunctival hemorrhages and retinal emboli (Roth spots), which manifest as petechiae, retinal hemorrhage, and ischemia.

HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Epidemiology

Early in the AIDS epidemic, injection drug use was a high-risk factor for contracting the disease. In the United States the incidence of HIV infection among IDUs has steadily decreased, with IDUs now accounting for 9% of new HIV infections.[378] Changes in the epidemiology of injection drug use in the United States may threaten this decline, as illustrated by the community outbreak of HIV infection associated with injection of prescription opioids in a rural area of southeastern Indiana in 2015.[308] In a county where fewer than 5 cases of new HIV infection were reported annually, 135 new infections were reported in a community of 4200 people. Investigation revealed that sharing of syringes and drug preparation equipment used to solubilize oral extended-release oxymorphone

to inject it were risk factors for HIV acquisition. Subsequent work has documented a high prevalence of high-risk injection practices among the population in this outbreak.[379] In high seroprevalence areas, female IDUs may be at a higher risk for HIV infection than male IDUs.[380] Sexual contact with IDUs still accounts for a significant number of cases among individuals whose primary risk is heterosexual contact. Epidemiologic studies continue to show high rates of injection and sexual risk behaviors among IDUs.[381] In the United States as well as the rest of the world, HIV infection associated with injection drug use disproportionally affects racial and ethnic minorities, particularly minority women and children.[382,383] Globally, injection drug use is the major risk for HIV acquisition in Asia (including Russia and the former Soviet republics).[384] Eastern Europe and Central Asia experienced a 13% increase in new infections from 2006 to 2012, and many countries in this region have seen a transition from an epidemic concentrated among IDUs to a generalized epidemic among heterosexuals.[385] In the United States different risk profiles have been described among users of different types of injection drugs; however, this may be changing. Previously, HIV was not found to be highly prevalent among individuals who inject methamphetamines, although both injection and sexual high-risk behavior were very common.[386] More recent reports have suggested that an increasing prevalence of methamphetamine injection, including methamphetamine injected with heroin (goofballs) coupled with high-risk injection practices, may increase the risk for HIV infection in this population both among MSM and heterosexuals.[387]

Prevention

IDUs have been underrepresented in HIV prevention research and in the global effort to increase access to prevention, treatment, and care. Syringe services programs have been shown to be an effective means of reducing the incidence of new HIV infections.[276,388] Multicomponent interventions that include needle and syringe access/exchange, voluntary counseling and testing, opioid substitution treatment, and ART for individuals already infected have the potential to substantially reduce the incidence of new infections.[389] The existence of supervised injection facilities, where IDUs can inject their drugs under the supervision of health care professionals, has been shown to reduce public injecting, syringe sharing, and drug overdose and increase access to addiction treatment.[390–392] Despite evidence for efficacy and no evidence to support the contention that safe injection programs lead to an increase in injection drug use, these programs remain controversial. Substitution therapy for opioid addiction appears to reduce injection-related HIV risk behaviors but has less effect on risky sexual behaviors.[393,394] Preexposure prophylaxis has been shown to reduce the risk of HIV infection in IDUs and should be offered as outlined in the CDC guidelines for preexposure prophylaxis for the prevention of HIV.[395]

Therapy and Prognosis

In the era before the availability of combination ART, cohort studies failed to demonstrate any difference in the rate of progression to AIDS among IDUs, MSM, and heterosexuals.[396] Since the availability of effective ART, studies of HIV outcomes among IDUs have yielded conflicting results. ART efficacy, as evidenced by $CD4^+$ cell response, appears to be similar for IDUs and non-IDUs, provided that there is sustained suppression of viremia.[397] IDUs may be at higher risk of medication non-adherence than other patient populations with HIV.[398] Injection drug use was previously shown to be an independent predictor for delay in initiation of care after the diagnosis of HIV infection,[399] but a more recent study has shown that this is no longer the case.[400] However, in the United States ART coverage for IDUs remains lower than for other groups at risk for HIV.[401] Homelessness and young age have been shown to be predictors of poor adherence and treatment response in IDUs, and periods of incarceration are associated with virologic failure even among individuals who had achieved virologic suppression.[402–404] Despite these barriers to adherence, as a group, IDUs are not at increased risk for resistance to ART compared with non-IDUs.[405] Intensive community-based programs to engage and retain IDUs in care have been associated with reductions in all-cause and HIV-related mortality.[406]

The medical management of HIV-infected IDUs must incorporate the diagnosis and treatment of substance abuse. Substitution therapy can facilitate social stability and support adherence to ART. Drug interactions between ART and methadone, buprenorphine, and other street drugs must be considered when managing IDUs with HIV infection.[407]

SEXUALLY TRANSMITTED DISEASES

Epidemiology

A major contributing factor to the prevalence of STDs is unsafe sexual practices associated with the use of illicit drugs.[408] A survey of young opioid users in New York City, 64% of whom reported injection drug use, revealed high rates of risky sexual behavior, including very low rates of condom use, multiple sexual partners, and participation in group sex events.[409] A study of young IDUs in Baltimore found that the prevalence of infection with *Chlamydia, Neisseria gonorrhoeae,* and *Trichomonas* was similar to that in the general population, despite the fact that 68% of participants had two or more sex partners in the past 3 months and less than half consistently used condoms.[410] A more recent study of IDUs in Camden, New Jersey, who were recruited from a syringe exchange program found high rates of gonorrhea and *Chlamydia* infection, with one-third of infections found at a nongenital site.[411] In this study, which included equal numbers of men and women, 60% of infections would have been missed if pharyngeal and rectal samples had not been obtained. Alcohol use and alcohol intoxication are associated with an increase in risky sexual behavior among IDUs.[412] The use of alcohol among drug users appears to be more strongly associated with risky sexual behavior than with risky injection practices.[413] IDUs who use methamphetamine have an increased risk of sexually transmitted infections compared with addicts who inject heroin.[414] Female sex workers who are IDUs have a higher prevalence of STDs and are more likely to engage in risky sexual behaviors and have unsafe sex with clients than sex workers who do not inject drugs.[415] Male IDUs who have sex with men, especially those who engage in commercial sex work, are much more likely to report risky sexual behavior.[416,417] It has been observed that reducing risky sexual behavior among IDUs is much more difficult than reducing risky injection behavior. Among IDUs who inject prescription opioids in Los Angeles and New York City, half reported risky injection behavior, but more than three-quarters engaged in risky sexual behavior.[418]

Syphilis

Risk factors for syphilis among IDUs include recent initiation of injection drug use, injecting drugs with other people, and injecting in public places.[419] The diagnosis and treatment of syphilis in IDUs may be complicated by the high rate of biologic false-positive, nonspecific serologic screening test results; the increasing availability of screening algorithms that use specific tests as the initial screening test may reduce the incidence of false-positive screening results. In contrast to the poor reliability of self-reported hepatitis serostatus, self-reports of syphilis infection history by IDUs were found to have good reliability.[420]

Given the importance of STDs as cofactors in the sexual transmission of HIV, reducing the prevalence of these diseases in IDUs is an additional strategy to diminish the spread of HIV among IDUs and from them to their non–drug-using sexual contacts.

Key References

The complete reference list is available online at Expert Consult.

4. Fleischauer AT, Ruhl L, Rhea S, et al. Hospitalizations for endocarditis and associated health care costs among persons with diagnosed drug Dependence—North Carolina, 2010-2015. *MMWR Morb Mortal Wkly Rep*. 2017;66:569–573.
5. Han B, Compton WM, Blanco C, et al. Prescription opioid use, misuse, and use disorders in U.S. Adults: 2015 National Survey on Drug Use and Health. *Ann Intern Med*. 2017;167:293–301.
13. O'Donnell JK, Halpin J, Mattson CL, et al. Deaths involving fentanyl, fentanyl analogs, and U-47700—10 States, July-December 2016. *MMWR Morb Mortal Wkly Rep*. 2017;66:1197–1202.
20. Kievlan DR, Gukasyan M, Gesch J, et al. Clinical profile of injection drug users presenting to the ED. *Am J Emerg Med*. 2015;33:674–676.
53. Wang JL, Chen SY, Wang JT, et al. Comparison of both clinical features and mortality risk associated with bacteremia due to community-acquired methicillin-resistant *Staphylococcus aureus* and methicillin-susceptible *S. aureus*. *Clin Infect Dis*. 2008;46:799–806.

56. Mihu MR, Roman-Sosa J, Varshney AK, et al. Methamphetamine alters the antimicrobial efficacy of phagocytic cells during methicillin-resistant *Staphylococcus aureus* skin infection. *MBio*. 2015;6:e01622-15.
60. Piepenbrink MS, Samuel M, Zheng B, et al. Humoral dysregulation associated with increased systemic inflammation among injection heroin users. *PLoS ONE*. 2016;11:e0158641.
67. Zhou Y, Sun L, Wang X, et al. Heroin use promotes HCV infection and dysregulates HCV-related circulating microRNAs. *J Neuroimmune Pharmacol*. 2015;10:102–110.
85. Murphy EL, DeVita D, Liu H, et al. Risk factors for skin and soft-tissue abscesses among injection drug users: a case-control study. *Clin Infect Dis*. 2001;33:35–40.
93. Jenkins TC, Knepper BC, Jason Moore S, et al. Microbiology and initial antibiotic therapy for injection drug users and non-injection drug users with cutaneous abscesses in the era of community-associated methicillin-resistant *Staphylococcus aureus*. *Acad Emerg Med*. 2015;22:993–997.
107. Talan DA, Mower WR, Krishnadasan A, et al. Trimethoprim-sulfamethoxazole versus placebo for uncomplicated skin abscess. *N Engl J Med*. 2016;374:823–832.
117. Waldron C, Solon JG, O'Gorman J, et al. Necrotizing fasciitis: the need for urgent surgical intervention and the impact of intravenous drug use. *Surgeon*. 2015;13:194–199.
136. Hicks CW, Sweeney DA, Cui X, et al. An overview of anthrax infection including the recently identified form of disease in injection drug users. *Intensive Care Med*. 2012;38:1092–1104.
142. Allison DC, Holtom PD, Patzakis MJ, et al. Microbiology of bone and joint infections in injecting drug abusers. *Clin Orthop Relat Res*. 2010;468:2107–2112.
147. Conterno LO, Turchi MD. Antibiotics for treating chronic osteomyelitis in adults. *Cochrane Database Syst Rev*. 2013;(9):CD004439.
149. Jewell C, Weaver M, Sgroi C, et al. Residential addiction treatment for injection drug users requiring intravenous antibiotics: a cost-reduction strategy. *J Addict Med*. 2013;7:271–276.
151. Ambrosioni J, Hernandez-Meneses M, Tellez A, et al. The changing epidemiology of infective endocarditis in the twenty-first century. *Curr Infect Dis Rep*. 2017;19:21.
177. Frontera JA, Gradon JD. Right-side endocarditis in injection drug users: review of proposed mechanisms of pathogenesis. *Clin Infect Dis*. 2000;30:374–379.
184. Chahoud J, Sharif Yakan A, Saad H, et al. Right-sided infective endocarditis and pulmonary infiltrates: an update. *Cardiol Rev*. 2016;24:230–237.
190. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132:1435–1486.
198. Chung-Esaki H, Rodriguez RM, Alter H, et al. Validation of a prediction rule for endocarditis in febrile injection drug users. *Am J Emerg Med*. 2014;32:412–416.
203. Axelsson A, Soholm H, Dalsgaard M, et al. Echocardiographic findings suggestive of infective endocarditis in asymptomatic Danish injection drug users attending urban injection facilities. *Am J Cardiol*. 2014;114:100–104.
204. Sekar P, Johnson JR, Thurn JR, et al. Comparative sensitivity of transthoracic and transesophageal echocardiography in diagnosis of infective endocarditis among veterans with *Staphylococcus aureus* bacteremia. *Open Forum Infect Dis*. 2017;4:ofx035.
211. Pasha AK, Lee JZ, Low SW, et al. Fungal endocarditis: update on diagnosis and management. *Am J Med*. 2016;129:1037–1043.
213. Pappas PG, Kauffman CA, Andes DR, et al. Executive summary: clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62:409–417.
214. Kim JB, Ejiofor JI, Yammine M, et al. Surgical outcomes of infective endocarditis among intravenous drug users. *J Thorac Cardiovasc Surg*. 2016;152:832–841.e1.
244. Qiu J, Zhou W, Zhou W, et al. The treatment of infected femoral artery pseudoaneurysms secondary to drug abuse: 11 years of experience at a single institution. *Ann Vasc Surg*. 2016;36:35–43.
251. Wolff AJ, O'Donnell AE. Pulmonary effects of illicit drug use. *Clin Chest Med*. 2004;25:203–216.
256. Nguyen VT, Chan ES, Chou SH, et al. Pulmonary effects of i.v. injection of crushed oral tablets: "excipient lung disease". *AJR Am J Roentgenol*. 2014;203:W506–W515.
265. Armenta RF, Collins KM, Strathdee SA, et al. *Mycobacterium tuberculosis* infection among persons who inject drugs in San Diego, California. *Int J Tuberc Lung Dis*. 2017;21:425–431.
269. Sadaphal P, Astemborski J, Graham NM, et al. Isoniazid preventive therapy, hepatitis C virus infection, and hepatotoxicity among injection drug users infected with *Mycobacterium tuberculosis*. *Clin Infect Dis*. 2001;33:1687–1691.
279. Harris AM, Iqbal K, Schillie S, et al. Increases in acute hepatitis B virus infections—Kentucky, Tennessee, and West Virginia, 2006-2013. *MMWR Morb Mortal Wkly Rep*. 2016;65:47–50.
295. Njei B, Do A, Lim JK. Prevalence of hepatitis delta infection in the United States: National Health and Nutrition Examination Survey, 1999-2012. *Hepatology*. 2016;64:681–682.
301. Zibbell JE, Asher AK, Patel RC, et al. Increases in acute hepatitis C virus infection related to a growing opioid epidemic and associated injection drug use, United States, 2004 to 2014. *Am J Public Health*. 2018;108:175–181.
307. Zibbell JE, Hart-Malloy R, Barry J, et al. Risk factors for HCV infection among young adults in rural New York who inject prescription opioid analgesics. *Am J Public Health*. 2014;104:2226–2232.
308. Conrad C, Bradley HM, Broz D, et al. Community outbreak of HIV infection linked to injection drug use of oxymorphone—Indiana, 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64:443–444.
309. Heimer R, Binka M, Koester S, et al. Recovery of infectious hepatitis C virus from injection paraphernalia: implications for prevention programs serving people who inject drugs. *J Infect Dis*. 2018;217:466–473.
319. Bhattacharya D, Belperio PS, Shahoumian TA, et al. Effectiveness of all-oral antiviral regimens in 996 human immunodeficiency virus/hepatitis C virus genotype 1-coinfected patients treated in routine practice. *Clin Infect Dis*. 2017;64:1711–1720.
348. Lin CT, Tranmer B, Durham S, et al. Ruptured mycotic aneurysm and cerebral vasospasm in the setting of endocarditis and heart failure requiring cardiothoracic surgery: case report and literature review. *World Neurosurg*. 2017;100:711.e13–711.e18.
352. Nussbaum ES, Rigamonti D, Standiford H, et al. Spinal epidural abscess: a report of 40 cases and review. *Surg Neurol*. 1992;38:225–231.
354. Artenstein AW, Friderici J, Holers A, et al. Spinal epidural abscess in adults: a 10-year clinical experience at a tertiary care academic medical center. *Open Forum Infect Dis*. 2016;3:ofw191.
358. Ghobrial GM, Beygi S, Viereck MJ, et al. Timing in the surgical evacuation of spinal epidural abscesses. *Neurosurg Focus*. 2014;37:E1.
366. Yuan J, Inami G, Mohle-Boetani J, et al. Recurrent wound botulism among injection drug users in California. *Clin Infect Dis*. 2011;52:862–866.
374. Tirpack AR, Duker JS, Baumal CR. An outbreak of endogenous fungal endophthalmitis among intravenous drug abusers in New England. *JAMA Ophthalmol*. 2017;135:534–540.
377. Patel SN, Rescigno RJ, Zarbin MA, et al. Endogenous endophthalmitis associated with intravenous drug abuse. *Retina*. 2014;34:1460–1465.
381. Burnett JC, Broz D, Spiller MW, et al. HIV infection and HIV-associated behaviors among persons who inject drugs—20 cities, United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2018;67:23–28.
395. Service UPH Preexposure prophylaxis for the prevention of HIV infection in the United States—2014. A clinical practice guideline. 2014.
401. Hoots BE, Finlayson TJ, Broz D, et al. Antiretroviral therapy use among HIV-infected people who inject drugs—20 cities, United States, 2009-2015. *J Acquir Immune Defic Syndr*. 2017;75(suppl 3):S392–S396.
406. Hayashi K, Dong H, Kerr T, et al. Declining mortality rates in HIV-infected people who inject drugs during a seek-and-treat initiative in Vancouver, Canada, 1996-2014: a prospective cohort study. *J Infect Dis*. 2017;217:64–68.
411. Roth AM, Goldshear JL, Martinez-Donate AP, et al. Reducing missed opportunities: pairing sexually transmitted infection screening with syringe exchange services. *Sex Transm Dis*. 2016;43:706–708.

