Enhanced Meatal Care

Reducing meatal colonization would seem to be a reasonable measure to reduce the risk of CAUTI, given that ascension of uropathogens along the catheter-urethra interface is the predominant source of catheter-associated bacteriuria.[67] However, periurethral cleansing with chlorhexidine solution versus water before insertion of an indwelling urinary catheter did not reduce the rate of catheter-associated bacteriuria in two different trials.[170,171] Moreover, results of large, randomized trials have shown no significant reduction in catheter-associated bacteriuria in men or women, compared with usual care (debris removal at daily baths), with one or more times daily meatal cleansing using nonantiseptic green soap or applications of povidone-iodine solution and ointment, polyantibiotic ointment or cream, or silver sulfadiazine 1% cream.[14,18,20,65] Likewise, simultaneous interventions to block bacterial entry at the urethral insertion site, catheter–drainage tube junction, and outflow tube of the drainage bag were not effective in preventing catheter-associated bacteriuria.[18] Possible reasons why enhanced meatal care has not been effective in reducing catheter-associated bacteriuria include the negative effect of increased catheter manipulation associated with the interventions, inadequate residual antiseptic activity of the topical agent, and lack of effect on the intraluminal route of infection.

Cranberry Products

Although there is conflicting evidence from randomized controlled trials about whether cranberry products are effective in reducing the risk of symptomatic UTIs in women with recurrent UTI, a Cochrane review concluded that cranberry did not significantly reduce the occurrence of symptomatic UTI in any subgroup, including people requiring catheterization.[172] Randomized, placebo-controlled studies of cranberry in doses up to 2 g daily to prevent catheter-associated bacteriuria or CAUTI in patients with neurogenic bladders are mostly negative.[168,172] The routine use of cranberry products for prevention of health care–associated UTI should be discouraged due to lack of clearly demonstrated efficacy in preventing catheter-associated ASB or CAUTI, problems of tolerance with long-term use, and cost. There are no published data on the use of cranberry products for prevention of ASB or CAUTI in catheterized adults without neurogenic bladder. More recently a double-blind, randomized, placebo-controlled trial of cranberry capsules in 185 noncatheterized women in nursing homes did not find any difference in the primary outcome of bacteriuria plus pyuria in the two arms of the study.[173]

Bladder Irrigation With Antimicrobial Therapy or Saline

Bladder irrigation with antimicrobial agents such as povidone-iodine, chlorhexidine, neomycin, or polymyxin B sulfate has shown little overall benefit in the era of closed urinary drainage.[14,20] In one demonstrative study, 187 adult patients who required short-term urinary catheterization were randomized to closed drainage with a triple-lumen, neomycin-polymyxin irrigated system, or with a double-lumen nonirrigated catheter system.[143] There was no significant difference in the rates of catheter-associated bacteriuria between the two groups, but uropathogens isolated from irrigated patients were significantly more resistant to the irrigating antimicrobial than those in the nonirrigated group. Bladder irrigation with saline or acidic solutions also does not have any clear benefit in reducing the risk of catheter blockage resulting from encrustation or in reducing symptomatic UTIs.[174] In summary, bladder irrigation does not appear to be effective in preventing or eradicating catheter-associated bacteriuria in the majority of patients with short-term or long-term indwelling catheterization, is time consuming, may damage the bladder mucosa, and may select for antimicrobial-resistant organisms. Catheter irrigation may have a role in reducing blood clots after urologic surgery, but this topic is outside the scope of this chapter.

Antimicrobial Drugs in the Drainage Bag

Once the drainage bag becomes contaminated, subsequent catheter-associated bacteriuria occurs in almost all patients who remain catheterized,[16] and positioning of the drainage tube above the level of the bladder or below the level of the collection bag is a predictor for an increased risk of catheter-associated bacteriuria.[21] Investigators have attempted to prevent catheter-associated bacteriuria by sterilizing the drainage bag, but results of randomized trials evaluating the addition of chlorhexidine, hydrogen peroxide, or povidone-iodine to the bag suggest that this intervention is not effective.[14,20,65,175] Such a strategy would not be expected to be effective if the integrity of the closed drainage system is carefully maintained because that should minimize bacterial entry into the drainage bag.

Routine Catheter Change

Urinary catheters readily develop biofilms on their inner and outer surfaces once they are inserted, and these biofilms protect uropathogens from antimicrobials and the host immune response.[56] In long-term catheterized patients, catheters are often changed routinely at periodic intervals (e.g., monthly) to reduce the risk of catheter-associated bacteriuria, as well as for aesthetic reasons. A meta-analysis found only one randomized, controlled trial of this practice; 17 men in a nursing home were randomized to catheter change only when obstructed/infected versus monthly scheduled changes as well as when necessary for obstruction/infection.[176] The trial was too small to provide reliable evidence about CAUTI or blockage. Moreover, it has been recommended that patients who experience repeated early catheter blockage should have their catheters changed every 7 to 10 days to avoid obstruction,[177] but this practice has not been evaluated in clinical trials. The practice of routine catheter change with the purpose of preventing infection or blockage, or both, is unlikely to change in the absence of data to address this issue.