References

1. World Drug Report 2017. United Nations Office on Drugs and Crime, 2017. 2017. Accessed November 29, 2017.
2. Hartman L, Barnes E, Bachmann L, et al. Opiate injection-associated infective endocarditis in the southeastern United States. *Am J Med Sci*. 2016;352:603–608.
3. Pollini RA, Banta-Green CJ, Cuevas-Mota J, et al. Problematic use of prescription-type opioids prior to heroin use among young heroin injectors. *Subst Abuse Rehabil*. 2011;2:173–180.
4. Fleischauer AT, Ruhl L, Rhea S, et al. Hospitalizations for endocarditis and associated health care costs among persons with diagnosed drug dependence—North Carolina, 2010-2015. *MMWR Morb Mortal Wkly Rep*. 2017;66:569–573.
5. Han B, Compton WM, Blanco C, et al. Prescription opioid use, misuse, and use disorders in U.S. adults: 2015 National Survey on Drug Use and Health. *Ann Intern Med*. 2017;167:293–301.
6. Administration SAaMHS. *Results From the 2013 National Survey on Drug Use and Health: Summary of National Findings*, NSDUH Series H-48, HHS Publication No. (SMA) 14-4863. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2014.
7. Evans JL, Tsui JI, Hahn JA, et al. Mortality among young injection drug users in San Francisco: a 10-year follow-up of the UFO study. *Am J Epidemiol*. 2012;175:302–308.
8. Charlebois ED, Bangsberg DR, Moss NJ, et al. Population-based community prevalence of methicillin-resistant *Staphylococcus aureus* in the urban poor of San Francisco. *Clin Infect Dis*. 2002;34:425–433.
9. Gordon RJ, Lowy FD. Bacterial infections in drug users. *N Engl J Med*. 2005;353:1945–1954.
10. Hayashi K, Wood E, Suwannawong P, et al. Methamphetamine injection and syringe sharing among a community-recruited sample of injection drug users in Bangkok, Thailand. *Drug Alcohol Depend*. 2011;115:145–149.
11. Thrombotic thrombocytopenic purpura (TTP)-like illness associated with intravenous Opana ER abuse—Tennessee, 2012. *MMWR Morb Mortal Wkly Rep*. 2013;62:1–4.
12. Reyes JC, Negron JL, Colon HM, et al. The emerging of xylazine as a new drug of abuse and its health consequences among drug users in Puerto Rico. *J Urban Health*. 2012;89:519–526.
13. O'Donnell JK, Halpin J, Mattson CL, et al. Deaths involving fentanyl, fentanyl analogs, and U-47700—10 states, July-December 2016. *MMWR Morb Mortal Wkly Rep*. 2017;66:1197–1202.
14. Shaw SY, Jolly AM, Wylie JL. Outlier populations: individual and social network correlates of solvent-using injection drug users. *PLoS ONE*. 2014;9:e88623.
15. Hope VD, Cullen KJ, Smith J, et al. Is the recent emergence of mephedrone injecting in the United Kingdom associated with elevated risk behaviours and blood borne virus infection? *Euro Surveill*. 2016;21.
16. Ojha SP, Sigdel S, Meyer-Thompson HG, et al. 'South Asian cocktail'—the concurrent use of opioids, benzodiazepines and antihistamines among injecting drug users in Nepal and associations with HIV risk behaviour. *Harm Reduct J*. 2014;11:17.
17. Loo HW, Yam AK, Tan TC, et al. Severe upper limb complications from parenteral abuse of Subutex. *Ann Acad Med Singapore*. 2005;34:575–578.
18. Ho RC, Ho EC, Mak A. Cutaneous complications among i.v. buprenorphine users. *J Dermatol*. 2009;36:22–29.
19. Efstratiou A, Emery M, Lamagni TL, et al. Increasing incidence of group A streptococcal infections amongst injecting drug users in England and Wales. *J Med Microbiol*. 2003;52:525–526.
20. Kievlan DR, Gukasyan M, Gesch J, et al. Clinical profile of injection drug users presenting to the ED. *Am J Emerg Med*. 2015;33:674–676.
21. Stein MD, Anderson B. Injection frequency mediates health service use among persons with a history of drug injection. *Drug Alcohol Depend*. 2003;70:159–168.
22. Cedarbaum ER, Banta-Green CJ. Health behaviors of young adult heroin injectors in the Seattle area. *Drug Alcohol Depend*. 2016;158:102–109.
23. Horyniak D, Dietze P, Degenhardt L, et al. The relationship between age and risky injecting behaviours among a sample of Australian people who inject drugs. *Drug Alcohol Depend*. 2013;132:541–546.
24. Cooper HL, Des Jarlais DC, Tempalski B, et al. Drug-related arrest rates and spatial access to syringe exchange programs in New York City health districts: combined effects on the risk of injection-related infections among injectors. *Health Place*. 2012;18:218–228.
25. Munoz F, Burgos JL, Cuevas-Mota J, et al. Individual and socio-environmental factors associated with unsafe injection practices among young adult injection drug users in San Diego. *AIDS Behav*. 2015;19:199–210.
26. Tassiopoulos K, Bernstein J, Bernstein E. Age and sharing of needle injection equipment in a cohort of Massachusetts injection drug users: an observational study. *Addict Sci Clin Pract*. 2013;8:20.
27. Marshall BD, Shoveller JA, Wood E, et al. Difficulty accessing syringes mediates the relationship between methamphetamine use and syringe sharing among young injection drug users. *AIDS Behav*. 2011;15:1546–1553.
28. Bassetti S, Battegay M. *Staphylococcus aureus* infections in injection drug users: risk factors and prevention strategies. *Infection*. 2004;32:163–169.
29. Lankenau SE, Schrager SM, Silva K, et al. Misuse of prescription and illicit drugs among high-risk young adults in Los Angeles and New York. *J Public Health Res*. 2012;1:22–30.
30. Vorobjov S, Des Jarlais DC, Abel-Ollo K, et al. Socio-demographic factors, health risks and harms associated with early initiation of injection among people who inject drugs in Tallinn, Estonia: evidence from cross-sectional surveys. *Int J Drug Policy*. 2013;24:150–155.
31. Mercure SA, Tetu I, Lamonde S, et al. Seeing is believing: an educational outreach activity on disinfection practices. *Harm Reduct J*. 2008;5:7.
32. Mackesy-Amiti ME, Donenberg GR, Ouellet LJ. Prevalence of psychiatric disorders among young injection drug users. *Drug Alcohol Depend*. 2012;124:70–78.
33. Hammett TM, Phan S, Gaggin J, et al. Pharmacies as providers of expanded health services for people who inject drugs: a review of laws, policies, and barriers in six countries. *BMC Health Serv Res*. 2014;14:261.
34. Hankins C, Palmer D, Singh R. Unintended subcutaneous and intramuscular injection by drug users. *CMAJ*. 2000;163:1425–1426.
35. Maxwell S, Bigg D, Stanczykiewicz K, et al. Prescribing naloxone to actively injecting heroin users: a program to reduce heroin overdose deaths. *J Addict Dis*. 2006;25:89–96.
36. Small W, Wood E, Lloyd-Smith E, et al. Accessing care for injection-related infections through a medically supervised injecting facility: a qualitative study. *Drug Alcohol Depend*. 2008;98:159–162.
37. Fairbairn N, Small W, Van Borek N, et al. Social structural factors that shape assisted injecting practices among injection drug users in Vancouver, Canada: a qualitative study. *Harm Reduct J*. 2010;7:20.
38. Bayoumi AM, Strike CJ. Making the case for supervised injection services. *Lancet*. 2016;387:1890–1891.
39. Ivsins A, Chow C, Macdonald S, et al. An examination of injection drug use trends in Victoria and Vancouver, BC after the closure of Victoria's only fixed-site needle and syringe programme. *Int J Drug Policy*. 2012;23:338–340.
40. Small D. Canada's highest court unchains injection drug users; implications for harm reduction as standard of healthcare. *Harm Reduct J*. 2012;9:34.
41. Syringe exchange programs —- United States, 2008. *MMWR Morb Mortal Wkly Rep*. 2010;59:1488–1491.
42. Miller CL, Firestone M, Ramos R, et al. Injecting drug users' experiences of policing practices in two Mexican-U.S. border cities: public health perspectives. *Int J Drug Policy*. 2008;19:324–331.
43. Ti L, Wood E, Shannon K, et al. Police confrontations among street-involved youth in a Canadian setting. *Int J Drug Policy*. 2013;24:46–51.
44. Phillips KT, Altman JK, Corsi KF, et al. Development of a risk reduction intervention to reduce bacterial and viral infections for injection drug users. *Subst Use Misuse*. 2013;48:54–64.
45. McNeil R, Small W, Wood E, et al. Hospitals as a 'risk environment': an ethno-epidemiological study of voluntary and involuntary discharge from hospital against medical advice among people who inject drugs. *Soc Sci Med*. 2014;105:59–66.
46. Libertin CR, Camsari UM, Hellinger WC, et al. The cost of a recalcitrant intravenous drug user with serial cases of endocarditis: need for guidelines to improve the continuum of care. *IDCases*. 2017;8:3–5.
47. Rosenthal ES, Karchmer AW, Theisen-Toupal J, et al. Suboptimal addiction interventions for patients hospitalized with injection drug use-associated infective endocarditis. *Am J Med*. 2016;129:481–485.
48. Ho J, Archuleta S, Sulaiman Z, et al. Safe and successful treatment of intravenous drug users with a peripherally inserted central catheter in an outpatient parenteral antibiotic treatment service. *J Antimicrob Chemother*. 2010;65:2641–2644.
49. Buehrle DJ, Shields RK, Shah N, et al. Risk factors associated with outpatient parenteral antibiotic therapy program failure among intravenous drug users. *Open Forum Infect Dis*. 2017;4:ofx102.
50. Jafari S, Joe R, Elliot D, et al. A community care model of intravenous antibiotic therapy for injection drug users with deep tissue infection for "Reduce Leaving Against Medical Advice". *Int J Ment Health Addict*. 2015;13:49–58.
51. Roy S. Drugs of abuse effects on immunity and microbial pathogenesis. *J Neuroimmune Pharmacol*. 2011;6:435–438.
52. Brack A, Rittner HL, Stein C. Immunosuppressive effects of opioids—clinical relevance. *J Neuroimmune Pharmacol*. 2011;6:490–502.
53. Wang JL, Chen SY, Wang JT, et al. Comparison of both clinical features and mortality risk associated with bacteremia due to community-acquired methicillin-resistant *Staphylococcus aureus* and methicillin-susceptible *S. aureus*. *Clin Infect Dis*. 2008;46:799–806.
54. Lanier RK, Ijames SG, Carrigan KA, et al. Self-administration of heroin produces alterations in the expression of inducible nitric oxide synthase. *Drug Alcohol Depend*. 2002;66:225–233.
55. Lysle DT, How T. Heroin modulates the expression of inducible nitric oxide synthase. *Immunopharmacology*. 2000;46:181–192.
56. Mihu MR, Roman-Sosa J, Varshney AK, et al. Methamphetamine alters the antimicrobial efficacy of phagocytic cells during methicillin-resistant *Staphylococcus aureus* skin infection. *MBio*. 2015;6:e01622-15.
57. Brown SM, Stimmel B, Taub RN, et al. Immunologic dysfunction in heroin addicts. *Arch Intern Med*. 1974;134:1001–1006.
58. Novick DM, Ochshorn M, Ghali V, et al. Natural killer cell activity and lymphocyte subsets in parenteral heroin abusers and long-term methadone maintenance patients. *J Pharmacol Exp Ther*. 1989;250:606–610.
59. Sacerdote P, Franchi S, Gerra G, et al. Buprenorphine and methadone maintenance treatment of heroin addicts preserves immune function. *Brain Behav Immun*. 2008;22:606–613.
60. Piepenbrink MS, Samuel M, Zheng B, et al. Humoral dysregulation associated with increased systemic inflammation among injection heroin users. *PLoS ONE*. 2016;11:e0158641.
61. Swann RE, Mandalou P, Robinson MW, et al. Anti-envelope antibody responses in individuals at high risk of hepatitis C virus who resist infection. *J Viral Hepat*. 2016;23:873–880.
62. Mina MM, Cameron B, Luciani F, et al. Natural killer cells in highly exposed hepatitis C-seronegative injecting drug users. *J Viral Hepat*. 2016;23:464–472.
63. Simonovska N, Chibishev A, Bozinovskal C, et al. The presence of some humoral immunologic indicators and clinical manifestations in cryoglobulin positive heroin addicts without evidence of hepatitis virus infection. *Srp Arh Celok Lek*. 2015;143:296–300.
64. Mehandru S, Deren S, Kang SY, et al. Behavioural, mucosal and systemic immune parameters in HIV-infected and uninfected injection drug users. *J Addict Res Ther*. 2015;6:1–8.
65. Stoll-Keller F, Schmitt C, Thumann C, et al. Effects of morphine on purified human blood monocytes. Modifications of properties involved in antiviral defences. *Int J Immunopharmacol*. 1997;19:95–100.
66. Guo CJ, Li Y, Tian S, et al. Morphine enhances HIV infection of human blood mononuclear phagocytes through modulation of beta-chemokines and CCR5 receptor. *J Investig Med*. 2002;50:435–442.
67. Zhou Y, Sun L, Wang X, et al. Heroin use promotes HCV infection and dysregulates HCV-related circulating microRNAs. *J Neuroimmune Pharmacol*. 2015;10:102–110.
68. Irish C, Maxwell R, Dancox M, et al. Skin and soft tissue infections and vascular disease among drug users, England. *Emerg Infect Dis*. 2007;13:1510–1511.
69. Szeto BKF, Herzig CTA, Befus M, et al. Drug use is associated with purulent skin and soft tissue infections in a large urban jail: 2011-2015. *Open Forum Infect Dis*. 2017;4:ofx135.
70. Larney S, Peacock A, Mathers BM, et al. A systematic review of injecting-related injury and disease among people who inject drugs. *Drug Alcohol Depend*. 2017;171:39–49.
71. Smith ME, Robinowitz N, Chaulk P, et al. Self-care and risk reduction habits in older injection drug users with chronic wounds: a cross-sectional study. *Harm Reduct J*. 2014;11:28.
72. Lloyd-Smith E, Tyndall M, Zhang R, et al. Determinants of cutaneous injection-related infections among injection drug users at an emergency department. *Open Infect Dis J*. 2012;6.
73. Lloyd-Smith E, Wood E, Zhang R, et al. Determinants of hospitalization for a cutaneous injection-related infection

among injection drug users: a cohort study. *BMC Public Health*. 2010;10:327.

74. Young DM, Harris HW, Charlebois ED, et al. An epidemic of methicillin-resistant *Staphylococcus aureus* soft tissue infections among medically underserved patients. *Arch Surg*. 2004;139:947–951, discussion 51–53.
75. Maliphant J, Scott J. Use of the femoral vein ('groin injecting') by a sample of needle exchange clients in Bristol, UK. *Harm Reduct J*. 2005;2:6.
76. Cregler LL, Mark H. Medical complications of cocaine abuse. *N Engl J Med*. 1986;315:1495–1500.
77. Zamora-Quezada JC, Dinerman H, Stadecker MJ, et al. Muscle and skin infarction after free-basing cocaine (crack). *Ann Intern Med*. 1988;108:564–566.
78. Risdahl JM, Khanna KV, Peterson PK, et al. Opiates and infection. *J Neuroimmunol*. 1998;83:4–18.
79. Strathdee SA, Case P, Lozada R, et al. The color of meth: is it related to adverse health outcomes? An exploratory study in Tijuana, Mexico. *Am J Addict*. 2008;17:111–115.
80. Spijkerman IJ, van Ameijden EJ, Mientjes GH, et al. Human immunodeficiency virus infection and other risk factors for skin abscesses and endocarditis among injection drug users. *J Clin Epidemiol*. 1996;49:1149–1154.
81. Hope V, Kimber J, Vickerman P, et al. Frequency, factors and costs associated with injection site infections: findings from a national multi-site survey of injecting drug users in England. *BMC Infect Dis*. 2008;8:120.
82. Pollini RA, Gallardo M, Hasan S, et al. High prevalence of abscesses and self-treatment among injection drug users in Tijuana, Mexico. *Int J Infect Dis*. 2010;14(suppl 3):e117–e122.
83. Roose RJ, Hayashi AS, Cunningham CO. Self-management of injection-related wounds among injecting drug users. *J Addict Dis*. 2009;28:74–80.
84. Takahashi TA, Merrill JO, Boyko EJ, et al. Type and location of injection drug use-related soft tissue infections predict hospitalization. *J Urban Health*. 2003;80:127–136.
85. Murphy EL, DeVita D, Liu H, et al. Risk factors for skin and soft-tissue abscesses among injection drug users: a case-control study. *Clin Infect Dis*. 2001;33:35–40.
86. Lloyd-Smith E, Kerr T, Hogg RS, et al. Prevalence and correlates of abscesses among a cohort of injection drug users. *Harm Reduct J*. 2005;2:24.
87. Tomolillo CM, Crothers LJ, Aberson CL. The damage done: a study of injection drug use, injection related abscesses and needle exchange regulation. *Subst Use Misuse*. 2007;42:1603–1611.
88. Chotai N, Gallagher K, Kieffer WK, et al. A comparative analysis of the patient characteristics and cost of managing intravenous drug users (IVDU) with soft tissue abscesses with non-IVDU. *Surgeon*. 2016;14:13–17.
89. Hillstrom RP, Cohn AM, McCarroll KA. Vocal cord paralysis resulting from neck injections in the intravenous drug use population. *Laryngoscope*. 1990;100:503–506.
90. Tom MB, Rice DH. Presentation and management of neck abscess: a retrospective analysis. *Laryngoscope*. 1988;98:877–880.
91. Torres J, Avalos N, Echols L, et al. Low yield of blood and wound cultures in patients with skin and soft-tissue infections. *Am J Emerg Med*. 2017;35:1159–1161.
92. Smith ME, Robinowitz N, Chaulk P, et al. Comparison of chronic wound culture techniques: swab versus curetted tissue for microbial recovery. *Br J Community Nurs*. 2014;S22-6:Suppl.
93. Jenkins TC, Knepper BC, Jason Moore S, et al. Microbiology and initial antibiotic therapy for injection drug users and non-injection drug users with cutaneous abscesses in the era of community-associated methicillin-resistant *Staphylococcus aureus*. *Acad Emerg Med*. 2015;22:993–997.
94. Cohen AL, Shuler C, McAllister S, et al. Methamphetamine use and methicillin-resistant *Staphylococcus aureus* skin infections. *Emerg Infect Dis*. 2007;13:1707–1713.
95. Stryjewski ME, Chambers HF. Skin and soft-tissue infections caused by community-acquired methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis*. 2008;46(suppl 5):S368–S377.
96. Hemingway DM, Balfour AE, McCartney AC, et al. *Streptococcus milleri* and complex groin abscesses in intravenous drug abusers. *Scott Med J*. 1992;37:116–117.
97. Hoeger PH, Haupt G, Hoelzle E. Acute multifocal skin necrosis: synergism between invasive streptococcal infection and cocaine-induced tissue ischaemia? *Acta Derm Venereol*. 1996;76:239–241.
98. Talan DA, Summanen PH, Finegold SM. Ampicillin/sulbactam and cefoxitin in the treatment of cutaneous and other soft-tissue abscesses in patients with or without histories of injection drug abuse. *Clin Infect Dis*. 2000;31:464–471.
99. Bergstein JM, Baker EJ, Aprahamian C, et al. Soft tissue abscesses associated with parenteral drug abuse: presentation, microbiology, and treatment. *Am Surg*. 1995;61:1105–1108.
100. Henriksen BM, Albrektsen SB, Simper LB, et al. Soft tissue infections from drug abuse. A clinical and microbiological review of 145 cases. *Acta Orthop Scand*. 1994;65:625–628.
101. Alcantara AL, Tucker RB, McCarroll KA. Radiologic study of injection drug use complications. *Infect Dis Clin North Am*. 2002;16:713–743, ix–x.
102. Towers JD. The use of intravenous contrast in MRI of extremity infection. *Semin Ultrasound CT MR*. 1997;18:269–275.
103. Squire BT, Fox JC, Anderson C. ABSCESS: applied bedside sonography for convenient evaluation of superficial soft tissue infections. *Acad Emerg Med*. 2005;12:601–606.
104. Eron LJ, Lipsky BA, Low DE, et al. Managing skin and soft tissue infections: expert panel recommendations on key decision points. *J Antimicrob Chemother*. 2003;52(suppl 1):i3–i17.
105. Tosti R, Trionfo A, Gaughan J, et al. Risk factors associated with clindamycin-resistant, methicillin-resistant *Staphylococcus aureus* in hand abscesses. *J Hand Surg Am*. 2015;40:673–676.
106. Clauson A, Mailhot T, Chilstrom ML. Ultrasound-guided diagnosis and aspiration of subdeltoid abscess from heroin injection. *West J Emerg Med*. 2014;15:819–821.
107. Talan DA, Mower WR, Krishnadasan A, et al. Trimethoprim-sulfamethoxazole versus placebo for uncomplicated skin abscess. *N Engl J Med*. 2016;374:823–832.
108. Schnall SB, Holtom PD, Lilley JC. Abscesses secondary to parenteral abuse of drugs. A study of demographic and bacteriological characteristics. *J Bone Joint Surg Am*. 1994;76:1526–1530.
109. Wallace JR, Lucas CE, Ledgerwood AM. Social, economic, and surgical anatomy of a drug-related abscess. *Am Surg*. 1986;52:398–401.
110. Simmen HP, Giovanoli P, Battaglia H, et al. Soft tissue infections of the upper extremities with special consideration of abscesses in parenteral drug abusers. A prospective study. *J Hand Surg [Br]*. 1995;20:797–800.
111. Foster SD, Lyons MS, Runyan CM, et al. A mimic of soft tissue infection: intra-arterial injection drug use producing hand swelling and digital ischemia. *World J Emerg Med*. 2015;6:233–236.
112. Pieper B. A retrospective analysis of venous ulcer healing in current and former users of injected drugs. *J Wound Ostomy Continence Nurs*. 1996;23:291–296.
113. Pieper B, Rossi R, Templin T. Pain associated with venous ulcers in injecting drug users. *Ostomy Wound Manage*. 1998;44:54–58, 60–67.
114. Dow G, Browne A, Sibbald RG. Infection in chronic wounds: controversies in diagnosis and treatment. *Ostomy Wound Manage*. 1999;45:23–27, 9–40; quiz 1–2.
115. Canales M, Gerhard J, Younce E. Lower extremity manifestations of "skin-popping" an illicit drug use technique: a report of two cases. *Foot (Edinb)*. 2015;25:114–119.
116. Iyer S, Pabari A, Khoo CT. A well vascularised muscle flap—drug user's dream. *J Plast Reconstr Aesthet Surg*. 2012;65:399–401.
117. Waldron C, Solon JG, O'Gorman J, et al. Necrotizing fasciitis: the need for urgent surgical intervention and the impact of intravenous drug use. *Surgeon*. 2015;13:194–199.
118. Gonzalez MH, Kay T, Weinzweig N, et al. Necrotizing fasciitis of the upper extremity. *J Hand Surg Am*. 1996;21:689–692.
119. Callahan TE, Schecter WP, Horn JK. Necrotizing soft tissue infection masquerading as cutaneous abcess following illicit drug injection. *Arch Surg*. 1998;133:812–817, discussion 7–9.
120. Frazee BW, Fee C, Lynn J, et al. Community-acquired necrotizing soft tissue infections: a review of 122 cases presenting to a single emergency department over 12 years. *J Emerg Med*. 2008;34:139–146.
121. Mittapalli D, Velineni R, Rae N, et al. Necrotizing soft tissue infections in intravenous drug users: a vascular surgical emergency. *Eur J Vasc Endovasc Surg*. 2015;49:593–599.
122. Lungstras-Bufler K, Bufler P, Abdullah R, et al. High cytokine levels at admission are associated with fatal outcome in patients with necrotizing fasciitis. *Eur Cytokine Netw*. 2004;15:135–138.
123. Wysoki MG, Santora TA, Shah RM, et al. Necrotizing fasciitis: CT characteristics. *Radiology*. 1997;203:859–863.
124. Falasca GF, Reginato AJ. The spectrum of myositis and rhabdomyolysis associated with bacterial infection. *J Rheumatol*. 1994;21:1932–1937.
125. Kimura AC, Higa JI, Levin RM, et al. Outbreak of necrotizing fasciitis due to *Clostridium sordellii* among black-tar heroin users. *Clin Infect Dis*. 2004;38:e87–e91.
126. Chen JL, Fullerton KE, Flynn NM. Necrotizing fasciitis associated with injection drug use. *Clin Infect Dis*. 2001;33:6–15.
127. Noone M, Tabaqchali M, Spillane JB. *Clostridium novyi* causing necrotising fasciitis in an injecting drug user. *J Clin Pathol*. 2002;55:141–142.
128. Sudarsky LA, Laschinger JC, Coppa GF, et al. Improved results from a standardized approach in treating patients with necrotizing fasciitis. *Ann Surg*. 1987;206:661–665.
129. Rieger UM, Gugger CY, Farhadi J, et al. Prognostic factors in necrotizing fasciitis and myositis: analysis of 16 consecutive cases at a single institution in Switzerland. *Ann Plast Surg*. 2007;58:523–530.
130. Marinis A, Voultsos M, Grivas P, et al. Vacuum-assisted therapy accelerates wound healing in necrotizing soft tissue infections: our experience in two intravenous drug abuse patients. *Infez Med*. 2013;21:305–311.
131. Lo TS, Mooers MG, Wright LJ. Pyomyositis complicating acute bacterial endocarditis in an intravenous drug user. *N Engl J Med*. 2000;342:1614–1615.
132. Prahlow JA, Cappellari JO, Washburn SA. Uterine pyomyoma as a complication of pregnancy in an intravenous drug user. *South Med J*. 1996;89:892–895.
133. Grau LE, Arevalo S, Catchpool C, et al. Expanding harm reduction services through a wound and abscess clinic. *Am J Public Health*. 2002;92:1915–1917.
134. Veitch J, Kansara A, Bailey D, et al. Severe systemic *Bacillus anthracis* infection in an intravenous drug user. *BMJ Case Rep*. 2014;2014.
135. Grunow R, Verbeek L, Jacob D, et al. Injection anthrax—a new outbreak in heroin users. *Dtsch Arztebl Int*. 2012;109:843–848.
136. Hicks CW, Sweeney DA, Cui X, et al. An overview of anthrax infection including the recently identified form of disease in injection drug users. *Intensive Care Med*. 2012;38:1092–1104.
137. Kak V, Chandrasekar PH. Bone and joint infections in injection drug users. *Infect Dis Clin North Am*. 2002;16:681–695.
138. Lamas C, Boia M, Eykyn SJ. Osteoarticular infections complicating infective endocarditis: a study of 30 cases between 1969 and 2002 in a tertiary referral centre. *Scand J Infect Dis*. 2006;38:433–440.
139. Munoz-Fernandez S, Macia MA, Pantoja L, et al. Osteoarticular infection in intravenous drug abusers: influence of HIV infection and differences with non drug abusers. *Ann Rheum Dis*. 1993;52:570–574.
140. Zalavras CG, Gupta N, Patzakis MJ, et al. Microbiology of osteomyelitis in patients infected with the human immunodeficiency virus. *Clin Orthop Relat Res*. 2005;439:97–100.
141. Chandrasekar PH, Narula AP. Bone and joint infections in intravenous drug abusers. *Rev Infect Dis*. 1986;8:904–911.
142. Allison DC, Holtom PD, Patzakis MJ, et al. Microbiology of bone and joint infections in injecting drug abusers. *Clin Orthop Relat Res*. 2010;468:2107–2112.
143. Swisher LA, Roberts JR, Glynn MJ. Needle licker's osteomyelitis. *Am J Emerg Med*. 1994;12:343–346.
144. Miller DJ, Mejicano GC. Vertebral osteomyelitis due to *Candida* species: case report and literature review. *Clin Infect Dis*. 2001;33:523–530.
145. Rahman I, Bhatt H, Chillag S, et al. *Mycobacterium chelonae* vertebral osteomyelitis. *South Med J*. 2009;102:1167–1169.
146. Wang Z, Lenehan B, Itshayek E, et al. Primary pyogenic infection of the spine in intravenous drug users: a prospective observational study. *Spine*. 2012;37:685–692.
147. Conterno LO, Turchi MD. Antibiotics for treating chronic osteomyelitis in adults. *Cochrane Database Syst Rev*. 2013;(9):CD004439.
148. Spellberg B, Lipsky BA. Systemic antibiotic therapy for chronic osteomyelitis in adults. *Clin Infect Dis*. 2012;54:393–407.
149. Jewell C, Weaver M, Sgroi C, et al. Residential addiction treatment for injection drug users requiring intravenous antibiotics: a cost-reduction strategy. *J Addict Med*. 2013;7:271–276.
150. Levine DP, Crane LR, Zervos MJ. Bacteremia in narcotic addicts at the Detroit Medical Center. II. Infectious endocarditis: a prospective comparative study. *Rev Infect Dis*. 1986;8:374–396.
151. Ambrosioni J, Hernandez-Meneses M, Tellez A, et al. The changing epidemiology of infective endocarditis in the twenty-first century. *Curr Infect Dis Rep*. 2017;19:21.
152. Griffith DJ, Mackintosh CL, Inverarity D. *Staphylococcus aureus* bacteraemia associated with injected new psychoactive substances. *Epidemiol Infect*. 2016;144:1257–1266.

153. Asgeirsson H, Thalme A, Weiland O. Low mortality but increasing incidence of *Staphylococcus aureus* endocarditis in people who inject drugs: experience from a Swedish referral hospital. *Medicine (Baltimore)*. 2016;95:e5617.
154. Starakis I, Mazokopakis EE. Injecting illicit substances epidemic and infective endocarditis. *Infect Disord Drug Targets*. 2010;10:22–26.
155. Wilson LE, Thomas DL, Astemborski J, et al. Prospective study of infective endocarditis among injection drug users. *J Infect Dis*. 2002;185:1761–1766.
156. Wang'ondu RW, Murray TS. Relapse of polymicrobial endocarditis in an intravenous drug user. *Yale J Biol Med*. 2011;84:321–324.
157. Baddour LM. Twelve-year review of recurrent native-valve infective endocarditis: a disease of the modern antibiotic era. *Rev Infect Dis*. 1988;10:1163–1170.
158. Chong E, Poh KK, Shen L, et al. Infective endocarditis secondary to intravenous Subutex abuse. *Singapore Med J*. 2009;50:34–42.
159. Mathew J, Addai T, Anand A, et al. Clinical features, site of involvement, bacteriologic findings, and outcome of infective endocarditis in intravenous drug users. *Arch Intern Med*. 1995;155:1641–1648.
160. Ruppen C, Rasmussen M, Casanova C, et al. A 10-year observational study of Streptococcus dysgalactiae bacteraemia in adults: frequent occurrence among female intravenous drug users. *Swiss Med Wkly*. 2017;147:w14469.
161. Reyes MP, Ali A, Mendes RE, et al. Resurgence of *Pseudomonas* endocarditis in Detroit, 2006-2008. *Medicine (Baltimore)*. 2009;88:294–301.
162. Cooper R, Mills J. Serratia endocarditis. A follow-up report. *Arch Intern Med*. 1980;140:199–202.
163. Mills J, Drew D. *Serratia marcescens* endocarditis: a regional illness associated with intravenous drug abuse. *Ann Intern Med*. 1976;84:29–35.
164. Phadke VK, Jacob JT. Marvelous but morbid: infective endocarditis due to *Serratia marcescens*. *Infect Dis Clin Pract (Baltim Md)*. 2016;24:143–150.
165. Morpeth S, Murdoch D, Cabell CH, et al. Non-HACEK gram-negative bacillus endocarditis. *Ann Intern Med*. 2007;147:829–835.
166. Lefort A, Chartier L, Sendid B, et al. Diagnosis, management and outcome of *Candida* endocarditis. *Clin Microbiol Infect*. 2012;18:E99–E109.
167. Petrosillo N, Pellicelli AM, Cicalini S, et al. Endocarditis caused by *Aspergillus* species in injection drug users. *Clin Infect Dis*. 2001;33:E97–E99.
168. Adler AG, Blumberg EA, Schwartz DA, et al. Seven-pathogen tricuspid endocarditis in an intravenous drug abuser. Pitfalls in laboratory diagnosis. *Chest*. 1991;99:490–491.
169. Tusgul S, Prod'hom G, Senn L, et al. *Bacillus cereus* bacteraemia: comparison between haematologic and nonhaematologic patients. *New Microbes New Infect*. 2017;15:65–71.
170. Szabo S, Lieberman JP, Lue YA. Unusual pathogens in narcotic-associated endocarditis. *Rev Infect Dis*. 1990;12:412–415.
171. Rieg S, Martin Bauer T, Peyerl-Hoffmann G, et al. *Paenibacillus larvae* bacteremia in injection drug users. *Emerg Infect Dis*. 2010;16:487–489.
172. Tuazon CU, Cardella TA, Sheagren JN. Staphylococcal endocarditis in drug users. Clinical and microbiologic aspects. *Arch Intern Med*. 1975;135:1555–1561.
173. Dressler FA, Roberts WC. Infective endocarditis in opiate addicts: analysis of 80 cases studied at necropsy. *Am J Cardiol*. 1989;63:1240–1257.
174. Reyes MP, Palutke WA, Wylin RF. *Pseudomonas endocarditis* in the Detroit Medical Center, 1969-1972. *Medicine (Baltimore)*. 1973;52:173–194.
175. Graves MK, Soto L. Left-sided endocarditis in parenteral drug abusers: recent experience at a large community hospital. *South Med J*. 1992;85:378–380.
176. Nazir S, Lohani S, Tachamo N, et al. Isolated pulmonary valve endocarditis masquerading as community-acquired pneumonia. *J Community Hosp Intern Med Perspect*. 2016;6:32827.
177. Frontera JA, Gradon JD. Right-side endocarditis in injection drug users: review of proposed mechanisms of pathogenesis. *Clin Infect Dis*. 2000;30:374–379.
178. Miro JM, Moreno A, Mestres CA. Infective endocarditis in intravenous drug abusers. *Curr Infect Dis Rep*. 2003;5:307–316.
179. Jain V, Yang MH, Kovacicova-Lezcano G, et al. Infective endocarditis in an urban medical center: association of individual drugs with valvular involvement. *J Infect*. 2008;57:132–138.
180. Crane LR, Levine DP, Zervos MJ, et al. Bacteremia in narcotic addicts at the Detroit Medical Center. I. Microbiology, epidemiology, risk factors, and empiric therapy. *Rev Infect Dis*. 1986;8:364–373.
181. El-Khatib MR, Wilson FM, Lerner AM. Characteristics of bacterial endocarditis in heroin addicts in Detroit. *Am J Med Sci*. 1976;271:197–201.
182. Stimmel B, Donoso E, Dack S. Comparison of infective endocarditis in drug addicts and nondrug users. *Am J Cardiol*. 1973;32:924–929.
183. Chambers HF, Korzeniowski OM, Sande MA. *Staphylococcus aureus* endocarditis: clinical manifestations in addicts and nonaddicts. *Medicine (Baltimore)*. 1983;62:170–177.
184. Chahoud J, Sharif Yakan A, Saad H, et al. Right-sided infective endocarditis and pulmonary infiltrates: an update. *Cardiol Rev*. 2016;24:230–237.
185. Corzo JE, Lozano de Leon F, Gomez-Mateos J, et al. Pneumothorax secondary to septic pulmonary emboli in tricuspid endocarditis. *Thorax*. 1992;47:1080–1081.
186. Saydain G, Singh J, Dalal B, et al. Outcome of patients with injection drug use-associated endocarditis admitted to an intensive care unit. *J Crit Care*. 2010;25:248–253.
187. Dressler FA, Roberts WC. Modes of death and types of cardiac diseases in opiate addicts: analysis of 168 necropsy cases. *Am J Cardiol*. 1989;64:909–920.
188. Roberts JH, Aponte V, Naidich DP, et al. Myocardial abscess resulting in a pseudoaneurysm: case report. *Cardiovasc Intervent Radiol*. 1991;14:307–310.
189. Sapico FL, Liquete JA, Sarma RJ. Bone and joint infections in patients with infective endocarditis: review of a 4-year experience. *Clin Infect Dis*. 1996;22:783–787.
190. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132:1435–1486.
191. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30:633–638.
192. Palepu A, Cheung SS, Montessori V, et al. Factors other than the Duke criteria associated with infective endocarditis among injection drug users. *Clin Invest Med*. 2002;25:118–125.
193. Young GP, Hedges JR, Dixon L, et al. Inability to validate a predictive score for infective endocarditis in intravenous drug users. *J Emerg Med*. 1993;11:1–7.
194. Weisse AB, Heller DR, Schimenti RJ, et al. The febrile parenteral drug user: a prospective study in 121 patients. *Am J Med*. 1993;94:274–280.
195. Rothman REWT, Weiss JL, Bartlett J, et al Diagnostic Importance of transthoracic echocardiography (TTE) in febrile intravenous drug users (IDUs) at risk for infective endocarditis (IE): is there a role for ultrasound in the emergency department (ED)? Poster #66. 7th International Symposium on Modern Concepts in Endocarditis and Cardiovascular Infections; 2003 June 26-28; Chamonix Mont Blanc, France.
196. Rothman REWT, Majumdar M, Bartlett J, et al Criteria for the diagnosis of infective endocarditis (IE) in febrile intravenous drug users: a new gold standard for the acute care setting, Abstract #38. 7th International Symposium on Modern Concepts in Endocarditis and Cardiovascular Infections; 2003 June 26-28; Chamonix Mont Blanc, France.
197. Rothman RE, Majmudar MD, Kelen GD, et al. Detection of bacteremia in emergency department patients at risk for infective endocarditis using universal 16S rRNA primers in a decontaminated polymerase chain reaction assay. *J Infect Dis*. 2002;186:1677–1681.
198. Chung-Esaki H, Rodriguez RM, Alter H, et al. Validation of a prediction rule for endocarditis in febrile injection drug users. *Am J Emerg Med*. 2014;32:412–416.
199. Pazin GJ, Saul S, Thompson ME. Blood culture positivity: suppression by outpatient antibiotic therapy in patients with bacterial endocarditis. *Arch Intern Med*. 1982;142:263–268.
200. Korzeniowski O, Sande MA. Combination antimicrobial therapy for *Staphylococcus aureus* endocarditis in patients addicted to parenteral drugs and in nonaddicts: a prospective study. *Ann Intern Med*. 1982;97:496–503.
201. Levine DP, Fromm BS, Reddy BR. Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant *Staphylococcus aureus* endocarditis. *Ann Intern Med*. 1991;115:674–680.
202. Pruitt AA, Rubin RH, Karchmer AW, et al. Neurologic complications of bacterial endocarditis. *Medicine (Baltimore)*. 1978;57:329–343.
203. Axelsson A, Soholm H, Dalsgaard M, et al. Echocardiographic findings suggestive of infective endocarditis in asymptomatic Danish injection drug users attending urban injection facilities. *Am J Cardiol*. 2014;114:100–104.
204. Sekar P, Johnson JR, Thurn JR, et al. Comparative sensitivity of transthoracic and transesophageal echocardiography in diagnosis of infective endocarditis among veterans with *Staphylococcus aureus* bacteremia. *Open Forum Infect Dis*. 2017;4:ofx035.
205. Brown PD, Levine DP. Infective endocarditis in the injection drug user. *Infect Dis Clin North Am*. 2002;16:645–665, viii–ix.
206. Klein EY, Mojica N, Jiang W, et al. Trends in methicillin-resistant *Staphylococcus aureus* hospitalizations in the United States, 2010-2014. *Clin Infect Dis*. 2017;65:1921–1923.
207. Chambers HF, Miller RT, Newman MD. Right-sided *Staphylococcus aureus* endocarditis in intravenous drug abusers: two-week combination therapy. *Ann Intern Med*. 1988;109:619–624.
208. Ribera E, Gomez-Jimenez J, Cortes E, et al. Effectiveness of cloxacillin with and without gentamicin in short-term therapy for right-sided *Staphylococcus aureus* endocarditis. A randomized, controlled trial. *Ann Intern Med*. 1996;125:969–974.
209. Heldman AW, Hartert TV, Ray SC, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. *Am J Med*. 1996;101:68–76.
210. Daikos GL, Kathpalia SB, Lolans VT, et al. Long-term oral ciprofloxacin: experience in the treatment of incurable infective endocarditis. *Am J Med*. 1988;84:786–790.
211. Pasha AK, Lee JZ, Low SW, et al. Fungal endocarditis: update on diagnosis and management. *Am J Med*. 2016;129:1037–1043.
212. Rivoisy C, Vena A, Schaeffer L, et al. Prosthetic valve *Candida* spp. endocarditis: new insights into long term prognosis—the ESCAPE study. *Clin Infect Dis*. 2017.
213. Pappas PG, Kauffman CA, Andes DR, et al. Executive summary: clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62:409–417.
214. Kim JB, Ejiofor JI, Yammine M, et al. Surgical outcomes of infective endocarditis among intravenous drug users. *J Thorac Cardiovasc Surg*. 2016;152:832–841.e1.
215. Prabhakar AM, Staziaki PV, Takx RA, et al. Preoperative evaluation for coronary atherosclerosis with computed tomography angiography in intravenous drug users: an emerging indication in the face of a growing threat. *Int J Cardiovasc Imaging*. 2016;32:131–135.
216. Yong MS, Saxena P, Killu AM, et al. The preoperative evaluation of infective endocarditis via 3-dimensional transesophageal echocardiography. *Tex Heart Inst J*. 2015;42:372–376.
217. Thiagaraj AK, Malviya M, Htun WW, et al. A novel approach in the management of right-sided endocarditis: percutaneous vegectomy using the AngioVac cannula. *Future Cardiol*. 2017;13:211–217.
218. Otome O, Guy S, Tramontana A, et al. A retrospective review: significance of vegetation size in injection drug users with right-sided infective endocarditis. *Heart Lung Circ*. 2016;25:466–470.
219. Rabkin DG, Mokadam NA, Miller DW, et al. Long-term outcome for the surgical treatment of infective endocarditis with a focus on intravenous drug users. *Ann Thorac Surg*. 2012;93:51–57.
220. Shetty N, Nagpal D, Koivu S, et al. Surgical and medical management of isolated tricuspid valve infective endocarditis in intravenous drug users. *J Card Surg*. 2016;31:83–88.
221. Osterdal OB, Salminen PR, Jordal S, et al. Cardiac surgery for infective endocarditis in patients with intravenous drug use. *Interact Cardiovasc Thorac Surg*. 2016;22:633–640.
222. Bromage DI, McLauchlan DJ, Nightingale AK. Do cardiologists and cardiac surgeons need ethics? Achieving happiness for a drug user with endocarditis. *Heart*. 2009;95:885–887.
223. Miljeteig I, Skrede S, Langorgen J, et al. Should patients who use illicit drugs be offered a second heart-valve replacement? *Tidsskr Nor Laegeforen*. 2013;133:977–980.
224. Hecht SR, Berger M. Right-sided endocarditis in intravenous drug users. Prognostic features in 102 episodes. *Ann Intern Med*. 1992;117:560–566.
225. Mathew J, Abreo G, Namburi K, et al. Results of surgical treatment for infective endocarditis in intravenous drug users. *Chest*. 1995;108:73–77.
226. Lemma M, Vanelli P, Beretta L, et al. Cardiac surgery in HIV-positive intravenous drug addicts: influence of cardiopulmonary bypass on the progression to AIDS. *Thorac Cardiovasc Surg*. 1992;40:279–282.
227. Frater RW. Surgical management of endocarditis in drug addicts and long-term results. *J Card Surg*. 1990;5:63–67.
228. Monsuez JJ, Vittecoq D, Acar C, et al. Recurrent infective endocarditis one year after mitral repair in a woman addicted to drugs. *J Thorac Cardiovasc Surg*. 1997;114:864–866.
229. Benitez PR, Newell MA. Vascular trauma in drug abuse: patterns of injury. *Ann Vasc Surg*. 1986;1:175–181.

230. Yeager RA, Hobson RW 2nd, Padberg FT, et al. Vascular complications related to drug abuse. *J Trauma*. 1987;27:305–308.
231. Dimitropoulou D, Lagadinou M, Papayiannis T, et al. Septic thrombophlebitis caused by *Fusobacterium necrophorum* in an intravenous drug user. *Case Rep Infect Dis*. 2013;2013:870846.
232. Kidambi TD, Lee C, Kohlwes RJ. MRSA-Associated Lemierre's syndrome in an intravenous drug user. *J Gen Intern Med*. 2015;30:1886–1887.
233. Ciccarone D, Harris M. Fire in the vein: heroin acidity and its proximal effect on users' health. *Int J Drug Policy*. 2015;26:1103–1110.
234. Yeo AK, Chan CY, Chia KH. Complications relating to intravenous buprenorphine abuse: a single institution case series. *Ann Acad Med Singapore*. 2006;35:487–491.
235. Mertz D, Khanlari B, Viktorin N, et al. Less than 28 days of intravenous antibiotic treatment is sufficient for suppurative thrombophlebitis in injection drug users. *Clin Infect Dis*. 2008;46:741–744.
236. Sharma G, Semel ME, McGillicuddy EA, et al. Ruptured and unruptured mycotic superior mesenteric artery aneurysms. *Ann Vasc Surg*. 2014;28:1931.e5–1931.e8.
237. Fiddes R, Khattab M, Abu Dakka M, et al. Patterns and management of vascular injuries in intravenous drug users: a literature review. *Surgeon*. 2010;8:353–361.
238. Reddy DJ, Smith RF, Elliott JP Jr, et al. Infected femoral artery false aneurysms in drug addicts: evolution of selective vascular reconstruction. *J Vasc Surg*. 1986;3:718–724.
239. Jayaraman S, Richardson D, Conrad M, et al. Mycotic pseudoaneurysms due to injection drug use: a ten-year experience. *Ann Vasc Surg*. 2012;26:819–824.
240. Papaioannou V, Mikroulis D, Chrysafis I, et al. Hemoptysis due to a mycotic pulmonary artery aneurysm in an injecting drug user. *Thorac Cardiovasc Surg*. 2014;62:453–455.
241. Jonasson SA, Jossang DE, Haaverstad R, et al. Arteriovenous fistula of the groin in a drug abuser with endocarditis. *J Surg Case Rep*. 2016;2016.
242. Tsao JW, Marder SR, Goldstone J, et al. Presentation, diagnosis, and management of arterial mycotic pseudoaneurysms in injection drug users. *Ann Vasc Surg*. 2002;16:652–662.
243. Shetty PC, Krasicky GA, Sharma RP, et al. Mycotic aneurysms in intravenous drug abusers: the utility of intravenous digital subtraction angiography. *Radiology*. 1985;155:319–321.
244. Qiu J, Zhou W, Zhou W, et al. The treatment of infected femoral artery pseudoaneurysms secondary to drug abuse: 11 years of experience at a single institution. *Ann Vasc Surg*. 2016;36:35–43.
245. Karkos CD, Kalogirou TE, Giagtzidis IT, et al. Ruptured mycotic common femoral artery pseudoaneurysm: fatal pulmonary embolism after emergency stent-grafting in a drug abuser. *Tex Heart Inst J*. 2014;41:634–637.
246. Tan KK, Chen K, Chia KH, et al. Surgical management of infected pseudoaneurysms in intravenous drug abusers: single institution experience and a proposed algorithm. *World J Surg*. 2009;33:1830–1835.
247. Hu ZJ, Wang SM, Li XX, et al. Tolerable hemodynamic changes after femoral artery ligation for the treatment of infected femoral artery pseudoaneurysm. *Ann Vasc Surg*. 2010;24:212–218.
248. Georgiadis GS, Lazarides MK, Polychronidis A, et al. Surgical treatment of femoral artery infected false aneurysms in drug abusers. *ANZ J Surg*. 2005;75:1005–1010.
249. Gonzalez I, Sarria C, Lopez J, et al. Symptomatic peripheral mycotic aneurysms due to infective endocarditis: a contemporary profile. *Medicine (Baltimore)*. 2014;93:42–52.
250. Kocovski L, Butany J, Nair V. Femoral artery pseudoaneurysm due to *Candida albicans* in an injection drug user. *Cardiovasc Pathol*. 2014;23:50–53.
251. Wolff AJ, O'Donnell AE. Pulmonary effects of illicit drug use. *Clin Chest Med*. 2004;25:203–216.
252. McGrath MM, Isakova T, Rennke HG, et al. Contaminated cocaine and antineutrophil cytoplasmic antibody-associated disease. *Clin J Am Soc Nephrol*. 2011;6:2799–2805.
253. Ho RC, Ho EC, Tan CH, et al. Pulmonary hypertension in first episode infective endocarditis among intravenous buprenorphine users: case report. *Am J Drug Alcohol Abuse*. 2009;35:199–202.
254. Kolinsky D, Keim SM, Cohn BG, et al. Is a prehospital treat and release protocol for opioid overdose safe? *J Emerg Med*. 2017;52:52–58.
255. Pare JA, Fraser RG, Hogg JC, et al. Pulmonary 'mainline' granulomatosis: talcosis of intravenous methadone abuse. *Medicine (Baltimore)*. 1979;58:229–239.
256. Nguyen VT, Chan ES, Chou SH, et al. Pulmonary effects of i.v. injection of crushed oral tablets: "excipient lung disease". *AJR Am J Roentgenol*. 2014;203:W506–W515.
257. Hind CR. Pulmonary complications of intravenous drug misuse. 2. Infective and HIV related complications. *Thorax*. 1990;45:957–961.
258. Le Moing V, Rabaud C, Journot V, et al. Incidence and risk factors of bacterial pneumonia requiring hospitalization in HIV-infected patients started on a protease inhibitor-containing regimen. *HIV Med*. 2006;7:261–267.
259. O'Donnell AE, Pappas LS. Pulmonary complications of intravenous drug abuse. Experience at an inner-city hospital. *Chest*. 1988;94:251–253.
260. Marantz PR, Linzer M, Feiner CJ, et al. Inability to predict diagnosis in febrile intravenous drug abusers. *Ann Intern Med*. 1987;106:823–828.
261. Samet JH, Shevitz A, Fowle J, et al. Hospitalization decision in febrile intravenous drug users. *Am J Med*. 1990;89:53–57.
262. Chalmers JD, Singanayagam A, Murray MP, et al. Risk factors for complicated parapneumonic effusion and empyema on presentation to hospital with community-acquired pneumonia. *Thorax*. 2009;64:592–597.
263. Park DR, Sherbin VL, Goodman MS, et al. The etiology of community-acquired pneumonia at an urban public hospital: influence of human immunodeficiency virus infection and initial severity of illness. *J Infect Dis*. 2001;184:268–277.
264. Jover F, Cuadrado JM, Andreu L, et al. A comparative study of bacteremic and non-bacteremic pneumococcal pneumonia. *Eur J Intern Med*. 2008;19:15–21.
265. Armenta RF, Collins KM, Strathdee SA, et al. Mycobacterium tuberculosis infection among persons who inject drugs in San Diego, California. *Int J Tuberc Lung Dis*. 2017;21:425–431.
266. Girardi E, Sabin CA, d'Arminio Monforte A, et al. Incidence of tuberculosis among HIV-infected patients receiving highly active antiretroviral therapy in Europe and North America. *Clin Infect Dis*. 2005;41:1772–1782.
267. Mazurek GH, Jereb J, Vernon A, et al. Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection—United States, 2010. *MMWR Recomm Rep*. 2010;59:1–25.
268. Kaplan JE, Benson C, Holmes KK, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep*. 2009;58:1–207, quiz CE1–CE4.
269. Sadaphal P, Astemborski J, Graham NM, et al. Isoniazid preventive therapy, hepatitis C virus infection, and hepatotoxicity among injection drug users infected with *Mycobacterium tuberculosis*. *Clin Infect Dis*. 2001;33:1687–1691.
270. Lutge EE, Wiysonge CS, Knight SE, et al. Material incentives and enablers in the management of tuberculosis. *Cochrane Database Syst Rev*. 2012;(1):CD007952.
271. Fairbairn N, Hayashi K, Milloy MJ, et al. Hazardous alcohol use associated with increased sexual risk behaviors among people who inject drugs. *Alcohol Clin Exp Res*. 2016;40:2394–2400.
272. Berson A, Gervais A, Cazals D, et al. Hepatitis after intravenous buprenorphine misuse in heroin addicts. *J Hepatol*. 2001;34:346–350.
273. Herve S, Riachi G, Noblet C, et al. Acute hepatitis due to buprenorphine administration. *Eur J Gastroenterol Hepatol*. 2004;16:1033–1037.
274. Hagan H, McGough JP, Thiede H, et al. Syringe exchange and risk of infection with hepatitis B and C viruses. *Am J Epidemiol*. 1999;149:203–213.
275. Mansson AS, Moestrup T, Nordenfelt E, et al. Continued transmission of hepatitis B and C viruses, but no transmission of human immunodeficiency virus among intravenous drug users participating in a syringe/needle exchange program. *Scand J Infect Dis*. 2000;32:253–258.
276. Palmateer N, Kimber J, Hickman M, et al. Evidence for the effectiveness of sterile injecting equipment provision in preventing hepatitis C and human immunodeficiency virus transmission among injecting drug users: a review of reviews. *Addiction*. 2010;105:844–859.
277. Kuo I, Mudrick DW, Strathdee SA, et al. Poor validity of self-reported hepatitis B virus infection and vaccination status among young drug users. *Clin Infect Dis*. 2004;38:587–590.
278. Schlicting EG, Johnson ME, Brems C, et al. Validity of injecting drug users' self report of hepatitis A, B, and C. *Clin Lab Sci*. 2003;16:99–106.
279. Harris AM, Iqbal K, Schillie S, et al. Increases in acute hepatitis B virus infections—Kentucky, Tennessee, and West Virginia, 2006-2013. *MMWR Morb Mortal Wkly Rep*. 2016;65:47–50.
280. Lemberg BD, Shaw-Stiffel TA. Hepatic disease in injection drug users. *Infect Dis Clin North Am*. 2002;16:667–679.
281. Murrill CS, Weeks H, Castrucci BC, et al. Age-specific seroprevalence of HIV, hepatitis B virus, and hepatitis C virus infection among injection drug users admitted to drug treatment in 6 US cities. *Am J Public Health*. 2002;92:385–387.
282. Nelson PK, Mathers BM, Cowie B, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet*. 2011;378:571–583.
283. Davis GL, Hoofnagle JH. Reactivation of chronic type B hepatitis presenting as acute viral hepatitis. *Ann Intern Med*. 1985;102:762–765.
284. Davis GL, Hoofnagle JH, Waggoner JG. Spontaneous reactivation of chronic hepatitis B virus infection. *Gastroenterology*. 1984;86:230–235.
285. Thio CL. Hepatitis B in the human immunodeficiency virus-infected patient: epidemiology, natural history, and treatment. *Semin Liver Dis*. 2003;23:125–136.
286. Torbenson M, Kannangai R, Astemborski J, et al. High prevalence of occult hepatitis B in Baltimore injection drug users. *Hepatology*. 2004;39:51–57.
287. Williams WW, Lu PJ, O'Halloran A, et al. Surveillance of vaccination coverage among adult populations—United States, 2014. *MMWR Surveill Summ*. 2016;65:1–36.
288. Baral S, Sherman SG, Millson P, et al. Vaccine immunogenicity in injecting drug users: a systematic review. *Lancet Infect Dis*. 2007;7:667–674.
289. Hu Y, Grau LE, Scott G, et al. Economic evaluation of delivering hepatitis B vaccine to injection drug users. *Am J Prev Med*. 2008;35:25–32.
290. Quaglio G, Lugoboni F, Vento S, et al. Isolated presence of antibody to hepatitis B core antigen in injection drug users: do they need to be vaccinated? *Clin Infect Dis*. 2001;32:E143–E144.
291. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol*. 2012;57:167–185.
292. De Cock KM, Govindarajan S, Chin KP, et al. Delta hepatitis in the Los Angeles area: a report of 126 cases. *Ann Intern Med*. 1986;105:108–114.
293. Lettau LA, McCarthy JG, Smith MH, et al. Outbreak of severe hepatitis due to delta and hepatitis B viruses in parenteral drug abusers and their contacts. *N Engl J Med*. 1987;317:1256–1262.
294. Ordieres C, Navascues CA, Gonzalez-Dieguez ML, et al. Prevalence and epidemiology of hepatitis D among patients with chronic hepatitis B virus infection: a report from Northern Spain. *Eur J Gastroenterol Hepatol*. 2017;29:277–283.
295. Njei B, Do A, Lim JK. Prevalence of hepatitis delta infection in the United States: National Health and Nutrition Examination Survey, 1999-2012. *Hepatology*. 2016;64:681–682.
296. Kucirka LM, Singer AL, Ros RL, et al. Underutilization of hepatitis C-positive kidneys for hepatitis C-positive recipients. *Am J Transplant*. 2010;10:1238–1246.
297. Smith HM, Alexander GJ, Webb G, et al. Hepatitis B and delta virus infection among "at risk" populations in south east London. *J Epidemiol Community Health*. 1992;46:144–147.
298. Shattock AG, Kelly MG, Fielding J, et al. Epidemic hepatitis B with delta-antigenaemia among Dublin drug-abusers. *Ir J Med Sci*. 1982;151:334–338.
299. Bonino F, Smedile A. Delta agent (type D) hepatitis. *Semin Liver Dis*. 1986;6:28–33.
300. Amon JJ, Garfein RS, Ahdieh-Grant L, et al. Prevalence of hepatitis C virus infection among injection drug users in the United States, 1994-2004. *Clin Infect Dis*. 2008;46:1852–1858.
301. Zibbell JE, Asher AK, Patel RC, et al. Increases in acute hepatitis C virus infection related to a growing opioid epidemic and associated injection drug use, United States, 2004 to 2014. *Am J Public Health*. 2018;108:175–181.
302. Garcia-Tejedor A, Maiques-Montesinos V, Diago-Almela VJ, et al. Risk factors for vertical transmission of hepatitis C virus: a single center experience with 710 HCV-infected mothers. *Eur J Obstet Gynecol Reprod Biol*. 2015;194:173–177.
303. Resti M, Azzari C, Galli L, et al. Maternal drug use is a preeminent risk factor for mother-to-child hepatitis C virus transmission: results from a multicenter study of 1372 mother-infant pairs. *J Infect Dis*. 2002;185:567–572.
304. Hagan H, Thiede H, Des Jarlais DC. Hepatitis C virus infection among injection drug users: survival analysis of time to seroconversion. *Epidemiology*. 2004;15:543–549.
305. Hahn JA, Page-Shafer K, Lum PJ, et al. Hepatitis C virus seroconversion among young injection drug users: relationships and risks. *J Infect Dis*. 2002;186:1558–1564.
306. Miller CL, Johnston C, Spittal PM, et al. Opportunities for prevention: hepatitis C prevalence and incidence in a

cohort of young injection drug users. *Hepatology*. 2002;36:737–742.

307. Zibbell JE, Hart-Malloy R, Barry J, et al. Risk factors for HCV infection among young adults in rural New York who inject prescription opioid analgesics. *Am J Public Health*. 2014;104:2226–2232.
308. Conrad C, Bradley HM, Broz D, et al. Community outbreak of HIV infection linked to injection drug use of oxymorphone—Indiana, 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64:443–444.
309. Heimer R, Binka M, Koester S, et al. Recovery of infectious hepatitis C virus from injection paraphernalia: implications for prevention programs serving people who inject drugs. *J Infect Dis*. 2018;217:466–473.
310. Phillips KT, Anderson BJ, Stein MD. Predictors of bacterial infections among HCV-negative injection drug users in Rhode Island. *Am J Drug Alcohol Abuse*. 2008;34:203–210.
311. Nolan S, Dias Lima V, Fairbairn N, et al. The impact of methadone maintenance therapy on hepatitis C incidence among illicit drug users. *Addiction*. 2014;109:2053–2059.
312. Grebely J, deVlaming S, Duncan F, et al. Current approaches to HCV infection in current and former injection drug users. *J Addict Dis*. 2008;27:25–35.
313. Mehta SH, Cox A, Hoover DR, et al. Protection against persistence of hepatitis C. *Lancet*. 2002;359:1478–1483.
314. Mizukoshi E, Eisenbach C, Edlin BR, et al. Hepatitis C virus (HCV)-specific immune responses of long-term injection drug users frequently exposed to HCV. *J Infect Dis*. 2008;198:203–212.
315. Aspinall EJ, Corson S, Doyle JS, et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. *Clin Infect Dis*. 2013;57(suppl 2):S80–S89.
316. Mehta SH, Genberg BL, Astemborski J, et al. Limited uptake of hepatitis C treatment among injection drug users. *J Community Health*. 2008;33:126–133.
317. Grebely J, Dore GJ. What is killing people with hepatitis C virus infection? *Semin Liver Dis*. 2011;31:331–339.
318. Young KL, Huang W, Horsburgh CR, et al. Eighteen- to 30-year-olds more likely to link to hepatitis C virus care: an opportunity to decrease transmission. *J Viral Hepat*. 2016;23:274–281.
319. Bhattacharya D, Belperio PS, Shahoumian TA, et al. Effectiveness of all-oral antiviral regimens in 996 human immunodeficiency virus/hepatitis C virus genotype 1-coinfected patients treated in routine practice. *Clin Infect Dis*. 2017;64:1711–1720.
320. Villano SA, Nelson KE, Vlahov D, et al. Hepatitis A among homosexual men and injection drug users: more evidence for vaccination. *Clin Infect Dis*. 1997;25:726–728.
321. Luquero FJ, Vallejo F, Fuente Lde L, et al. The role of injection versus socioeconomic factors in hepatitis A virus infection among young heroin users: implications for vaccination policies. *Vaccine*. 2009;27:2674–2679.
322. Keeffe EB. Is hepatitis A more severe in patients with chronic hepatitis B and other chronic liver diseases? *Am J Gastroenterol*. 1995;90:201–205.
323. Vento S, Garofano T, Renzini C, et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *N Engl J Med*. 1998;338:286–290.
324. Mahajan R, Collier MG, Kamili S, et al. Hepatitis E virus among persons who inject drugs, San Diego, California, USA, 2009-2010. *Emerg Infect Dis*. 2013;19:1664–1666.
325. Nallathambi MN, Ivatury RR, Lankin DH, et al. Pyogenic splenic abscess in intravenous drug addiction. *Am Surg*. 1987;53:342–346.
326. Dettmeyer R, Schlamann M, Madea B. Cocaine-associated abscesses with lethal sepsis after splenic infarction in an 17-year-old woman. *Forensic Sci Int*. 2004;140:21–23.
327. Fry DE, Richardson JD, Flint LM. Occult splenic abscess: an unrecognized complication of heroin abuse. *Surgery*. 1978;84:650–654.
328. Chun CH, Raff MJ, Contreras L, et al. Splenic abscess. *Medicine (Baltimore)*. 1980;59:50–65.
329. Sastre J, Casas E, Sierra J, et al. Splenic abscess due to *Fusobacterium necrophorum*. *Rev Infect Dis*. 1991;13:1249–1250.
330. Soriano V, Tor J, Gabarre E, et al. Multifocal splenic abscesses caused by *Mycobacterium tuberculosis* in HIV-infected drug users. *AIDS*. 1991;5:901–902.
331. Elsayes KM, Narra VR, Mukundan G, et al. MR imaging of the spleen: spectrum of abnormalities. *Radiographics*. 2005;25:967–982.
332. Kang M, Kalra N, Gulati M, et al. Image guided percutaneous splenic interventions. *Eur J Radiol*. 2007;64:140–146.
333. Conzo G, Docimo G, Palazzo A, et al. The role of percutaneous US-guided drainage in the treatment of splenic abscess. Case report and review of the literature. *Ann Ital Chir*. 2012;83:433–436.
334. Ferraioli G, Brunetti E, Gulizia R, et al. Management of splenic abscess: report on 16 cases from a single center. *Int J Infect Dis*. 2009;13:524–530.
335. Carbonell AM, Kercher KW, Matthews BD, et al. Laparoscopic splenectomy for splenic abscess. *Surg Laparosc Endosc Percutan Tech*. 2004;14:289–291.
336. Corcione F, Pirozzi F, Aragiusto G, et al. Laparoscopic splenectomy: experience of a single center in a series of 300 cases. *Surg Endosc*. 2012;26:2870–2876.
337. Adler CH, Stern MB, Brooks ML. Parkinsonism secondary to bilateral striatal fungal abscesses. *Mov Disord*. 1989;4:333–337.
338. Tunkel AR, Pradhan SK. Central nervous system infections in injection drug users. *Infect Dis Clin North Am*. 2002;16:589–605.
339. Garvey GJ, Neu HC. Infective endocarditis—an evolving disease. A review of endocarditis at the Columbia-Presbyterian Medical Center, 1968-1973. *Medicine (Baltimore)*. 1978;57:105–127.
340. Roberts WC, Buchbinder NA. Right-sided valvular infective endocarditis. A clinicopathologic study of twelve necropsy patients. *Am J Med*. 1972;53:7–19.
341. Lerner PI. Neurologic complications of infective endocarditis. *Med Clin North Am*. 1985;69:385–398.
342. Gilroy J, Andaya L, Thomas VJ. Intracranial mycotic aneurysms and subacute bacterial endocarditis in heroin addiction. *Neurology*. 1973;23:1193–1198.
343. White PM, Teasdale EM, Wardlaw JM, et al. Intracranial aneurysms: CT angiography and MR angiography for detection prospective blinded comparison in a large patient cohort. *Radiology*. 2001;219:739–749.
344. Ducruet AF, Hickman ZL, Zacharia BE, et al. Intracranial infectious aneurysms: a comprehensive review. *Neurosurg Rev*. 2010;33:37–46.
345. Turtz AR, Yocom SS. Contemporary approaches to the management of neurosurgical complications of infective endocarditis. *Curr Infect Dis Rep*. 2001;3:337–346.
346. Chalouhi N, Tjoumakaris S, Gonzalez LF, et al. Endovascular treatment of distal intracranial aneurysms with Onyx 18/34. *Clin Neurol Neurosurg*. 2013;115:2528–2532.
347. Frazee JG, Cahan LD, Winter J. Bacterial intracranial aneurysms. *J Neurosurg*. 1980;53:633–641.
348. Lin CT, Tranmer B, Durham S, et al. Ruptured mycotic aneurysm and cerebral vasospasm in the setting of endocarditis and heart failure requiring cardiothoracic surgery: case report and literature review. *World Neurosurg*. 2017;100:711.e13–711.e18.
349. Hazama A, Galgano M, Fullmer J, et al. Affinity of mucormycosis for basal ganglia in intravenous drug users: case illustration and review of literature. *World Neurosurg*. 2017;98:872.e1–872.e3.
350. Abbott SP, Sigler L, McAleer R, et al. Fatal cerebral mycoses caused by the ascomycete *Chaetomium strumarium*. *J Clin Microbiol*. 1995;33:2692–2698.
351. Farrar DJ, Flanigan TP, Gordon NM, et al. Tuberculous brain abscess in a patient with HIV infection: case report and review. *Am J Med*. 1997;102:297–301.
352. Nussbaum ES, Rigamonti D, Standiford H, et al. Spinal epidural abscess: a report of 40 cases and review. *Surg Neurol*. 1992;38:225–231.
353. Nagar VR, Springer JE, Salles S. Increased incidence of spinal abscess and substance abuse after implementation of state mandated prescription drug legislation. *Pain Med*. 2015;16:2031–2035.
354. Artenstein AW, Friderici J, Holers A, et al. Spinal epidural abscess in adults: a 10-year clinical experience at a tertiary care academic medical center. *Open Forum Infect Dis*. 2016;3:ofw191.
355. Ziu M, Dengler B, Cordell D, et al. Diagnosis and management of primary pyogenic spinal infections in intravenous recreational drug users. *Neurosurg Focus*. 2014;37:E3.
356. Fraimow HS, Wormser GP, Coburn KD, et al. *Salmonella* meningitis and infection with HIV. *AIDS*. 1990;4:1271–1273.
357. Bakhsh W, Childs S, Ikpeze T, et al. Lumbar spine infection by *Granulicatella* and *Abiotrophia* species. *World Neurosurg*. 2017.
358. Ghobrial GM, Beygi S, Viereck MJ, et al. Timing in the surgical evacuation of spinal epidural abscesses. *Neurosurg Focus*. 2014;37:E1.
359. Epstein NE. Timing and prognosis of surgery for spinal epidural abscess: a review. *Surg Neurol Int*. 2015;6:S475–S486.
360. Koppel BS, Daras M, Duffy KR. Intramedullary spinal cord abscess. *Neurosurgery*. 1990;26:145–146.
361. Sverzut JM, Laval C, Smadja P, et al. Spinal cord abscess in a heroin addict: case report. *Neuroradiology*. 1998;40:455–458.
362. Iwasaki M, Yano S, Aoyama T, et al. Acute onset intramedullary spinal cord abscess with spinal artery occlusion: a case report and review. *Eur Spine J*. 2011;20(suppl 2):S294–S301.
363. Wound botulism—California, 1995. From the Center for Disease Control and Prevention. *JAMA*. 1996;275:95–96.
364. From the Centers for Disease Control and Prevention. Tetanus among injecting-drug users—California, 1997. *JAMA*. 1998;279:987.
365. Passaro DJ, Werner SB, McGee J, et al. Wound botulism associated with black tar heroin among injecting drug users. *JAMA*. 1998;279:859–863.
366. Yuan J, Inami G, Mohle-Boetani J, et al. Recurrent wound botulism among injection drug users in California. *Clin Infect Dis*. 2011;52:862–866.
367. Gonzales y Tucker RD, Frazee B. View from the front lines: an emergency medicine perspective on clostridial infections in injection drug users. *Anaerobe*. 2014;30:108–115.
368. Redmond J, Stritch M, Blaney P. Severe tetanus in a narcotic addict. *Ir Med J*. 1984;77:325–326.
369. Schulte M, Hamsen U, Schildhauer TA, et al. Effective and rapid treatment of wound botulism, a case report. *BMC Surg*. 2017;17:103.
370. Connell PP, O'Neill EC, Fabinyi D, et al. Endogenous endophthalmitis: 10-year experience at a tertiary referral centre. *Eye (Lond)*. 2011;25:66–72.
371. Keyashian K, Malani PN. Endophthalmitis associated with intravenous drug use. *South Med J*. 2007;100:1219–1220.
372. Aboltins CA, Allen P, Daffy JR. Fungal endophthalmitis in intravenous drug users injecting buprenorphine contaminated with oral *Candida* species. *Med J Aust*. 2005;182:427.
373. Albini TA, Sun RL, Holz ER, et al. Lemon juice and *Candida* endophthalmitis in crack-cocaine misuse. *Br J Ophthalmol*. 2007;91:702–703.
374. Tirpack AR, Duker JS, Baumal CR. An outbreak of endogenous fungal endophthalmitis among intravenous drug abusers in New England. *JAMA Ophthalmol*. 2017;135:534–540.
375. Bui DK, Carvounis PE. Evidence for and against intravitreous corticosteroids in addition to intravitreous antibiotics for acute endophthalmitis. *Int Ophthalmol Clin*. 2014;54:215–224.
376. Kumar N, Garg N, Kumar N, et al. *Bacillus cereus* panophthalmitis associated with injection drug use. *Int J Infect Dis*. 2014;26:165–166.
377. Patel SN, Rescigno RJ, Zarbin MA, et al. Endogenous endophthalmitis associated with intravenous drug abuse. *Retina*. 2014;34:1460–1465.
378. US Department of Health and Human Services C. CDC. Diagnoses of HIV infection in the United States and dependent areas, 2015. 2017.
379. Broz D, Zibbell J, Foote C, et al. Multiple injections per injection episode: High-risk injection practice among people who injected pills during the 2015 HIV outbreak in Indiana. *Int J Drug Policy*. 2017;52:97–101.
380. Des Jarlais DC, Feelemyer JP, Modi SN, et al. Are females who inject drugs at higher risk for HIV infection than males who inject drugs: an international systematic review of high seroprevalence areas. *Drug Alcohol Depend*. 2012;124:95–107.
381. Burnett JC, Broz D, Spiller MW, et al. HIV infection and HIV-associated behaviors among persons who inject drugs—20 cities, United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2018;67:23–28.
382. Des Jarlais DC, Bramson HA, Wong C, et al. Racial/ethnic disparities in HIV infection among people who inject drugs: an international systematic review and meta-analysis. *Addiction*. 2012;107:2087–2095.
383. Santibanez SS, Garfein RS, Swartzendruber A, et al. Update and overview of practical epidemiologic aspects of HIV/AIDS among injection drug users in the United States. *J Urban Health*. 2006;83:86–100.
384. de Mendoza C. Hot News: HIV epidemics—current burden and future prospects. *AIDS Rev*. 2017;19:239.
385. DeHovitz J, Uuskula A, El-Bassel N. The HIV epidemic in Eastern Europe and Central Asia. *Curr HIV/AIDS Rep*. 2014;11:168–176.
386. Kral AH, Lorvick J, Gee L, et al. Trends in human immunodeficiency virus seroincidence among street-recruited injection drug users in San Francisco, 1987-1998. *Am J Epidemiol*. 2003;157:915–922.
387. Glick SN, Burt R, Kummer K, et al. Increasing methamphetamine injection among non-MSM who inject drugs in King County, Washington. *Drug Alcohol Depend*. 2018;182:86–92.
388. Hyshka E, Strathdee S, Wood E, et al. Needle exchange and the HIV epidemic in Vancouver: lessons learned from 15 years of research. *Int J Drug Policy*. 2012;23:261–270.

389. Strathdee SA, Shoptaw S, Dyer TP, et al. Towards combination HIV prevention for injection drug users: addressing addictophobia, apathy and inattention. *Curr Opin HIV AIDS*. 2012;7:320–325.
390. Kerr T, Kimber J, Debeck K, et al. The role of safer injection facilities in the response to HIV/AIDS among injection drug users. *Curr HIV/AIDS Rep*. 2007;4:158–164.
391. Kerr T, Montaner J, Wood E. Supervised injecting facilities: time for scale-up? *Lancet*. 2008;372:354–355.
392. Reddon H, Wood E, Tyndall M, et al. Use of North America's first medically supervised safer injecting facility among HIV-positive injection drug users. *AIDS Educ Prev*. 2011;23:412–422.
393. Gowing L, Farrell MF, Bornemann R, et al. Oral substitution treatment of injecting opioid users for prevention of HIV infection. *Cochrane Database Syst Rev*. 2011;(8):CD004145.
394. Sullivan LE, Moore BA, Chawarski MC, et al. Buprenorphine/naloxone treatment in primary care is associated with decreased human immunodeficiency virus risk behaviors. *J Subst Abuse Treat*. 2008;35:87–92.
395. Service UPH Preexposure prophylaxis for the prevention of HIV infection in the United States—2014. A clinical practice guideline. 2014.
396. Pezzotti P, Galai N, Vlahov D, et al. Direct comparison of time to AIDS and infectious disease death between HIV seroconverter injection drug users in Italy and the United States: results from the ALIVE and ISS studies. AIDS Link to Intravenous Experiences. Italian Seroconversion Study. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1999;20:275–282.
397. Calkins KL, Lesko CR, Chander G, et al. Influence of injection drug use-related HIV acquisition on CD4 response to first antiretroviral therapy regimen among virally suppressed individuals. *J Acquir Immune Defic Syndr*. 2017.
398. Gonzalez A, Mimiaga MJ, Israel J, et al. Substance use predictors of poor medication adherence: the role of substance use coping among HIV-infected patients in opioid dependence treatment. *AIDS Behav*. 2013;17:168–173.
399. Torian LV, Wiewel EW, Liu KL, et al. Risk factors for delayed initiation of medical care after diagnosis of human immunodeficiency virus. *Arch Intern Med*. 2008;168:1181–1187.
400. Fatukasi TV, Cole SR, Moore RD, et al. Risk factors for delayed antiretroviral therapy initiation among HIV-seropositive patients. *PLoS ONE*. 2017;12:e0180843.
401. Hoots BE, Finlayson TJ, Broz D, et al. Antiretroviral therapy use among HIV-infected people who inject drugs—20 cities, United States, 2009-2015. *J Acquir Immune Defic Syndr*. 2017;75(suppl 3):S392–S396.
402. Hadland SE, DeBeck K, Kerr T, et al. Use of a medically supervised injection facility among street youth. *J Adolesc Health*. 2014;55:684–689.
403. Palepu A, Milloy MJ, Kerr T, et al. Homelessness and adherence to antiretroviral therapy among a cohort of HIV-infected injection drug users. *J Urban Health*. 2011;88:545–555.
404. Westergaard RP, Kirk GD, Richesson DR, et al. Incarceration predicts virologic failure for HIV-infected injection drug users receiving antiretroviral therapy. *Clin Infect Dis*. 2011;53:725–731.
405. Werb D, Mills EJ, Montaner JS, et al. Risk of resistance to highly active antiretroviral therapy among HIV-positive injecting drug users: a meta-analysis. *Lancet Infect Dis*. 2010;10:464–469.
406. Hayashi K, Dong H, Kerr T, et al. Declining mortality rates in HIV-infected people who inject drugs during a seek-and-treat initiative in Vancouver, Canada, 1996-2014: a prospective cohort study. *J Infect Dis*. 2017;217:64–68.
407. Gruber VA, McCance-Katz EF. Methadone, buprenorphine, and street drug interactions with antiretroviral medications. *Curr HIV/AIDS Rep*. 2010;7:152–160.
408. Kanno MB, Zenilman J. Sexually transmitted diseases in injection drug users. *Infect Dis Clin North Am*. 2002;16:771–780.
409. Friedman SR, Mateu-Gelabert P, Ruggles KV, et al. Sexual risk and transmission behaviors, partnerships and settings among young adult nonmedical opioid users in New York City. *AIDS Behav*. 2017;21:994–1003.
410. Plitt SS, Garfein RS, Gaydos CA, et al. Prevalence and correlates of *Chlamydia Trachomatis, Neisseria Gonorrhoeae, Trichomonas Vaginalis* infections, and bacterial vaginosis among a cohort of young injection drug users in Baltimore, Maryland. *Sex Transm Dis*. 2005;32:446–453.
411. Roth AM, Goldshear JL, Martinez-Donate AP, et al. Reducing missed opportunities: pairing sexually transmitted infection screening with syringe exchange services. *Sex Transm Dis*. 2016;43:706–708.
412. Arasteh K, Des Jarlais DC, Perlis TE. Alcohol and HIV sexual risk behaviors among injection drug users. *Drug Alcohol Depend*. 2008;95:54–61.
413. Rees V, Saitz R, Horton NJ, et al. Association of alcohol consumption with HIV sex- and drug-risk behaviors among drug users. *J Subst Abuse Treat*. 2001;21:129–134.
414. Roth AM, Armenta RA, Wagner KD, et al. Patterns of drug use, risky behavior, and health status among persons who inject drugs living in San Diego, California: a latent class analysis. *Subst Use Misuse*. 2015;50:205–214.
415. Strathdee SA, Philbin MM, Semple SJ, et al. Correlates of injection drug use among female sex workers in two Mexico-U.S. border cities. *Drug Alcohol Depend*. 2008;92:132–140.
416. Bacon O, Lum P, Hahn J, et al. Commercial sex work and risk of HIV infection among young drug-injecting men who have sex with men in San Francisco. *Sex Transm Dis*. 2006;33:228–234.
417. Deiss RG, Brouwer KC, Loza O, et al. High-risk sexual and drug using behaviors among male injection drug users who have sex with men in 2 Mexico-US border cities. *Sex Transm Dis*. 2008;35:243–249.
418. Johnson KM, Fibbi M, Langer D, et al. Prescription drug misuse and risk behaviors among young injection drug users. *J Psychoactive Drugs*. 2013;45:112–121.
419. Lopez-Zetina J, Ford W, Weber M, et al. Predictors of syphilis seroreactivity and prevalence of HIV among street recruited injection drug users in Los Angeles County, 1994-6. *Sex Transm Infect*. 2000;76:462–469.
420. Fisher DG, Reynolds GL, Jaffe A, et al. Reliability, sensitivity and specificity of self-report of HIV test results. *AIDS Care*. 2007;19:692–696.

313 Surgical Site Infections and Antimicrobial Prophylaxis

Thomas R. Talbot

SHORT VIEW SUMMARY

Background
- Surgical site infections (SSIs) are a common and unwanted outcome from most surgical procedures.
- The development of an SSI depends on patient-related, procedure-related, and pathogen-related factors and the application of evidenced-based prevention methods.
- Causative organisms of SSI are predominantly the flora present at the incision site.

Risk Factors for Surgical Site Infections (see Table 313.2)
- Patient factors, including comorbid illness, colonization with pathogenic bacteria, perioperative hyperglycemia, and elevated body mass index
- Procedural factors, including breaks in sterile technique, operating room ventilation, and traffic
- Proceduralist factors, including surgical technique, improper application of skin antisepsis, teamwork incoordination, and provider impairment

Prevention of Surgical Site Infections (see Table 313.4)
- Practices to reduce bacterial inoculation into wound, including antiseptic use, sterile attire, decolonization strategies, and proper hair removal
- Practices to improve host containment of introduced bacteria, including maintenance of normothermia, minimizing tissue hypoxia, glucose control, and antimicrobial prophylaxis

Surgical Antimicrobial Prophylaxis
- Key principles
  - Maintain tissue concentration of drug above mean inhibitory concentration of common flora (see Fig. 313.4)
  - Provide "right" drug—targets flora at incision site, adequately penetrates incision site, minimal adverse events
  - Provide "right" dose at the "right" time—dose in the window before incision to allow penetration into tissues (see Fig. 313.5), use higher doses for obese patients, redose in prolonged procedures
  - Provide "right" duration of drug; stop once incision closed
- Prophylaxis targeting resistant organisms may be warranted in select situations (e.g., known colonization with organism)

Surgical Site Infections Surveillance
- SSIs surveillance requires standardized definitions.
- Postdischarge surveillance of SSIs may lead to variability in reported outcomes and must be addressed as part of any surveillance system.
- SSI rates are being increasingly used as measures of quality of care tied to reimbursement from payers.

HISTORICAL BACKGROUND

In 1862 Louis Pasteur's ingenious experiments into the nature of putrefaction were officially endorsed by the Paris Academy of Science. The endorsement signaled an end to the long-held belief that the exposure of organic material to air brought about the spontaneous generation of microorganisms, and the concepts of *sepsis* and *asepsis* became firmly established. A mere 3 years later, Joseph Lister demonstrated the incredible implications of antisepsis in his practice of orthopedic surgery. For the first time in recorded history, major surgical procedures could be performed with a reasonable expectation of primary wound healing and recovery. Essential enhancements for preventing and controlling wound sepsis were provided by the antibiotic revolution of the 1940s, ushering in the highly technical, highly invasive, and highly successful era of modern surgery. As noted by McDermott and Rogers,[1] the great achievements of the antibiotic era may be related, in the long run, to its essential role in supporting the advancements of modern surgery. Indeed, surgery as we know it today would be impossible in an environment in which infection was likely or, once established, untreatable.

Despite the fundamental role of antisepsis and antibiotics in the development of modern surgery, implementation of these discoveries in the practice of surgery has not occurred without opposition. As late as 1880, for example, William Halstead was ordered from the operating theater when he challenged a senior surgeon's disregard for antiseptic techniques. The early use of antibiotics for prophylaxis in surgical procedures was also questioned as respected academicians freely voiced their disapproval of antimicrobial prophylaxis in clean surgical procedures.[2] For a number of years the value of prophylactic antibiotics in preventing infections of the surgical wound remained in doubt. A consensus in favor of their use did not emerge until two concepts of perioperative prophylaxis and infection were established. First, investigators in Cincinnati and Boston demonstrated that, despite the use of standard aseptic techniques, *Staphylococcus aureus* could be regularly isolated from the operative field.[3–5] It became apparent that aseptic technique could decrease but not eliminate bacterial contamination of the surgical field; therefore it appeared plausible that perioperative antibiotics could supplement aseptic techniques in containing the inevitable contamination of the operative wound.

The second major finding involved the timing of the administration of the prophylactic antibiotic. As early as 1946, Howes[6] had noted a correlation between the amelioration of infection and the interval between the contamination of the wounds and the administration of antibiotics. Several years later, Miles and colleagues[7] and Burke,[8] working with a guinea pig model of wound infection, demonstrated the remarkable brevity of the "window" of prophylactic efficacy. They noted that antibiotics given shortly before or at the time of bacterial inoculation of the subcutaneous tissue of the guinea pig produced a notable diminution in the size of the subsequent wound induration compared with lesions in animals not receiving antimicrobial prophylaxis (Fig. 313.1). By delaying the administration of antibiotics by only 3 or 4 hours, resulting lesions were identical in size to those of animals receiving no antimicrobial prophylaxis whatsoever. Thus "failures" of antimicrobial prophylaxis that had been noted in earlier clinical studies were related to the fact that administration of preoperative antibiotics had been inappropriately timed.[9–11] Although these observations have been challenging to reproduce in vitro,[12] the experience of current practice has evolved to mandate that whenever possible surgical antimicrobial prophylaxis should be administered so as to ensure adequate tissue levels of antimicrobials from the time of the initial surgical incision until closure. The efficacy of prophylactic antibiotics has now been verified for most major surgical procedures, with a wide variety of antimicrobials when care has been given to provide adequate serum and tissue levels of antibiotics during the surgical procedure. Perioperative

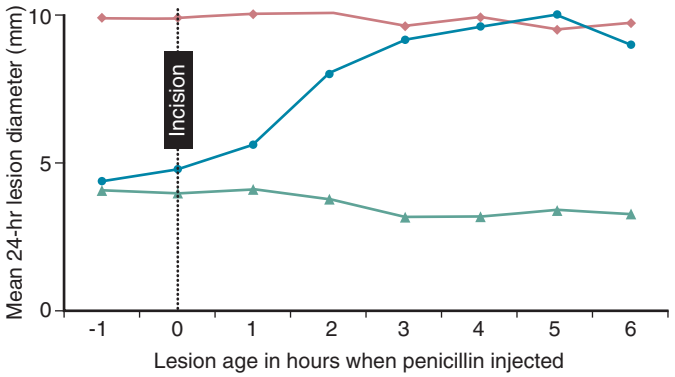

FIG. 313.1 Importance of the timing of antimicrobial administration. Relationship between the timing of antimicrobial administration and the effectiveness of prophylaxis as shown by the size of wound infection in a guinea pig model.[8] Lesion sizes were measured as mean diameter (mm) of induration developing 24 hours after intradermal inoculation of *Staphylococcus aureus* (SA). Red line indicates animals injected with live SA who received placebo; blue line indicates animals injected with live SA who received penicillin; green line indicates animals injected with killed SA.

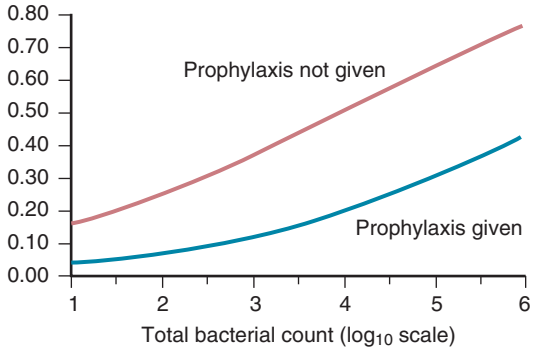

FIG. 313.2 Wound infection and febrile morbidity. Plot of the probability of wound infection, febrile morbidity, or both, according to total bacterial counts at the operative site in patients undergoing abdominal hysterectomy. The administration of antimicrobial prophylaxis reduces the likelihood of infection or fever for a given level of bacterial contamination of the wound. Stated another way, the administration of prophylaxis increases the magnitude of the bacterial inoculum needed to produce infection. *(From Houang ET, Ahmet Z. Intraoperative wound contamination during abdominal hysterectomy.* J Hosp Infect. *1991;19:181–189.)*

antibiotics and aseptic techniques have become routine aspects of care in most major surgical procedures.

Despite efforts to prevent surgical site infections (SSIs), these outcomes are not uncommon. The 2014 Healthcare-Associated Infection Prevalence study from the Centers for Disease Control and Prevention (CDC) estimated an annual national burden of more than 157,000 SSIs among hospitalized adult patients,[13] a figure that does not include those patients with an SSI that did not require hospitalization. Often neglected in these estimates, SSIs associated with ambulatory surgical procedures result in a substantial rate of postsurgical acute care visits for clinically significant SSIs in 4.8 per 1000 procedures across the eight states studied.[14] Another analysis estimated that SSIs led to an added $20,785 and 11.2 days length of stay per event and a total of $3.2 billion in attributable costs in the United States in 2008.[15] A patient who develops an SSI while hospitalized has a greater than 60% greater risk of being admitted to the intensive care unit, is 15 times more likely to be readmitted to the hospital within 30 days after discharge, and incurs an attributable extra hospital stay of 6.5 days, leading to a direct cost of an additional $3000 per infection.[16] SSIs due to methicillin-resistant *S. aureus* (MRSA), in particular, have also been shown to have a higher mortality than those due to methicillin-sensitive strains of the organism.[17]

Technologic advances (e.g., the introduction of minimally invasive procedures and robotic surgery) and the emergence of antibiotic-resistant organisms have led to additional challenges in the prevention of SSIs. In addition, the prevention of SSI has moved to the forefront of surgical quality improvement programs, highlighting important issues regarding antimicrobial prophylaxis (e.g., drug dosing in obese patients, the specific timing of antibiotic administration, and the role of anti-MRSA prophylaxis). Reflecting the increasing desire for transparency of infection prevention program effectiveness, public reporting of facility-specific colon and abdominal hysterectomy SSI performance is now tied directly to reimbursement.[18] Despite these advances over 150 years since the discoveries of Pasteur and Lister, much remains to be learned about the pathophysiology, prevention, and surveillance of SSIs.

PRINCIPLES OF SURGICAL SITE INFECTION PREVENTION

Determinants and Pathophysiology

Whether a wound infection occurs after surgery depends on a complex interaction between the following: (1) patient-related factors (e.g., host immunity, nutritional status, comorbid conditions); (2) procedure-related factors (e.g., implantation of foreign bodies, degree of trauma to the host tissues); (3) microbial factors (e.g., tissue adherence and invasion); and (4) use of preventive measures (e.g., perioperative antimicrobial prophylaxis).

TABLE 313.1 Classification of Operative Wounds by Level of Bacterial Contamination

Class I: Clean Wound
An uninfected operative wound in which no inflammation is encountered, and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow nonpenetrating (blunt) trauma should be included in this category if they meet the criteria.
Class II: Clean-Contaminated Wound
An operative wound in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered.
Class III: Contaminated Wound
Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent inflammation is encountered are included in this category.
Class IV: Dirty-Infected Wound
Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.

Modified from Mangram AJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol. *1999;20:250–278.*

Species and Sources of Wound Bacteria

Bacterial contamination of the surgical wound is inevitable. State-of-the-art aseptic technique has been associated with a dramatic drop in, but not the elimination of, this phenomenon. Even under laminar flow operating room (OR) environments, bacteria can be isolated from wound surfaces at the close of the surgical procedure.[19] The importance of the microbial load in determining whether or not a wound becomes infected has been long appreciated and is relevant even in the era of the routine administration of antimicrobial prophylaxis for most major surgical procedures (Fig. 313.2).[20] Historically, operations have been stratified on the basis of the expected quantity of bacteria introduced into the operative site during surgery (Table 313.1). Although the magnitude of bacterial inoculation into the wound still has some predictive value regarding the risk of developing a wound infection, patient- and procedure-related risk factors also contribute greatly to this risk (Table 313.2).[21]

TABLE 313.2 Selected Factors Associated With an Increased Risk for Surgical Site Infection

Patient Factors

Diabetes mellitus/perioperative hyperglycemia
Concurrent tobacco use
Remote infection at time of surgery
Obesity
Low preoperative serum albumin
Malnutrition
Concurrent steroid use
Prolonged preoperative stay[a]
Prior site irradiation
Colonization with *Staphylococcus aureus*

Procedural Factors

Shaving of site the night before procedure
Use of razor for hair removal
Improper preoperative skin preparation/use of non–alcohol-based skin preparation
Improper antimicrobial prophylaxis (wrong drug, wrong dose, wrong time of administration)
Failure to timely redose antibiotics in prolonged procedures
Inadequate operating room ventilation
Increased operating room traffic
Perioperative hypothermia
Perioperative hypoxia

Proceduralist Factors

Surgical technique (poor hemostasis, tissue trauma)
Lapses in sterile technique and asepsis
Glove micropenetrations
Behavioral factors/proceduralist impairment

[a]Likely a surrogate marker for severity of underlying illness and comorbidities.
Modified from Mangram AJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol. *1999;20:250–278.*

TABLE 313.3 Percentage of Surgical Site Infection Pathogen Isolates Resistant to Selected Antimicrobial Agents, National Healthcare Safety Network, 2014

PATHOGEN	NO. OF ISOLATES TESTED	PERCENT OF ISOLATES RESISTANT
Staphylococcus aureus		
Resistant to oxacillin/methicillin (MRSA)	8738	42.6%
Enterococcus faecium		
Resistant to vancomycin (VRE)	1342	58.4%
Escherichia coli		
Extended-spectrum cephalosporin resistant	6816	15.3%
Fluoroquinolone resistant	6816	30.9%
Carbapenem resistant	6816	0.7%
Multidrug resistant	6816	6.5%
Pseudomonas aeruginosa		
Extended-spectrum cephalosporin resistant	2617	9.9%
Fluoroquinolone resistant	2617	11.5%
Carbapenem resistant	2617	7.7%
Multidrug resistant	2617	4.3%
***Enterobacter* spp.**		
Extended-spectrum cephalosporin resistant	2056	27.5%
Carbapenem resistant	2056	3.4%
Multidrug resistant	2056	2.4%
***Klebsiella* spp.**		
Extended-spectrum cephalosporin resistant	2319	11.3%
Carbapenem resistant	2319	3.3%
Multidrug resistant	2319	4.6%
***Acinetobacter* spp.**		
Carbapenem resistant	174	33.3%
Multidrug resistant	174	32.9%

MRSA, Methicillin-resistant *Staphylococcus aureus; VRE,* vancomycin-resistant enterococci.
Modified from Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011–2014. Infect Control Hosp Epidemiol. *2016;37:1288–1301.*

Numerous organisms have been described as wound pathogens, and the origin of the inoculum is not established with certainty for most infections. The patient's endogenous skin flora, with gram-positive organisms in general, and staphylococcal species in particular, are the predominant cause of incisional infections of clean surgical procedures. Over the past decade, the microbiology of SSIs has evolved due to the emergence of various multidrug-resistant pathogens, with a concerning proportion of reported SSIs due to multidrug-resistant gram-negative pathogens (Table 313.3).[22] *S. aureus* colonization of the patient's nares is a major risk factor for developing a *S. aureus* SSI, a particular concern in selected populations, such as diabetic individuals and recipients of hemodialysis, who have *S. aureus* colonization rates in excess of 50%. *S. aureus* and *Streptococcus epidermidis* and streptococcal wound infections can also occur in clusters, sometimes with a particular surgeon or nurse implicated in their spread. Unusual and hard-to-culture species, including nontuberculous mycobacteria, *Nocardia* spp., *Legionella* spp., *Mycoplasma hominis*, and *Cutibacterium (Propionibacterium) acnes* (an organism associated with shoulder arthroplasty SSI), have caused surgical site infections as well.

Modern methods of antisepsis can reduce but not eliminate the skin-associated bacteria of surgical patients. This limitation derives, in part, from the localization of up to 20% of skin-associated bacteria in skin appendages, such as hair follicles and sebaceous glands (Fig. 313.3).[23] Because these sites are beneath the skin's surface, bacteria residing there are not eliminated by topical antisepsis. Transection of these skin structures by surgical incision may carry the patient's resident bacteria deep into the wound and set the stage for subsequent infection.

For contaminated procedures, wound pathogens frequently are among the bacterial species that comprise the normal flora of the viscus entered during the surgical procedure. Enteric gram-negative pathogens and anaerobic bacteria (e.g., *Bacteroides fragilis*) are common pathogens of wounds after colonic procedures, and polymicrobial infections are common in this setting. Infection by a particular species, however, does not correlate directly with its quantitative presence among the normal flora, but by the particular virulence attributes of bacteria.

Although numerous sources of bacterial contamination of surgical wounds have been described, it is virtually impossible to identify with certainty the source(s) and route(s) of contamination. The direct inoculation of a patient's endogenous flora at the time of surgery is believed to be the most common mechanism; however, others undoubtedly occur. Transmission from contaminated surgical instruments or surgical material; hematogenous seeding from preexisting infection of a nonwound site; and contamination from either the skin, mucous membranes, or clothing of operating room staff have been implicated as potential sources of microbial contamination. Outbreaks of group A streptococcal wound infection have been traced to the anal or vaginal carriage of this organism by operating room personnel,[24,25] and epidemiologic investigation of these outbreaks indicated that airborne contamination of the operative field had occurred. Infections, including *Candida albicans* osteomyelitis and diskitis after lumbar laminectomy,

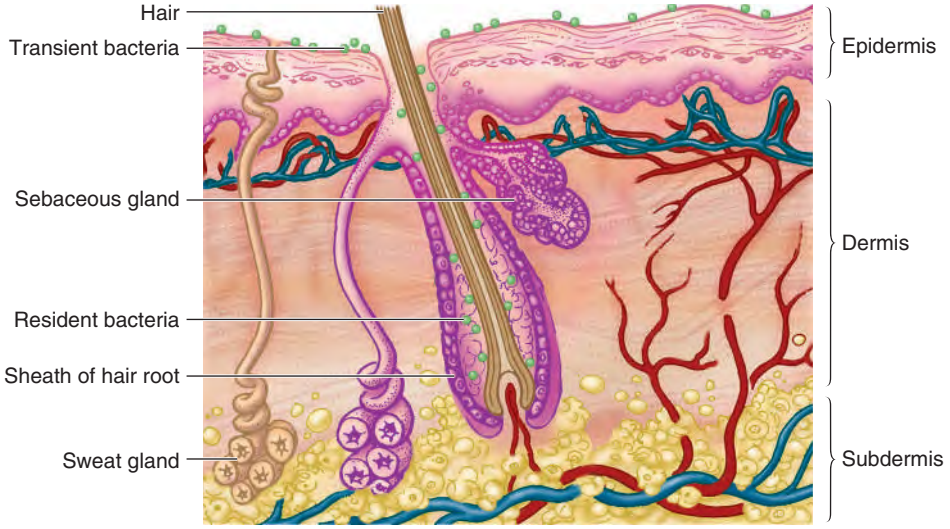

FIG. 313.3 Diagram of the skin. Diagram of the skin demonstrating the location of the transient bacteria on the skin surface, which are easily removed, and the deep resident bacteria, which cannot be destroyed by skin antiseptics. *(From Postlethwaite RW. Principles of operative surgery: antisepsis, technique, sutures, and drains. In: Sabiston DC, ed.* Davis-Christopher Textbook of Surgery. *12th ed. Philadelphia: Saunders; 1981:322.)*

have been traced to the use of artificial fingernails worn by surgical staff,[26] leading many hospitals to ban the use of artificial or long natural fingernails in health care workers with direct patient care responsibilities. A worldwide outbreak of SSI in cardiac surgery patients associated with aerosol dissemination of and surgical field contamination with *Mycobacterium chimaera* by heater-cooler units used intraoperatively illustrates the potential for airborne spread and development of SSI due to pathogens with low pathogenic potential, incubation periods of months to years, and the unintended consequences of new technologies used in the operating suite.[27]

The relative importance of hematogenous seeding (i.e., *inside-to-out*) of the surgical wound is somewhat unclear. Evidence of this route of seeding of the surgical wound site has been mainly noted with procedures involving implantation of prosthetic devices.[23] In addition, although it is generally accepted that prosthetic valves and hips are at risk for an indefinite period of time for hematogenous seeding and infection postoperatively, it is difficult to ascertain with certainty whether a late postoperative infection results from intraoperative bacterial seeding of the prosthetic device, followed by prolonged dormancy, or from a true postoperative hematogenous event. In a randomized, prospective, controlled study of antimicrobial prophylaxis in total hip replacement, Carlsson and coworkers[28] demonstrated that deep wound infections that developed over 2.5 years after surgery were more likely to have occurred among placebo versus cloxacillin recipients (13.7% vs. 3.3%, respectively; $P < .05$). These data suggest that bacteria inoculated into wounds at the time of surgery may lie dormant for years, rendering differentiation of the precise source of late wound infection virtually impossible. If late hematogenous seeding of a surgical wound with or without prosthetic material can occur, it is reasonable to assume that wounds are even more vulnerable to seeding and secondary infection during the immediate postoperative period. During this time, surgical incisions are hyperemic from the trauma of the surgery and endothelialization of intravascular prosthetic materials has not yet had time to occur. Moreover, the regular use of indwelling intravascular catheters probably increases the risk of bacteremia; however, information with which to judge the relative contribution of intraoperative versus postoperative hematogenous seeding of the surgical incision is unavailable.

Virulence Factors of Major Wound Pathogens

Clean Wound Infections

The requirement for large inocula in the early models of *S. aureus* soft tissue infection gave the misleading impression that cooperative interaction between bacteria may be required to establish a wound infection.[7,8] Later models involving foreign bodies demonstrated median infective dose (ID_{50}) values of fewer than 100 colony-forming units (CFU) with polytetrafluoroethylene (PTFE) tissue cages,[29] 10 CFU with PTFE vascular grafts,[30] and as low as 1 CFU with dextran microbeads.[31] These data demonstrate the pathogenic potential of a single bacterium to produce wound infection, provided that it is inoculated into a suitable niche.

Contaminated Wound Infections

The role of coliforms and anaerobes in abdominal sepsis has been elucidated in a model that involves inserting a gelatin capsule containing a standardized inoculum of pooled cecal contents into the peritoneal cavities of rats.[32,33] Acute peritonitis and septicemia from coliforms caused rapid death in 37% of the animals, and all of the survivors developed abscesses with anaerobes as the predominant organisms. The capsular polysaccharide of *Bacteroides fragilis* promotes abscess formation and may reduce phagocytosis. In experimental models, immunization against capsular polysaccharide can protect against abscess formation after inoculation with *B. fragilis* by a T-cell–dependent mechanism, except in the presence of foreign material.[34] Also, *B. fragilis* produces a variety of tissue-damaging enzymes, including hemolysin, chondroitin sulfatase, neuraminidase, and hyaluronidase.[35]

Wound Microenvironment and Operative Effects on Immunity

Much of our understanding of the pathophysiology of wound infection and the nature of the surgical wound derives from investigational models. Early investigations suggesting that the efficacy of antibiotics in preventing wound infection is limited to only a few hours after the moment of bacterial inoculation suggested that the wound microenvironment is not static.[6,7] It is likely that rapid changes are occurring among microbial factors, such as a shift from exponential to stationary-phase growth with an accompanying decrease in bacterial susceptibility to antibiotics and possibly the expression of different microbial virulence factors. Wound-related changes must also occur, such as gradually diminishing tissue perfusion and antibiotic delivery related to increased tissue oncotic pressure brought about by the effect of inflammatory mediators on vascular permeability.

Foreign Material and Operative Trauma to Tissue

Investigations of *S. aureus* infection in the skin of human volunteers by Elek and Conen[36] conclusively established the role of foreign material in potentiating wound infection. By including suture material with the intradermal staphylococcal inoculum, the number of organisms required to establish a skin pustule could be reduced 10,000-fold relative to lesions without sutures (i.e., a fall from 5×10^6 organisms to 3×10^2 organisms in the inoculum). These investigators further suggested that

"other circumstances may lead to the unhindered growth of small inocula, including heavily traumatized tissues, burns, or devitalized tissues distal to the ligated vessels. This may be the explanation of the traditional surgical view that untidy operative techniques predispose to infection."[36] Because in clean and clean-contaminated surgical procedures, quantitative bacterial inoculation into the wound is small, tissue devitalization at a gross or microscopic level provides a niche wherein a small bacterial inoculum may grow in relative isolation from the host's defenses, which plays a major role in the pathogenesis of infection.

Investigational models have demonstrated how technical variables of the surgical procedure influence the risk of infection. Some suture materials appear to have a stronger adjuvant effect on infection than others.[37] Whether the use of the electrosurgical knife, which can damage host tissues via the transfer of heat, is an adjuvant for infection is controversial.[38–40] Clinical studies examining the use of electrocautery have not revealed an increased risk for SSI with the use of this technique, with a recent Cochrane analysis noting a nonsignificant difference (7.7% vs. 7.4%) in wound infection rates between electrosurgery vs. scalpel.[41–43]

Effect of Operative Procedures on Systemic and Local Immunity

Operative procedures produce systemic and local changes in the immune defense mechanisms of the host. Neutrophil function and serum opsonizing capacity become impaired. The microbicidal activity of neutrophils obtained postoperatively from patients undergoing abdominal hysterectomy is 25% less than that of neutrophils harvested from the same patients preoperatively, and it takes 9 days to return to normal.[44] The depletion of opsonizing factors within the abscess milieu also may contribute to decreased neutrophilic bactericidal function.[45]

Major surgical procedures compromise the host defenses in other ways. Surface levels of human leukocyte antigen–DR antigens on the circulating monocytes of patients are reduced after major surgery.[46] However, it has been shown that defects in T-cell proliferation and cytokine secretion after major surgery involve an inability of T cells to respond to T-cell receptor- and CD28 coreceptor-mediated signals rather than problems with antigen presentation by monocytes-macrophages.[47] Many factors can reduce core body temperature during a surgical procedure, including ambient OR temperatures, lack of body covering, and intravenous (IV) fluids administration. Anesthetic agents also impair thermoregulatory control and may impact vasoconstriction and shivering thresholds.[48] In the setting of perioperative hypothermia, neutrophils have reduced chemotaxis, impaired ingestion of staphylococci, and diminished superoxide production.[49] Hypothermia can also trigger vasoconstriction and lead to low tissue oxygen tension, which is itself a risk factor for SSI.[50] Because of these risks, interventions aimed at reducing perioperative normothermia and hypoxia have been examined to prevent SSIs (see "Prevention of Surgical Site Infections").

Perioperative blood transfusion has been associated with an increased rate of postoperative infections, including wound infection, with donated white blood cell (WBC)-induced immunosuppression implicated as the culprit.[51] Decreases in cell-mediated immunity and increases in cytokine levels (interleukin [IL]-2 receptor, IL-6) have been demonstrated in mice and humans after transfusion.[52] However, clinical trials comparing the receipt of standard whole or buffy-coat–depleted blood products (which, despite the moniker, still retain some donor WBCs) with WBC-depleted products, or the administration of allogenic versus autologous blood, have failed to provide a consensus answer to transfusion's role in the development of postoperative infections.[53] A restrictive transfusion approach (transfusion once hemoglobin falls below 7–8 g/dL) was associated with a reduced risk for the development of health care–associated infections when compared with more liberal strategies, but only six studies included in this meta-analysis examined surgical wound infections as a study outcome.[54] Studies describing this potential transfusion effect have been criticized for using nonstandardized outcome definitions, failing to account for known risk factors for postoperative infection, and using only univariate analyses.[53] Blood transfusion may simply serve as a marker for unidentified patient comorbidities, and more rigorously designed studies are needed before general conclusions regarding the role of blood transfusion in wound infection can be determined.

In cardiac surgery the patient may be exposed to hypothermia, cardiopulmonary bypass (CPB), and relative arterial hypotension throughout much of the procedure. Exposure of blood to CPB depletes serum complement, causes systemic release of proinflammatory cytokines, and adversely affects neutrophilic function.[55–58] Furthermore, protein denaturation and chylomicron aggregation may contribute to small vessel occlusion and tissue hypoxia, as well as overwhelm the capacity of the reticuloendothelial system to clear infectious agents from the blood.[59] This raises the possibility that postbypass patients may be predisposed to develop infections via hematogenous bacterial seeding as a result of reduced reticuloendothelial clearance.

Risk Factors for Surgical Site Infections

Patient Factors

Various host factors have been associated with an increased risk of SSI (see Table 313.2), including underlying comorbid illnesses (e.g., diabetes mellitus),[60] malnutrition,[61] obesity,[62] history of irradiation at the site of the procedure,[63] and use of immunosuppressants.[64] Tobacco use has been associated with an increased risk for SSI,[65] possibly due to nicotine's effects of vasoconstriction, local hypoxia, and inhibition of wound healing.[65] As noted earlier, colonization with *S. aureus* can also increase one's risk for developing a staphylococcal SSI.

Although diabetes mellitus is a risk for SSI, acute fluctuations in glucose control are also important. In a prospective study of 1000 cardiothoracic surgery patients, hyperglycemia (serum glucose > 200 mg/dL) in the 48 hours postprocedure was associated with a 102% increase in the risk for wound infection.[66] Risk also increased incrementally with further elevations in glucose; however, the degree of long-term glucose control, as measured by glycosylated hemoglobin levels at time of surgery, did not impact infection risk. As a result of this and similar studies, glucose control during the perioperative period is now considered an important SSI prevention practice[67,68]; however, the appropriate glucose target and intensity of insulin therapy to maintain these targets are controversial,[69] and care must be taken to prevent hypoglycemia and its associated morbidity.[70]

Procedural and Proceduralist Factors

Attributes of the surgical procedure may lead to an increased risk for SSI, such as improper ventilation of the operative suite and uncovered and exposed sterile instrument trays.[71] Proper application of an antiseptic at the incision site is important, as is the specific type of preparation used. A randomized, placebo-controlled trial in patients undergoing clean-contaminated surgery found that the use of a chlorhexidine gluconate (CHG)-alcohol preparation reduced the risk of superficial and deep incisional SSI by 41% when compared with povidone-iodine.[72] Without an alcohol-based comparison product, it is unclear if this benefit was due to the CHG, to the immediate-killing effects of the alcohol, or to a combination of both. Recently updated SSI prevention guidelines from both the CDC and World Health Organization (WHO) recommend an alcohol-based antiseptic agent for surgical site preparation for all procedures unless contraindicated, but the CDC does not specify a preference for CHG-based agents,[67] whereas the WHO guideline recommends CHG-alcohol preferentially.[73] Microperforations of surgical gloves in the setting of no antimicrobial prophylaxis, increased OR traffic, and shaving with a razor (vs. use of clippers or no hair removal at all) have also been associated with an increased SSI risk.[74–78] Finally, failure to appropriately administer prophylactic antibiotics (correct drug, correct dose, correct timing before incision) is a major factor in the development of SSI (see discussion later in this chapter).

Perhaps as important as procedure-related factors and certainly more challenging to investigate are aspects germane to the surgeon and other proceduralists and their potential for increasing SSI risk. Variations in surgical technique have often been espoused as major drivers in the development of SSIs, but evidence supporting this supposition is limited.[40] Such surgeon-specific risk was suggested in a prospective cohort study of 2393 colon surgery patients in which specific surgeons were associated with an increased risk for SSI development in their patients after adjustment for patient-specific risk factors.[79] A study in Michigan examined the risk of surgical complications, including SSI, after bariatric surgery and identified a significantly increased risk in surgeries performed by

surgeons in the bottom quartile of surgical skill as rated by peers when compared with top quartile surgeons (complication rates of 14.5% vs. 5.2%).[80] Lapses in asepsis discipline (including improper skin preparation, operative room noise, incorrect wearing of personal protective equipment, and repetitive breaks in aseptic technique) have also been noted to significantly increase the risk for SSI in general surgical patients.[81] Patients whose surgeons have a large number of unsolicited patient complaints have a significantly increased risk of surgical complications, including SSI, attributed to dysfunctional interactions with the surgical team that may impede effective collaboration intraoperatively.[82] Surgeon impairment may also lead to an increase in SSI risk, nicely illustrated by a case report of an increased SSI rate in a physician affected by the systemic side effects of treatment for hepatitis C infection.[83]

Postoperative Factors

Finally, postoperative factors may play a role in the pathophysiology of SSI. Nicely articulated in a review by Manian,[84] these factors have not been routinely considered in SSI risk factor studies or prevention bundles. Wound-related factors, such as hematoma, incision oozing, the presence of drains, and closure type have been associated with SSI risk. Hematogenous spread from endovascular sources has been suggested in an analysis of postcardiac surgical SSI and central venous catheter (CVC)-related bacteremia based on similar pathogen isolation in patients with both infections.[85] An analysis of closure type in orthopedic surgery noted a three to four times greater risk for SSI when staples were used instead of sutures for wound closure.[86] A Cochrane analysis examining the effect of various wound dressings (vs. no dressing) on SSI risk prevention, however, found no clear benefit from the use of a variety of dressing types (including film, hydrocolloid, and silver-containing products).[87] Further examination of such postprocedural interventions are needed to better quantify their potential impact on SSI risk.

PREVENTION OF SURGICAL SITE INFECTIONS

General Concepts

Given the presence of some of the risk factors noted earlier that may be unalterable, it is unlikely that all SSIs are preventable. Therefore the goal should be to eliminate all *potentially preventable* infections through the use of evidenced-based processes. Stemming from the concepts of wound infection pathogenesis and the risk factors noted earlier, a number of such interventions exist to reduce SSI risk. These interventions can be grouped into two major categories (Table 313.4). The first line of defense involves measures that reduce bacterial inoculation into the wound site. These include familiar practices, such as the application of antiseptics to the incision site, the washing and gloving of OR personnel's hands, the use of sterile drapes, strict adherence to sterile technique, airflow control, and the use of appropriate attire by OR personnel.

Efforts to reduce patient colonization with pathogenic bacteria, especially staphylococci, with topical antiseptic agents, such as intranasal mupirocin and povidone-iodine, may also be of benefit. A randomized, placebo-controlled trial found that mupirocin applied to the nares of patients undergoing elective cardiothoracic, neurosurgical, oncologic, gynecologic, and general surgical procedures, beginning on the day before surgery and continued for up to 5 consecutive days, resulted in a reduction in *S. aureus* nosocomial infections from 7.7% to 4.0% in those with preoperative nasal carriage of *S. aureus.* However, the rates of nosocomial and, specifically, SSIs in all patients, regardless of *S. aureus* carriage status, were not reduced with the use of mupirocin.[88] Another large multicenter trial noted a significant reduction in deep SSI risk with the use of a protocol to screen for *S. aureus* nasal carriage and subsequent decolonization of carriers with intranasal mupirocin and CHG bathing (relative risk [RR] = 0.21 when compared with placebo recipients).[89] In one of the largest investigations of preoperative decolonization, involving more than 42,000 procedures at 20 hospitals, *S. aureus* deep and organ/space SSIs were significantly decreased among patients colonized with the organism with the use of intranasal mupirocin and CHG 5 days before cardiac and joint arthroplasty surgery.[90] Antimicrobial prophylaxis was also adjusted to cover MRSA in patients with MRSA colonization. Preoperative CHG bathing has also been examined as an SSI prevention strategy for use with all surgical patients (not just those colonized with *S. aureus*). A meta-analysis of eight trials encompassing more than 10,000 patients undergoing clean surgery, however, did not find a significant impact of universal CHG bathing on SSI rates.[91] Such findings may be due to the removal of the CHG during or soon after showering, which may minimize CHG's beneficial quality of prolonged bacterial killing.

For preoperative hair removal, methods that do not create microabrasions, such as clippers or depilatories, are preferred.[78] This recommendation is supported by a large randomized trial of 1013 patients in which SSIs occurred in 3.2% of patients after hair removal with clippers the morning of surgery versus 10.0% in those who underwent day-of-surgery shaving with a razor.[92] Although some recommendations advocate no preoperative hair removal,[21] there is minimal evidence to support an increased risk of wound infection with hair removal by clippers or depilatories on the morning of surgery compared with no hair removal.[93] Avoidance of hair removal is particularly challenging in cranial procedures, where hair is often removed to prevent wound contamination, allow for incision visualization, and aid in dressing application. A systematic review questioned this practice, noting scalp shaving does not protect against SSI development and may result in higher infection rates.[94] Infection at sites remote from the operative field is a host risk factor for postoperative infection that is potentially correctable before surgery.[95] Drains and intravascular devices should be removed as quickly as possible to avoid the risk of direct and hematogenous seeding of the operative site, as well as device-associated infections.

The second major class of prevention measures is directed toward improving host containment and elimination of bacteria that have

TABLE 313.4 Surgical Site Infection Prevention Interventions

Maneuvers to Diminish Inoculation of Bacteria Into Wound
Preoperative Factors
Avoid preoperative antibiotic use (excluding surgical prophylaxis)
Minimize preoperative hospitalization
Treat remote sites of infection before surgery
Avoid shaving or razor use at operative site
Delay hair removal at operative site until time of surgery and remove hair (*only* if necessary) with electric clippers or depilatories
Ensure timely administration (including appropriate dose) of prophylactic antibiotics
Consider elimination of *Staphylococcus aureus* nasal carriage via decolonization techniques (especially in cardiac and arthroplasty procedures)
Use standardized checklist for implementation at preprocedural time-out
Intraoperative and Postoperative Factors
Carefully prepare patient's skin with antiseptic + alcohol-based skin preparation agent (e.g., povidone-iodine-alcohol– or chlorhexidine-alcohol–containing solution)
Rigorously adhere to aseptic techniques
Isolate clean from contaminated surgical fields (e.g., reglove, regown, and change instruments after bowel resection before commencing fascial and skin closure)
Maintain high flow of filtered air
Redose prophylactic antibiotics in prolonged procedures
Minimize operative personnel traffic
Minimize immediate-use steam sterilization of surgical instruments
Minimize use of drains
Bring drains, if used, through a separate stab wound
Maneuvers to Improve Host Containment of Contaminating Bacteria
Preoperative Factors
Resolve malnutrition
Discontinue tobacco use for at least 30 days preoperatively
Maximize diabetes mellitus control
Intraoperative and Postoperative Factors
Minimize dead space, devitalized tissue, and hematomas
Use supplemental oxygen therapy in patients with normal pulmonary function undergoing general anesthesia with endotracheal intubation
Maintain perioperative normothermia (core temperature at or above 36.0°C)
Identify and minimize hyperglycemia via intensive insulin protocols in diabetic and nondiabetic patients
Maintain adequate hydration and nutrition

circumvented the front line of defense and have been inoculated into the wound. Most authorities have emphasized that the single most important factor in preventing wound infection is surgical technique. Gentle handling of wound tissues, avoidance of dead space, devitalized tissues, and hematomas, and careful approximation of tissue planes are believed to be critical in maintaining an infection-free incision. Prophylaxis with antimicrobial therapy is another essential component of SSI prevention, which is highlighted in detail later in this chapter.

Several strategies, first noted to benefit patients undergoing colorectal surgery, have now been broadly recommended for most adult surgical patients in both the 2016 WHO and 2017 CDC prevention guidelines.[67,68] Active measures to maintain intraoperative normothermia (often defined as a core temperature at or above 36°C) have been associated in multiple studies with a reduction in SSIs compared with patients allowed to experience routine mild perioperative hypothermia.[96,97] Given the acute impact of anesthetic agents on thermoregulation, the most vulnerable period for hypothermia is likely the start of the surgical procedure, highlighting the importance of prewarming surgical patients as opposed to waiting until induction of anesthesia.[48,98]

In colorectal patients, administration of supplemental oxygen (fraction of inspired oxygen [F_{IO_2}], 80%) resulted in significantly lower SSI rates (5.2% vs. 11.2% in those receiving 30% F_{IO_2}).[99] A second randomized, double-blind trial of patients undergoing major intraabdominal surgical procedures randomized to receive either 80% or 35% F_{IO_2} intraoperatively, however, found that the incidence of infection was significantly *higher* in those patients who received the higher oxygen concentration (25.0% in the 80% F_{IO_2} group vs. 11.3% in the 35% F_{IO_2} group).[100] Subsequent trials, some using nitrous oxide in the control arm, have noted either reductions or no change in SSI risk with supplemental oxygen.[101] Of importance, Meyhoff and colleagues[102] did not find a significant increase in pulmonary complications, such as atelectasis or pneumonia in those receiving 80% FiO_2. Provision of perioperative supplemental oxygen (specified as 80% F_{IO_2} in WHO guideline) is now recommended for all adult surgical patients with normal pulmonary function undergoing general anesthesia with endotracheal intubation.[67,68]

Intensive glucose control via continuous insulin infusion (CII) targeted to maintain glucose levels less than 200 mg/dL during the perioperative period (lasting through the second postoperative day) was first shown to reduce SSI in cardiac surgery patients.[103] When compared in a study of more than 2400 diabetic patients, intensive glucose control with CII led to a reduction in the incidence of deep wound infection in diabetic cardiac surgery patients from 2.0% to 0.8% ($P = .01$).[104] Intensive glucose control is now recommended for both diabetic and nondiabetic adult surgical patients, although there is not consensus on delivery method and target glucose level.[67,68]

Perioperative Antimicrobial Prophylaxis

The in vivo interaction between inoculated bacteria and prophylactically administered antibiotics is one of the most important determinants of the fate of the wound. For example, without antimicrobial prophylaxis the reported risk of developing a *S. aureus* SSI after cardiac surgery is 21% to 44%.[105,106] Through a multitude of clinical trials, the efficacy of antimicrobial prophylaxis in clean and clean contaminated procedures has been clearly established. The guiding principle of systemic antimicrobial prophylaxis is the belief that antibiotics in the host tissues augment natural immune defense mechanisms and help to kill bacteria that are inoculated into the wound. The rationale for the administration of oral antibiotics in colonic surgery differs in that, although some agents exhibit systemic absorption and penetrate into host tissues (e.g., erythromycin and metronidazole, but not neomycin), the primary goal in this setting is a reduction in potential pathogens among the normal intestinal flora at the time of surgery. Oral prophylaxis is generally combined with mechanical preparation of the bowel to reduce colonic flora (see discussion later).

Every effort should be made to ensure that adequate antibiotic levels are maintained above the minimal inhibitory concentration (MIC) of the pathogens of concern throughout the surgical procedure (Fig. 313.4). Although prolonged surgical procedures are associated with a higher infection rate, it is not clear whether this increased risk is inevitable or primarily attributable to the greater likelihood of there being low or undetectable tissue concentrations of antibiotics during long procedures. In cardiothoracic procedures in particular, the use of cardiopulmonary bypass (CPB) can dramatically alter antibiotic concentrations, either increasing or decreasing drug levels as a result of factors such as drug sequestration within the CPB circuit. In addition, CPB can increase in the volume of distribution, in part due to the priming of the CPB circuit with crystalloid and possibly systemic inflammatory responses related to CPB.[107] Some have advocated for an additional dose of cefazolin given at the time of CPB institution or continuous cefazolin infusion to address the challenge of dosing with CPB.[108,109] Understanding the pharmacokinetics of the various antimicrobials used in perioperative prophylaxis is vital to ensure adequate antibiotic levels at the surgical wound site during the entire procedure.

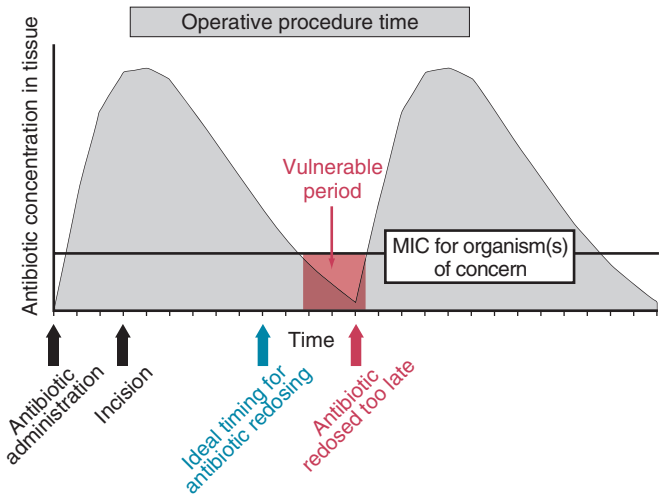

FIG. 313.4 Tissue antibiotic concentration over time. Dynamics of tissue antibiotic concentration during the course of a surgical procedure. After an initial dose of antibiotic (noted on the far left of the *x* axis), tissue concentrations reach their peak rapidly *(black arrows),* with a subsequent decline over time. As illustrated, the goal of antibiotic prophylaxis is to have tissue concentrations above the minimal inhibitory concentration *(MIC)* for the specific pathogens of concern at the time of the incision and throughout the procedure. Antibiotics should be redosed in prolonged procedures to prevent a period with tissue levels less than the MIC *(blue arrow).* Failure to redose antibiotics appropriately *(red arrow)* may result in a period during which the wound is vulnerable.

The efficacy of antimicrobial prophylaxis in preventing SSI after many surgical procedures is unquestioned. Not only have the benefits of early antibiotic administration been duplicated by numerous investigators using different animal models, different pathogens, and different antibiotics, literally hundreds of clinical trials have verified the efficacy of perioperative antibiotics. Nevertheless, nuanced issues regarding the optimal choice, frequency, and duration of perioperative antimicrobial prophylaxis remain.

Antimicrobial Prophylaxis: Drug Selection and Dosing

Basic Principles

Antimicrobial prophylaxis should be used for all clean-contaminated procedures and certain clean procedures, that is, those in which intravascular prosthetic material or a prosthetic joint will be inserted and those in which an incisional or organ/space SSI would pose catastrophic risk.[110] Dirty or contaminated procedures usually do not require specific antimicrobial prophylaxis because patients undergoing these procedures are already on targeted antimicrobial therapy for established infections; however, if the treatment regimen does not adequately cover all pathogens of concern, consideration should be given to providing additional prophylaxis, that is, in a procedure with a high incidence of MRSA SSI, additional prophylaxis with vancomycin may be warranted if the treatment regimen does not include MRSA coverage. The use of antimicrobial prophylaxis for all clean procedures, however, is less clear. For some clean, minimally invasive procedures with low risk for SSI,

TABLE 313.5 Typical Microbiologic Flora and Recommended Antimicrobial Drugs for Surgical Prophylaxis for Commonly Performed Surgical Procedures in Adults

PROCEDURE	TYPICAL MICROBIOLOGIC FLORA[a]	RECOMMENDED ANTIMICROBIALS
Cardiac	*Staphylococcus aureus*, CoNS, (GNR less common)	
Coronary artery bypass		Cefazolin, cefuroxime; addition of vancomycin if patient is colonized with *S. aureus*
Cardiac device insertion (e.g., pacemaker)		Cefazolin, cefuroxime
Ventricular assist device placement		Cefazolin, cefuroxime
Thoracic	*S. aureus*, CoNS	Cefazolin, ampicillin-sulbactam
Gastroduodenal (involving entry into lumen of gastrointestinal tract or without entry into lumen in high-risk patients)	Coliform GNR, streptococci, staphylococci	Cefazolin
Biliary	GNR (less commonly, anaerobes and enterococci)	
Open		Cefazolin, cefoxitin, cefotetan, ceftriaxone, ampicillin-sulbactam
Laparoscopic, high risk		Cefazolin, cefoxitin, cefotetan, ceftriaxone, ampicillin-sulbactam
Appendectomy	GNR, anaerobes	Cefoxitin, cefotetan, cefazolin + metronidazole
Colorectal	GNR, anaerobes (especially *Bacteroides fragilis* and *Escherichia coli*)	Cefazolin + metronidazole, cefoxitin, cefotetan, ampicillin-sulbactam, ceftriaxone + metronidazole, ertapenem; IV agent used along with mechanical bowel preparation and oral antimicrobial (neomycin sulfate + erythromycin base or neomycin sulfate + metronidazole)
Neurosurgery (craniotomy, CSF shunting, intrathecal pump implantation)	*S. aureus*, CoNS	Cefazolin
Cesarean section	*S. aureus*, streptococci, enterococci, vaginal anaerobes	Cefazolin
Hysterectomy (vaginal or abdominal)	*S. aureus*, streptococci, enterococci, *E. coli*, vaginal anaerobes	Cefazolin, cefoxitin, cefotetan, ampicillin-sulbactam
Orthopedic	*S. aureus*, CoNS, GNR (*Propionibacterium* spp. in shoulder procedures)	
Clean procedure of hand, knee, foot without implantation of foreign materials		None
Spinal procedures, hip fracture repair, internal fixation procedure, total joint arthroplasty		Cefazolin; addition of vancomycin if patient is colonized with *S. aureus* (arthroplasty)
Urologic	GNR (*E. coli*—increasing fluoroquinolone resistance noted), rarely enterococci	
Lower tract instrumentation (includes transrectal prostate biopsy)		Ciprofloxacin,[b] trimethoprim-sulfamethoxazole
Clean procedure (with or without entry into urinary tract		Cefazolin (single-dose aminoglycoside may be added for placement of prosthetic material)
Clean contaminated		Cefazolin + metronidazole, cefoxitin
Vascular	*S. aureus*, CoNS	Cefazolin

[a]Staphylococci will be associated with surgical site infections after all types of operations.
[b]Increasing reports of fluoroquinolone-resistant *E. coli* infections in postprostatic biopsy patients warrants careful monitoring of patients and infection surveillance to assess appropriate prophylactic antibiotic choice
CSF, Cerebrospinal fluid; *CoNS,* coagulase-negative staphylococci; *GNR,* gram-negative rods/bacilli; *IV,* intravenous.
Modified from Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm. *2013;70:195–283.*

concerns have been raised that the benefit of prophylaxis is not clear or may be outweighed by the potential risks of antimicrobial therapy. For example, a 2017 randomized controlled trial among patients undergoing removal of orthopedic implants used for below-the-knee fractures found a nonsignificant difference in SSI rates with the use of preoperative cefazolin versus saline placebo, although the study appears underpowered and did show a marked 2.5% reduction in deep SSIs.[111] Adequately powered randomized clinical trials of antimicrobial prophylaxis in such procedures are limited because of the need for very large sample sizes to demonstrate a significant reduction in SSI.[112] A 2009 meta-analysis noted that the risk reduction from antimicrobial prophylaxis is similar in all types of wounds, including clean, and that the assumption that prophylaxis is ineffective in a specific procedure unless proven otherwise should be revised.[113]

The key factors in selecting an appropriate prophylactic antibiotic regimen include coverage against the expected endogenous flora at the surgical site (Table 313.5), consideration of patient allergies and antimicrobial costs, knowledge of the ecology of local nosocomial wound pathogens, consideration of antibiotic penetration into the specific surgical site tissue, drug availability, and assurance of appropriate antibiotic dosing and delivery. Based on prospective studies of antibiotic prophylaxis, prophylactic regimens have been recommended for a wide variety of surgical procedures, and in 2013, a consensus guideline on surgical antimicrobial prophylaxis from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Surgical Infection Society, and the Society for Healthcare Epidemiology of America was released, helping to further harmonize recommend practices (see Tables 313.5 and 313.6).[110] Although only some regimens have been tested in controlled clinical trials, others with similar antimicrobial coverage and tissue penetration should provide similar protection, provided dosing guidelines are followed. In addition, appropriate assessment of a patient's antibiotic allergy can have SSI ramifications. In an analysis of more than 8000 surgical patients, those who reported a penicillin allergy had a significantly increased odds of SSI, thought to be due to receipt of second-line prophylactic antibiotics that may not cover as wide a spectrum of pathogens.[114] Because many who report penicillin allergy are not truly allergic, this study highlights the need to clarify a patient's allergy status as part of routine perioperative care.

Based on their antibacterial spectrum and low incidence of side effects, the cephalosporins (in particular, cefazolin) have been the traditional drugs of choice for the vast majority of operative procedures. Even in clean-contaminated procedures, such as hysterectomy and cholecystectomy, in which cephalosporins with improved in vitro activity against anaerobic bacteria are often advocated, clinical studies indicate that

cefazolin is equivalent in its prophylactic efficacy. For procedures in which anaerobic coverage is also justified (e.g., distal gastrointestinal tract, major head and neck, biliary, and gynecologic procedures) addition of metronidazole or other agents with anaerobic activity (e.g., cefoxitin) are appropriate selections for prophylaxis.[110]

Drug Selection With Rising Incidence of Antibiotic-Resistant Pathogens (e.g., MRSA)

It should not be presumed that cephalosporins will remain the prophylactic agents of choice. Various classes of antibiotics have been shown to differ appreciably in activity against bacteria regarding the stationary phase of growth, postantibiotic effect, diffusibility into devitalized tissue or fibrin clots, resistance to enzymatic degradation, activity within abscesses, and penetration of and activity within neutrophils that may have ingested but be unable to kill wound bacteria. Each of these variables may affect the efficacy of an agent used for prophylaxis, and it is likely that preferred prophylactic regimens will change over time in response to an improved understanding of the pathophysiology of infection and to antimicrobial resistance among wound pathogens.

Because cephalosporins are the mainstay of prophylaxis, the increasing prevalence of cephalosporin-resistant pathogens has important implications for prophylaxis.

In addition, multidrug-resistant organisms (MDROs) have increasingly become important pathogens in the postsurgical patient.[22] The impact of the increase of MDROs is illustrated by reports of an increase in infectious complications after transrectal ultrasound-guided prostate biopsy attributed in part to organisms resistant to fluoroquinolones, leading to a reevaluation of the use of these agents as routine prophylaxis for this procedure.[115] The arrival of these MDROs portends an ominous change in the complexity of the ecology of nosocomial infections and a need to assess the epidemiology of pathogens causing SSIs, to ensure appropriate coverage as a part of surgical prophylaxis. An examination from the CDC of pathogens causing SSI after coronary artery bypass graft (CABG) and joint arthroplasty surgery noted that between 55% and 59% were not susceptible to standard prophylactic agents;[116] however, the overall SSI rates were very low, indicating that a large majority of potential SSI pathogens were covered by standard regimens, leading some to argue that expansion of regimens may be inappropriate and unsafe.[117]

Methicillin-Resistant *S. aureus*–Specific Prophylaxis

In particular, the emergence of community-acquired (CA)-MRSA as a cause of SSI has clouded the issue of appropriate antimicrobial prophylaxis.[118] Previous recommendations suggested consideration of using vancomycin as empirical therapy for treatment and prophylaxis of presumptive staphylococcal infection when the local rates of MRSA are high; however, the exact threshold at which vancomycin use should occur was not clearly defined. Routine administration of vancomycin for surgical prophylaxis is not recommended.[110] A randomized trial of 855 cardiac surgical patients comparing routine use of vancomycin versus cefazolin for prophylaxis noted that, although the rate of MRSA SSI was higher in the cefazolin group, those who received vancomycin had a higher rate of methicillin-sensitive *S. aureus* (MSSA) SSI. Thus there was no significant difference in overall SSI rates between the two groups.[119] An interrupted time series analysis of more than 6000 cardiac surgery patients, however, found that in CABG patients, after a switch from cefazolin to vancomycin, the monthly SSI rates decreased by 2.1 per 100 procedures, primarily because of a decrease in SSI due to vancomycin-sensitive pathogens (e.g., MRSA).[120] This decline was significant when compared with rates in patients undergoing valve replacement and who had received routine prophylaxis with vancomycin during the entire study period, suggesting that other infection prevention interventions performed during the study period in both populations may not explain the reduction in the CABG patients.[120]

Practical limitations that may affect the use of vancomycin in surgery include its narrow spectrum of antimicrobial activity (less effective against MSSA) and the need for a slower rate of infusion. Failure to adequately dose vancomycin, even when indicated, can also lead to failure of antimicrobial prophylaxis, as illustrated by an assessment of joint arthroplasty patients who received vancomycin prophylaxis in which a higher SSI rate was noted in those receiving vancomycin alone (odds ratio, 1.58, vs. cefazolin prophylaxis).[121] Strikingly, only 28% of patients received an adequate dose of vancomycin based on weight-based dosage recommendations. Furthermore, the growing prevalence of vancomycin-resistant enterococci and the emergence of vancomycin-resistant *S. aureus* raise concerns about potential adverse effects on the antimicrobial susceptibility of nosocomial pathogens induced by the selective pressure of surgical antimicrobial prophylaxis.[122] A risk-based approach in which persons with specific risk factors for MRSA (e.g., history of recurrent furunculosis, prior MRSA infection, history of dialysis, or recent health care exposure) may help limit vancomycin use to those at higher risk of developing MRSA SSI. The Society of Thoracic Surgeons recommends use of vancomycin with cefazolin in persons with a known history of MRSA colonization, those undergoing placement of a prosthetic valve or vascular graft, and those "susceptible to colonization" (e.g., hospitalized longer than 3 days, transfer from an inpatient facility, or on antibiotics at time of procedure).[123] CA-MRSA complicates these recommendations, however, because healthy patients with few of these traditional comorbidities and risk factors may be at increased risk of MRSA colonization and subsequent infection. The addition of cefazolin to vancomycin is important because vancomycin appears less effective than cefazolin against MSSA, and cefazolin will provide some coverage against gram-negative organisms.[110]

Screening of patients for nasal carriage of MRSA before surgery, followed by adaptation of prophylactic regimens to include anti-MRSA coverage in carriers (± decolonization), has been used as a "bundled" strategy to address the growing issue of MRSA SSI.[90,124] Increasingly, the use of an MRSA-active agent such as vancomycin, in combination with an agent more active against MSSA, in patients known to be colonized with this organism or at high risk for colonization (e.g., recent hospitalization, nursing home residence, hemodialysis patient) is recommended rather using a specific incidence-rate threshold.[110,125] Patients undergoing elective surgical procedures could be screened during the initial preoperative evaluation, but clarifications of other issues related to screening (i.e., need for a second screening test to identify intermittent MRSA carriers, type of screening test to be used, and cost-effectiveness of screening in the presurgical population) must be determined.

Special Considerations With Prophylaxis in Colorectal Surgery

For colorectal procedures, the following three approaches to antimicrobial prophylaxis have generally been used: (1) use of oral (often nonabsorbable) agents, (2) use of IV agents, and (3) combination therapy using both types of agents.[126] Many surgeons use combination IV and oral therapy, with the rationale to decrease intraluminal flora and to provide adequate subcutaneous tissue concentrations. A Cochrane review has helped clarify the question of optimal antimicrobial prophylaxis before colorectal surgery; this analysis included 260 trials with more than 43,000 total subjects and noted a significant reduction in surgical infection with the use of combination oral and IV prophylaxis versus IV prophylaxis alone (RR, 0.56; 95% CI, 0.43 to 0.74) and versus oral prophylaxis alone (RR, 0.56; 95% CI, 0.40 to 0.76),[127] a finding mirrored in an analysis of the Veterans Affairs Surgical Quality Improvement Program data (SSI rate 6.3% with IV and oral vs. 16.7% wit h IV alone).[128] The addition of oral antimicrobials may increase the risk of development of nausea and vomiting, and patients should be advised of these symptoms.[110] Mechanical bowel preparation (MBP) to cleanse the bowel lumen before incision has also been used for some time in colorectal surgery patients, but there has been debate regarding the optimal approach and utility of MBP, with some studies noting a higher rate of anastomotic leakage with MBP use.[129,130] A retrospective propensity analysis of colectomy patients at Michigan hospitals participating in a statewide surgical collaborative noted that MBP in conjunction with oral antimicrobials resulted in significantly lower rates of SSI when compared with MBP without oral antimicrobial.[131] A larger study within the National Surgical Quality Improvement Program found that MBP with oral antibiotics was significantly associated with lower rates of anastomotic leak, SSI, and postoperative ileus.[132] The 2013 consensus guideline on surgical prophylaxis now recommend use of MBP combined with oral and IV antimicrobials for most colorectal procedures.[110]

Dosing in Obese Patients

The use of higher doses of antibiotic is needed for obese patients. After administration of a 1-g dose of cefazolin, tissue and serum concentrations of the antibiotic were significantly decreased in morbidly obese patients when compared with nonobese controls.[133] A higher (2-g) dose of cefazolin did provide tissue levels greater than the MIC for the most likely infecting pathogens. Another study of obese patients given 2-g doses of cefazolin, however, found therapeutic tissue levels of the drug in only 48% of persons with a body mass index (BMI) between 40 and 49, 29% in those with a BMI between 50 and 59, and 10% in those with a BMI 60 or higher, leading the authors to propose using continuous cefazolin administration in the morbidly obese patient to improve tissue concentrations.[134] The 2013 consensus guideline notes that, given the low cost and favorable safety profile of cefazolin, using a 2-g dose for patients weighing 80 kg and a 3-g dose for those greater than 120 kg is justified; however, the optimal approach for weight-based dosing of other prophylactic antibiotics, including whether to use actual versus ideal body weight, has not been determined.[110]

Antimicrobial Prophylaxis: Timing of Administration and Redosing

Initial Dose Timing

The initial dose of systemic antibiotics must be administered in a timely fashion so that antibiotic levels in the tissue at the time of the incision are adequate. Administration too early before or too late after the time of incision will result in suboptimal tissue levels and potentially increased risk of postoperative wound infection. Guidelines and studies have traditionally varied on the exact timing, ranging from 2 hours to no more than 30 minutes before incision, but the 2013 consensus guideline defines appropriately timed antimicrobial prophylaxis as delivery of the antibiotic within 60 minutes before incision, with the exception that vancomycin and the fluoroquinolones should be given within 120 minutes before incision because of the need for a longer infusion time.[110] This definition has become widely used as a metric that indicates delivery of standard, high-quality surgical care.[135] One exception to this recommendation is the 2016 WHO SSI prevention guideline, which argued that, although evidence supported an increased SSI risk with administration after incision or earlier than 120 minutes before incision, the evidence supporting prophylactic antibiotic administration within 60 minutes before incision was not strong enough to make a firm recommendation.[73]

Several large-scale studies have examined the relationship between the timing of delivery of antimicrobial prophylaxis and the risk of SSI. The seminal study by Classen and colleagues[9] noted that SSI risk was reduced when antibiotics were administered within 2 hours before incision (Fig. 313.5A). More recently, the Trial to Reduce Antimicrobial Prophylaxis Errors (TRAPE) examined the association between SSI and timing of prophylaxis in cardiac, orthopedic, and hysterectomy patients.[136] The TRAPE investigators found that SSI risk was lowest in those patients who received prophylaxis within 30 minutes (if given cephalosporins) or within 1 hour (if given vancomycin or a fluoroquinolone) before incision (see Fig. 313.5B). Postincision administration was associated with a significantly increased risk for SSI. These results have also been reproduced in a study of 1922 patients undergoing total hip arthroplasty in which the rate of SSI was lowest in those who received antibiotics 1 to 30 minutes before incision.[137] A large retrospective study using data from the Veterans Administration system noted a higher risk for SSI with dosing more than 60 minutes before incision, but a significant difference was not noted with antibiotics dosed after the incision. This effect was also lost with adjustment for patient, procedural, and antibiotic variables; however, in this study a majority of patients had prophylactic antibiotics dosed within 60 minutes, there was no consideration for the longer dosing window needed for vancomycin and quinolone agents, and there may have been confounding by procedures with an infection present at the time of surgery.[138]

Attempts have been made to further refine the dosing window, although with decreasing SSI rates the power necessary to define such timing with more granularity is becoming increasingly challenging. There may be a threshold where, even though penetration into tissue for many drugs occurs in minutes, administration of antibiotic right before the incision may not provide enough time for tissue concentrations of the drug to reach the desired level at the time of incision. A study in more than 28,000 cardiac surgery patients noted an increased risk of infection if cefuroxime was given more than 45 and more than 60 minutes preincision and a reduced risk if the drug was given within 15 minutes before incision. This effect differed with use of vancomycin, with the lowest rate of infection occurring with administration less than 45 minutes preincision, likely reflecting the need for a more prolonged infusion of this agent.[139] Weber and colleagues[140] noted a twofold increased odds of SSI when cefuroxime prophylaxis was delivered less than 30 minutes before incision, as opposed to between 30 and 59 minutes preincision. Curiously, when examined with more granularity, the risk was higher in those who received the antibiotic between 15 and 29 minutes versus those who received a dose between 0 and 14 minutes preincision. A study of vancomycin use in cardiac surgery patients found that prophylaxis was most effective when given between 16 and 60 minutes before incision (RR, 7.8; compared with receipt between 15 and 0 minutes preincision).[141] This may be explained by the need for an hour-long infusion of vancomycin to prevent infusion-related side effects, suggesting that a small proportion of the dose had been infused at the time of the incision. What is curious, however, is that those given a dose between 16 and 60 minutes preincision may not have had complete infusion of the drug dose, but perhaps enough to allow adequate tissue penetration.[139] In another analysis the lowest risk for SSI among general surgical patients was determined with administration of antibiotics (not including vancomycin) at 4 minutes before incision (95% CI, 0 to 18 minutes).[142] Countering these studies,

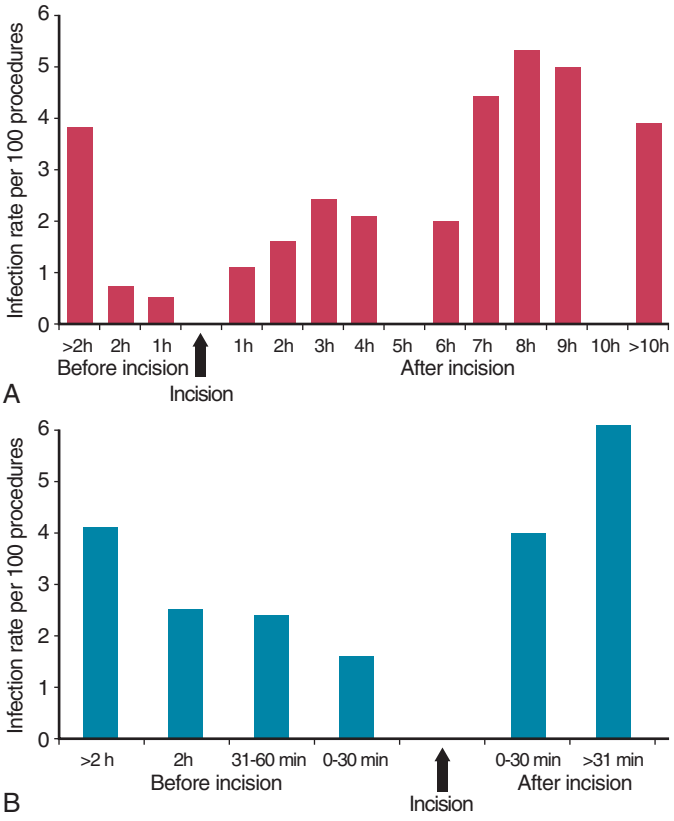

FIG. 313.5 Timing of administration and infection rate. Relationship between timing of administration of prophylactic antibiotics and surgical site infection rate from two large studies. (A) Data from 2847 elective surgical patients. (B) Data from 3656 cardiac, orthopedic, and gynecologic surgical patients. *(A from Classen DC, Evans RS, Pestotnik SL, et al. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection.* N Engl J Med. *1992;326:281–286; and B from Steinberg JP, Braun BI, Hellinger WC, et al. Timing of antimicrobial prophylaxis and the risk of surgical site infections: results from the Trial to Reduce Antimicrobial Prophylaxis Errors.* Ann Surg. *2009;250:10–16.)*

a randomized controlled trial among 5580 general surgery patients found no difference in SSI rates between those with cefuroxime administration early (median, 42 minutes before incision) versus administration closer to the time of incision (median, 16 minutes before incision).[143] Finally, a meta-analysis on this topic noted that SSI rates significantly increased with administration more than 120 minutes before incision and with administration after incision, but no further refinement of the timing window could be made.[144] Thus, although a near consensus has developed regarding timing (within 60 minutes before incision, unless using vancomycin or quinolones), more investigation is needed into such nuances of the delivery of surgical prophylaxis before alterations in timing recommendations can be made.[138]

Administration of prophylaxis in patients undergoing cesarean section had historically been held until after umbilical cord clamping to address concerns about delivery of drug to the neonate, which may mask signs of developing neonatal sepsis. Such a strategy, however, does not provide the mother with desired tissue concentrations of antibiotics at the time of incision. Several studies and analyses have now demonstrated that administration of prophylactic antibiotics before incision results in a reduced endometritis and SSI risk and does not lead to an increase in adverse neonatal outcomes (e.g., neonatal sepsis, sepsis workups, and admissions to the intensive care unit), indicating that provision of antibiotic before incision is acceptable.[145–147] For orthopedic procedures in which a tourniquet is used, full infusion of the drug has often been recommended to occur before tourniquet inflation[126]; however, a randomized placebo-controlled trial in knee arthroplasty procedures noted no difference in deep SSI rates when prophylaxis was given before tourniquet deflation, calling this long-held practice into question.[148]

Intraoperative Redosing

As critical as providing an appropriately timed initial dose of antibiotic is, it is important to ensure that tissue concentrations remain well above the MIC values of common pathogens during the entire procedure. Failure to do so was associated with an increased risk for SSI (RR, 4.6) across a variety of procedures in an analysis from the University of Washington,[149] an effect that remained after adjustment for inpatient status, smoking, emergency surgery, procedure type, multiple procedures, and intraoperative blood transfusion greater than 500 mL.[149] To achieve this goal, antibiotics should also be readministered in adults with normal renal function if the procedure duration exceeds two half-lives of the drug used or in the event of excessive blood loss (>1500 mL),[110] as introduction of bacteria into the surgical wound occurs not only at the time of incision but often throughout the procedure. In prolonged procedures or with antibiotics with short half-lives, patients may be inadequately protected if redosing is not routinely provided.[150] The 2013 consensus guideline provides detailed information on the timing of intraoperative doses for most common prophylactic antibiotics (Table 313.6).[110] Some groups have also used the now-commonplace "time-out" before incision or computer-generated dosing reminders to ensure appropriate delivery of antimicrobial prophylaxis.[151,152]

TABLE 313.6 Recommended Doses and Redosing Intervals for Adults for Commonly Used Antimicrobials for Surgical Prophylaxis

ANTIMICROBIAL	RECOMMENDED DOSE FOR ADULTS	RECOMMENDED REDOSING INTERVAL (FROM INITIATION OF PREOPERATIVE DOSE) (h)[a]
Intravenous Agents		
Ampicillin-sulbactam	3 g (ampicillin 2 g/sulbactam 1 g)	2
Ampicillin	2 g	2
Aztreonam	2 g	4
Cefazolin	2 g; 3 g for persons with weight ≥120 kg	4
Cefotaxime	1 g	3
Cefoxitin	2 g	2
Cefotetan	2 g	6
Ceftriaxone	2 g	NA
Ciprofloxacin	400 mg	NA
Clindamycin	900 mg	6
Ertapenem	1 g	NA
Fluconazole	400 mg	NA
Gentamicin	5 mg/kg	NA
Levofloxacin	500 mg	NA
Metronidazole	500 mg	NA
Moxifloxacin	400 mg	NA
Piperacillin-tazobactam	3.375 g	2
Vancomycin	15 mg/kg	NA
Oral Agents for Colorectal Procedures (in Conjunction With Mechanical Bowel Preparation)		
Erythromycin base	1 g	NA
Metronidazole	2 g	NA
Neomycin	1–2 g	NA

[a]Based on typical case length; for prolonged cases, antibiotics noted as "NA" (not applicable) may require redosing.
Modified from Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm. *2013;70:195–283.*

Antimicrobial Prophylaxis: Duration

In the early years of surgical prophylaxis prolonged courses (7–10 days) of antibiotics seemed routine.[153] Over time the benefit of prolonged courses of antimicrobials has been appropriately questioned, particularly due to pathophysiologic changes at the area of incision (i.e., coagulative necrosis, induced hemostasis via cautery of blood vessels) that likely limit the ability of antibiotics to reach the wound bed during the early postoperative period.[153]

Although some studies have noted a benefit with prolonged prophylaxis in select subpopulations of patients,[154–157] many more have found no increase in infection rates among the short-course recipients when compared with those receiving a longer duration of prophylaxis. A systematic review of 28 randomized trials of single versus multiple doses of antimicrobial prophylaxis found no advantage of prolonged duration of prophylaxis in preventing SSI in a wide array of surgical procedures.[158] Prolonged antimicrobial prophylaxis (>48 hours postincision) has been significantly associated with an increased risk of acquiring an antibiotic-resistant pathogen.[159] A commonly espoused rationale for prolonging the duration of surgical prophylaxis after incision closure includes a desire to "cover" the wound while surgical drains remain in place or to "protect" against infection of CVCs. However, a study in the United Kingdom found that prolonged prophylaxis until the patient's CVC was removed (vs. three doses of cefuroxime perioperatively) did not lead to a reduction in CVC colonization, a surrogate for CVC infection.[160] WHO SSI Prevention Guideline advises against continuing prophylaxis in the presence of a drain.[68]

The effectiveness of surgical prophylaxis is minimized after incision closure. Most guidelines for surgical prophylaxis recommend discontinuation of prophylactic antibiotics within 24 hours, a metric of appropriate surgical care for quality and regulatory programs. For cardiac surgery, some groups recommend continuing prophylaxis for 48 hours, based on concerns that more data are needed before uniformly recommending a shorter duration in this population.[161,162] The 2013 surgical prophylaxis guideline challenged this recommendation, stating prophylaxis for the procedure's duration and, at most, 24 hours is appropriate for cardiothoracic procedures as well.[110] The 2017 CDC SSI Prevention Guideline narrows the recommended duration of surgical prophylaxis a step further, recommending "[i]n clean and clean-contaminated procedures, do not

administer additional prophylactic antimicrobial agent doses after the surgical incision is closed in the operating room, even in the presence of a drain."[67] Prompt discontinuation of prophylaxis does not appear to impact the risk of developing SSI, as is the case with timely administration of antibiotics, but failure to do so contributes to unnecessary antimicrobial use and its subsequent related problems (e.g., antibiotic resistance). One recent study raises a potential exception to this rule. A randomized, double-blind trial among obese (prepregnancy BMI ≥30 kg/m^2) women noted that the addition of oral cephalexin and metronidazole for 48 hours after cesarean delivery, in conjunction with routine preoperative prophylaxis, was associated with a significantly lower SSI rate (6.4% vs. 15.4%).[163] This effect was more pronounced among women with ruptured membranes, suggesting a very specific patient population that may benefit from an extended-duration strategy.

Novel Methods of Antimicrobial Prophylaxis: Local and Topical Compounds

Newer methods for delivery of antimicrobial prophylaxis, such as antimicrobial washes, cement, sutures, powder, and other compounds, have been increasingly used for the prevention of SSIs.[164] First introduced in 1939,[165] antibiotic-impregnated cement placed directly into the operative wound (as a local antimicrobial "brachytherapy") has been used as a method of antimicrobial prophylaxis and treatment, particularly in procedures involving the replacement of infected prosthetic joints. Brachytherapy uses powdered antibiotic mixed with a cement polymer, such as polymerized polymethylmethacrylate, to form a compound that may be directly applied onto prosthetic material or manufactured into beads (usually 3–10 mm in diameter) that are placed into the wound. Candidate antibiotics for use as brachytherapy must be available as a pharmaceutical-grade powder, must be heat stable (because of the exothermic reaction induced with polymerization), and must have an appropriate microbiologic spectrum of activity for the predominant pathogens at the operative site.[165] The aminoglycosides and vancomycin are the compounds most commonly used for brachytherapy; oxacillin and cefazolin have comparable elution characteristics but are less frequently used because of concerns regarding β-lactam allergy.

The majority of antibiotic elution occurs in the first days after implantation, but elution from impregnated cement has been detected years after surgery.[165,166] The use of antibiotic-impregnated cement (in conjunction with systemic prophylaxis) was significantly associated with a reduction in SSIs in studies from several large clinical registries in Europe.[167] Concerns remain, however, regarding routine use of this mode of prophylaxis because of possible adverse effects, such as allergic reactions.[168] Systemic absorption of antibiotic brachytherapy is also a concern because potentially high boluses of antibiotic may lead to toxicity. In one series of 14 subjects, 1 patient developed permanent and 2 others temporary high-frequency hearing loss after implantation of gentamicin-impregnated beads.[169] The frequency of detectable serum aminoglycoside levels was substantial (22% of patients) in one series of patients with tobramycin cement spacer placement.[170] Renal failure attributed to impregnated cement, although rare, has also been reported.[171] Two randomized controlled trials examining the use of another type of brachytherapy, implantable gentamicin-collagen sponges, to prevent SSIs noted no impact in cardiac surgery patients[172] and a significant increase in infection in colorectal surgery patients.[173] Further studies into the systemic absorption, efficacy, and adverse effects of these brachytherapeutic compounds appear warranted before recommendations for routine use can be made.

The use of two other local forms of antimicrobial prophylaxis has garnered increased attention: powder and irrigation solutions instilled directly within the surgical bed. Use of vancomycin powder in spinal and craniotomy surgery has generated an amount of discussion and assessment. Some argue that the level of evidence for benefit is limited and has substantial bias,[174,175] whereas others have concluded that the use of intraincisional vancomycin powder leads to a significant reduction in SSIs.[176,177] The use of antibiotic irrigation solutions, although widespread, also suffer from a lack of clear evidence supporting their use, possibly related to the need for more prolonged exposure of the agent to the infecting pathogens in order to have an effect.[178] The 2016 WHO SSI Prevention Guidelines recommend against the use of antibiotic irrigation, although use of an aqueous povidone-iodine irrigant is noted for consideration.[68]

Adverse Effects of Prophylaxis

Adverse effects of prophylaxis include allergic reactions ranging in severity from minor skin rashes to anaphylaxis. *Clostridioides difficile* (formerly *Clostridium difficile*)–associated diarrhea (CDAD) has been noted with several prophylactic agents, and in one study the rate of CDAD was 14.9 cases per 1000 in surgical patients who received antimicrobial prophylaxis as their sole antibiotic exposure.[179,180] Another notable adverse effect is profound hypotension and flushing associated with vancomycin prophylaxis (the red man syndrome), usually associated with rapid infusions of the antibiotic.[181]

The use of prophylactic antibiotics has consequences for the institution and the individual patient. Antibiotic use, and specifically prophylactic use, has been shown to have a critical role in the selection of antibiotic-resistant bacteria to become the dominant colonizing flora and nosocomial pathogens of hospitalized patients.[182] At least two mechanisms for this process have been documented. First, the antibiotic-resistant flora may be endemic within the institution and transferred to the patient during the course of hospitalization.[183] Second, a small population of antibiotic-resistant bacteria that are part of the patient's endogenous flora at the time of hospitalization may emerge under the selective pressure of perioperative prophylaxis to become the dominant flora.[184] In view of the improvement in overall surgical wound infection rates over recent decades, the benefit of prophylactic antibiotics outweigh the risk of this potential side effect, but judicious use (including early discontinuation) of antibiotics for this purpose should be followed.

Cost-Benefit of Prophylaxis

Prophylactic antibiotics add some cost to the routine care of surgical patients. In major surgical centers, the perioperative use of antibiotics may represent a substantial portion of the pharmacy's expenditures for antibiotics, and surgeons may be encouraged to reduce or eliminate antibiotics given for prophylaxis in certain settings. For example, in carotid endarterectomy and cholecystectomy, infections develop only infrequently, are seldom life threatening, and may cost more to prevent than to treat. However, it is inappropriate to evaluate antibiotic use on the basis of cost alone. When a particular form of prophylaxis offers a clear advantage to the patient, the health care system should advocate the better treatment without consideration of its cost. Moreover, an analysis of the cost of prophylactic antibiotics can be complicated. Not only the cost of the antibiotic per se but the cost of preparing, transporting, and administering multiple doses of antibiotic must be included. Perhaps of more importance, the cost in terms of mortality, morbidity, and resources of managing SSIs that develop when using inadequate prophylaxis must be considered.[185]

Use of Surgical Prophylaxis Compliance as a Reported Measure of Health Care Quality

Historically, adherence to the key aspects of preoperative and intraoperative antimicrobial prophylaxis (i.e., right drug at the right dose given at the right time) was poor. An analysis in 2001 of Medicare patients undergoing major surgical procedures for which antimicrobial prophylaxis is recommended found that only 55.7% received an antibiotic within 1 hour before incision, whereas only 40.7% had prophylaxis discontinued at 24 hours after surgery.[135] Because of this suboptimal performance, quality metrics targeting delivery of antimicrobial prophylaxis and other evidence-based SSI reduction methods were developed. Led by the Surgical Improvement Project (SIP), which morphed into the Surgical Care Improvement Project (SCIP), performance and reimbursement measures focused on surgical prophylaxis drug choice, timing, and duration, as well as hair removal, and prevention of hyperglycemia and hypothermia helped improve adherence to these basic standards and have been associated with lower SSI rates.[186] In contrast, another retrospective analysis argued that improved compliance with the individual components of the SCIP metrics were not associated with a reduction in SSI, leading to pointed criticism of the program.[187,188] Unfortunately, critics failed to also note the significant reduction in SSI

risk, with improved compliance to *all* measures together, suggesting that quality improvement efforts focused at harmonizing overall surgical care improvement rather than specific metrics can make an impact.[189] The antimicrobial prophylaxis measures within SCIP were retired in 2015 due to uniformly high compliance. Whether compliance has subsequently slipped with less visibility and accountability to these metrics remains to be seen but is a concern.

Surgical Site Infection Surveillance

A key component in the prevention of SSIs is the establishment of a surveillance infrastructure to regularly detect and monitor rates of procedure-specific infections, to define the changing ecology of resistant pathogens that cause surgical infections, and to provide accurate analysis of the pervading antimicrobial sensitivity patterns in each specific institution to allow tailoring of prophylactic regimens. Adequate surveillance for postsurgical infections with comparisons of infection rates to national benchmarks also allows continued evaluation and assessment of the quality of an individual hospital's prevention strategies. To allow such comparisons, such surveillance must use standardized infection definitions, such as those used by the CDC's National Healthcare Safety Network (Table 313.7). Studies of risk factors for SSI and evaluations of interventions to reduce postsurgical infections use a wide array of outcome definitions, such as purulence at the incision site with a positive wound culture or attending physician diagnosis of wound infection. Thus care must be taken when assessing the literature and comparing the results of different studies because the outcome of interest may vary considerably.[190] The presence of purulence within a surgical incision generally serves as initial evidence of a SSI, but culture results of surgical wounds or exudates should not be used solely as a guide to the presence or absence of infection. Surveillance systems should also use the input of representatives with surgical, infectious diseases, infection prevention, and hospital epidemiology expertise in the analysis and evaluation of data.

In health care settings associated with a high volume of surgical procedures, surgical wound isolates should be maintained, if possible, for several weeks after isolation. Clusters or outbreaks of SSIs caused by a common pathogen are usually identified retrospectively, and the availability of infecting pathogens for molecular typing may be instrumental in identifying and eliminating the cause of the outbreak.

Highlighted by the landmark Study on the Efficacy of Nosocomial Infection Control project, maintaining and publicizing surgeon-specific infection rates may be used to indirectly decrease SSI rates.[191] Such data may identify unsuspected problems among the surgical staff or may encourage individual surgeons to rigorously adhere to standards of perioperative aseptic techniques. If such a program is used, it is vital that any analysis include an assessment of procedure-specific infection rates. Wide differences in infection rates exist among surgical procedures, even among those procedures within the same surgical subspecialty and category of bacterial contamination. For example, in vascular surgery, infection rates after carotid endarterectomy are exceedingly low (<0.1%). In contrast, bypass grafting in the femoral-popliteal area may be associated with an infection rate of 2% to 3%, despite the fact that both procedures are clean and may be performed by the same vascular surgeons. Other important variables, such as the incidence of underlying patient risk factors, must also be considered when comparing infection rates among surgeons.

TABLE 313.7 National Healthcare Safety Network Definitions for Surgical Site Infections

INFECTION TYPE	DEFINITION
Superficial incisional surgical site infection (SSI)	Infections involving only skin and subcutaneous tissue of the incision occurring within 30 days after the procedure with *one or more* of the following: • Purulent drainage from the superficial incision • Positive aseptically obtained culture of fluid or tissue from superficial incision • Pain or tenderness, swelling, erythema, or heat at surgical wound that has been deliberately opened by a surgeon or attending physician; *or* • Diagnosis by a surgeon or attending physician
Deep incisional SSI	Infections involving deep soft tissue (fascia/muscle layers) occurring within 30 or 90 days (dependent on the procedure type) after the procedure with *one* of the following: • Purulent drainage from deep incision but not from organ space • Spontaneous dehiscence or deliberate opening by a surgeon with a positive incision/wound culture or is not cultured and has the presence of fever or local pain • Abscess involving a deep incision found by direct examination, during invasive procedure, or by histopathologic examination or imaging test; *or* Diagnosis by a surgeon or attending physician
Organ/space SSI	Infections that involve any part of the body opened or manipulated during the operative procedure, excluding skin incision/fascia/muscle layers, within 30 or 90 days (dependent on the procedure type) with *one* of the following: • Purulent drainage from a drain that is placed into the organ/space • Positive culture growth of a specimen of tissue or fluid aseptically obtained • Evidence of infection by direct examination, during invasive procedure, or by histopathologic examination or imaging test

Postdischarge Surgical Site Infection Surveillance

Surveillance systems for postsurgical infections can be challenging, given the migration of surgical procedures to the outpatient arena and the growing push to decrease lengths of hospital stay with earlier discharge postsurgery. Sands and colleagues[192] noted that 84% of SSIs occurred after hospital discharge and would therefore have been missed with traditional hospital-based surveillance. Methods to improve detection of surgical site infections that arise postdischarge, including direct examination of wounds during follow-up visits, patient and practitioner surveys, computerized queries of billing claims, outpatient diagnostic codes, and antibiotic prescriptions, have met with variable success and concerns regarding costs and the ability to generalize results.[183,193–196] Any method of postdischarge surveillance must address these concerns and accommodate the unique attributes of each specific hospital and patient population.

Key References

The complete reference list is available online at Expert Consult.

7. Miles AA, Miles EM, Burke J. The value and duration of defence reactions of the skin to the primary lodgement of bacteria. *Br J Exp Pathol*. 1957;38:79–96.
8. Burke JF. The effective period of preventive antibiotic action in experimental incisions and dermal lesions. *Surgery*. 1961;50:161–168.
9. Classen DC, Evans RS, Pestotnik SL, et al. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *N Engl J Med*. 1992;326:281–286.
13. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med*. 2014;370:1198–1208.
14. Owens PL, Barrett ML, Raetzman S, et al. Surgical site infections following ambulatory surgery procedures. *JAMA*. 2014;311:709–716.
21. Mangram AJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol*. 1999;20:250–278, quiz 79–80.
22. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. *Infect Control Hosp Epidemiol*. 2016;37:1288–1301.
27. Schreiber PW, Sax H. *Mycobacterium chimaera* infections associated with heater-cooler units in cardiac surgery. *Curr Opin Infect Dis*. 2017;30:388–394.
43. Charoenkwan K, Iheozor-Ejiofor Z, Rerkasem K. Matovinovic E. Scalpel versus electrosurgery for major abdominal incisions. *Cochrane Database Syst Rev*. 2017;(6):CD005987.
48. Sessler DI. Perioperative thermoregulation and heat balance. *Lancet*. 2016;387:2655–2664.
54. Rohde JM, Dimcheff DE, Blumberg N, et al. Health care-associated infection after red blood cell transfusion: a systematic review and meta-analysis. *JAMA*. 2014;311:1317–1326.
65. Nolan MB, Martin DP, Thompson R, et al. Association between smoking status, preoperative exhaled carbon monoxide levels, and postoperative surgical site infection in patients undergoing elective surgery. *JAMA Surg*. 2017;152:476–483.

66. Latham R, Lancaster AD, Covington JF, et al. The association of diabetes and glucose control with surgical-site infections among cardiothoracic surgery patients. *Infect Control Hosp Epidemiol*. 2001;22:607–612.
67. Berrios-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for Disease Control and Prevention guideline for the prevention of surgical site infection, 2017. *JAMA Surg*. 2017;152:784–791.
68. Allegranzi B, Zayed B, Bischoff P, et al. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. *Lancet Infect Dis*. 2016;16:e288–e303.
72. Darouiche RO, Wall MJ Jr, Itani KM, et al. Chlorhexidine-alcohol versus povidone-iodine for surgical-site antisepsis. *N Engl J Med*. 2010;362:18–26.
73. Allegranzi B, Bischoff P, de Jonge S, et al. New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. *Lancet Infect Dis*. 2016;16:e276–e287.
74. Misteli H, Weber WP, Reck S, et al. Surgical glove perforation and the risk of surgical site infection. *Arch Surg*. 2009;144:553–558, discussion 8.
76. Pryor F, Messmer PR. The effect of traffic patterns in the OR on surgical site infections. *AORN J*. 1998;68:649–660.
78. Lefebvre A, Saliou P, Lucet JC, et al. Preoperative hair removal and surgical site infections: network meta-analysis of randomized controlled trials. *J Hosp Infect*. 2015;91:100–108.
82. Cooper WO, Guillamondegui O, Hines OJ, et al. Use of unsolicited patient observations to identify surgeons with increased risk for postoperative complications. *JAMA Surg*. 2017;152:522–529.
84. Manian FA. The role of postoperative factors in surgical site infections: time to take notice. *Clin Infect Dis*. 2014;59:1272–1276.
87. Dumville JC, Gray TA, Walter CJ, et al. Dressings for the prevention of surgical site infection. *Cochrane Database Syst Rev*. 2016;(12):CD003091.
89. Bode LG, Kluytmans JA, Wertheim HF, et al. Preventing surgical-site infections in nasal carriers of *Staphylococcus aureus*. *N Engl J Med*. 2010;362:9–17.
90. Schweizer ML, Chiang HY, Septimus E, et al. Association of a bundled intervention with surgical site infections among patients undergoing cardiac, hip, or knee surgery. *JAMA*. 2015;313:2162–2171.
91. Franco LM, Cota GF, Pinto TS, et al. Preoperative bathing of the surgical site with chlorhexidine for infection prevention: systematic review with meta-analysis. *Am J Infect Control*. 2017;45:343–349.
97. Beltramini AM, Salata RA, Ray AJ. Thermoregulation and risk of surgical site infection. *Infect Control Hosp Epidemiol*. 2011;32:603–610.
101. Munoz-Price LS, Sands L, Lubarsky DA. Effect of high perioperative oxygen supplementation on surgical site infections. *Clin Infect Dis*. 2013;57:1465–1472.
104. Furnary AP, Zerr KJ, Grunkemeier GL, et al. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. *Ann Thorac Surg*. 1999;67:352–360, discussion 60–62.
107. Paruk F, Sime FB, Lipman J, et al. Dosing antibiotic prophylaxis during cardiopulmonary bypass-a higher level of complexity? A structured review. *Int J Antimicrob Agents*. 2017;49:395–402.
110. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm*. 2013;70:195–283.
114. Blumenthal KG, Ryan EE, Li Y, et al. The impact of a reported penicillin allergy on surgical site infection risk. *Clin Infect Dis*. 2018;66:329–336.
123. Engelman R, Shahian D, Shemin R, et al. The Society of Thoracic Surgeons practice guideline series: antibiotic prophylaxis in cardiac surgery, part II: antibiotic choice. *Ann Thorac Surg*. 2007;83:1569–1576.
126. Bratzler DW, Houck PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. *Clin Infect Dis*. 2004;38:1706–1715.
127. Nelson RL, Gladman E, Barbateskovic M. Antimicrobial prophylaxis for colorectal surgery. *Cochrane Database Syst Rev*. 2014;(5):CD001181.
132. Kiran RP, Murray AC, Chiuzan C, et al. Combined preoperative mechanical bowel preparation with oral antibiotics significantly reduces surgical site infection, anastomotic leak, and ileus after colorectal surgery. *Ann Surg*. 2015;262:416–425, discussion 23–25.
135. Bratzler DW, Hunt DR. The surgical infection prevention and surgical care improvement projects: national initiatives to improve outcomes for patients having surgery. *Clin Infect Dis*. 2006;43:322–330.
136. Steinberg JP, Braun BI, Hellinger WC, et al. Timing of antimicrobial prophylaxis and the risk of surgical site infections: results from the Trial to Reduce Antimicrobial Prophylaxis Errors. *Ann Surg*. 2009;250:10–16.
148. Soriano A, Bori G, Garcia-Ramiro S, et al. Timing of antibiotic prophylaxis for primary total knee arthroplasty performed during ischemia. *Clin Infect Dis*. 2008;46:1009–1014.
149. Kasatpibal N, Whitney JD, Dellinger EP, et al. Failure to redose antibiotic prophylaxis in long surgery increases risk of surgical site infection. *Surg Infect (Larchmt)*. 2017;18:474–484.
158. McDonald M, Grabsch E, Marshall C, et al. Single- versus multiple-dose antimicrobial prophylaxis for major surgery: a systematic review. *Aust N Z J Surg*. 1998;68:388–396.
161. Edwards FH, Engelman RM, Houck P, et al. The society of thoracic surgeons practice guideline series: antibiotic prophylaxis in cardiac surgery, part i: duration. *Ann Thorac Surg*. 2006;81:397–404.
164. McHugh SM, Collins CJ, Corrigan MA, et al. The role of topical antibiotics used as prophylaxis in surgical site infection prevention. *J Antimicrob Chemother*. 2011;66:693–701.
174. Kang DG, Holekamp TF, Wagner SC, et al. Intrasite vancomycin powder for the prevention of surgical site infection in spine surgery: a systematic literature review. *Spine J*. 2015;15:762–770.
178. Barnes S, Spencer M, Graham D, et al. Surgical wound irrigation: a call for evidence-based standardization of practice. *Am J Infect Control*. 2014;42:525–529.
189. Dellinger EP. Adherence to Surgical Care Improvement Project measures: the whole is greater than the parts. *Future Microbiol*. 2010;5:1781–1785.
191. Haley RW, Culver DH, White JW, et al. The efficacy of infection surveillance and control programs in preventing nosocomial infections in US hospitals. *Am J Epidemiol*. 1985;121:182–205.
192. Sands K, Vineyard G, Platt R. Surgical site infections occurring after hospital discharge. *J Infect Dis*. 1996;173:963–970.