Prophylactic Antimicrobial Therapy at Catheter Removal or Replacement

Fever and bacteremia can occur at the time of removal or replacement of a urethral catheter, and prophylactic antimicrobials are sometimes used to prevent such events. Among catheterized and bacteriuric women in LTCFs, transient fever is twice as common within 24 hours of catheter replacement, compared with other days.[29] Studies in chronically catheterized and bacteriuric men and women have shown that bacteremia occurs in 4% to 10% of patients after urethral catheter removal or replacement, but episodes are transient and asymptomatic.[178–180] The effect of antimicrobial prophylaxis on prevention of bacteremia is unknown. A prospective, randomized, placebo-controlled trial of antimicrobial treatment of catheter-associated ASB persisting 48 hours after removal of short-term catheters in hospitalized women reported significantly improved microbiologic and clinical outcomes at 14 days in treated women.[181] Seven (17%) of 42 women randomized to receive no therapy developed symptomatic UTI by 14 days, whereas no women in the treatment group became symptomatic. Whether these results are generalizable to current medical practice is unclear, because all had persistent bacteriuria documented at 48 hours after catheter removal; checking for bacteriuria postcatheterization is not a standard practice or even feasible in discharged patients. Screening for and eradicating postcatheterization catheter-associated ASB to prevent CAUTI is currently not recommended.

A meta-analysis of whether prophylactic antimicrobials at the time of removal of a short-term urinary catheter reduced the risk of symptomatic UTI found seven controlled studies on this topic, of which five were in surgical patients and six were randomized controlled trials.[182] Overall, a benefit was seen with prophylactic antimicrobials, with a 5.8% absolute reduction in symptomatic UTI and a risk ratio of 0.45 (95% CI, 0.28–0.72). Nevertheless, prophylactic antimicrobial agents are not routinely recommended for catheter removal or replacement because it is unclear whether these findings apply to the more general medical inpatient population, and widespread implementation of prophylactic antimicrobials at the time of catheter removal has potential to cause harm in terms of cost, side effects, and resistance.

Preclinical Strategies for CAUTI Prevention

Many novel approaches have been studied in vitro, with the goal of prevention or eradication of the catheter-associated biofilm of uropathogens.[183] Of these, mannosides—small molecule inhibitors of the type 1 pilus adhesin, FimH—seem likely to move to clinical trials in

humans and could potentially impact prevention of UTI more generally. In a study in mice, mannosides provided significant protection against uropathogenic *E. coli* catheter-associated bacteriuria by preventing bacterial invasion and shifting the *E. coli* niche primarily to the extracellular milieu.[184] Mannosides can be targeted to the fimbrial adhesins on uropathogenic *E. coli* while having less affinity for the adhesins of commensal gut *E. coli*; thus mannosides were able to deplete the mouse gut of uropathogenic *E. coli* without perturbing the commensal *E. coli*.[185] A selective agent that could reduce colonization by urinary pathogens without disrupting the gut microbiota would have obvious advantages over prophylactic antimicrobials for UTI prevention.

HEALTH CARE–ASSOCIATED ASYMPTOMATIC BACTERIURIA

Routine Screening and Treatment

Screening and treatment of ASB have not been shown to be beneficial, will select for antimicrobial resistance, and are not recommended, except in pregnant women and patients who undergo traumatic genitourinary procedures associated with mucosal bleeding.[5,186] Populations that have been extensively studied and for whom these recommendations apply include premenopausal, nonpregnant women; diabetic women; older people living in the community; elderly, institutionalized subjects; persons with SCI; and catheterized patients.[5] For example, in 35 patients undergoing long-term catheterization, a prospective randomized trial of cephalexin or no antibiotic therapy for episodes of catheter-associated ASB caused by susceptible organisms reported no differences between the two groups in incidence and prevalence of catheter-associated bacteriuria, CAUTI, or catheter obstruction in patients followed up to 44 weeks.[187] In addition, 47% of reinfecting organisms in the cephalexin group compared with 26% in the control group were highly resistant to cephalexin. Even if treatment of catheter-associated ASB was found to be useful, one study in which daily catheter urine cultures were obtained found that 60% of 25 episodes of CAUTI occurred on the same day that catheter-associated bacteriuria was first detected,[26] complicating attempts at preemptive therapy. It is not known whether eradication of catheter-associated ASB might be beneficial in reducing cross-infection or inappropriate antimicrobial usage.

Prevention of Overtreatment of Asymptomatic Bacteriuria in Health Care Settings

The greatest impact that ASB has on clinical care is probably the excessive testing and treatment done for this condition in health care settings.[188] Prevention of inappropriate treatment of ASB is probably the second most beneficial strategy for patients related to health care–associated UTI, secondary only to avoidance of unnecessary urinary catheterization. Estimates vary a bit by site of care delivery, but studies in acute-care hospitals, LTCFs, SCI clinics, and emergency departments have documented that 20% to 83% of episodes of detected ASB are treated with antimicrobials.[189–191] Thus prevention of inappropriate treatment of ASB is essential to antimicrobial stewardship in acute and long-term care settings, as endorsed by the American Board of Internal Medicine's Choosing Wisely campaign.[192,193] A positive urine culture is a powerful stimulus for subsequent use of antimicrobials, as demonstrated by surveys of practitioners and also by an innovative study in which urine culture results from the microbiology laboratory were suppressed.[194,195] A stewardship intervention that focused on the "culture of culturing,"[196] discouraging unnecessary cultures in patients without urinary-specific symptoms, successfully reduced both urine cultures and antimicrobial treatment of ASB in acute and long-term care wards of a large medical facility.[197] Unnecessary urine cultures in patients with ASB can lead to false elevation of the reported CAUTI rates, because a positive urine culture in a febrile patient must be reported to the NSHN as a CAUTI, regardless of whether the fever can be attributed to another cause.[198] The co-occurrence of fever and bacteriuria is particularly common in ICU and long-term care patients. A tertiary care academic medical center reduced CAUTI rates significantly in its ICUs through a multifaceted program that centered on the stewardship of urine culturing.[199] Likewise, emphasis on judicious use of urine cultures in a nationwide project in nursing homes was associated with a decrease in both urine cultures and CAUTI.[85] Removing unnecessary urinary catheters through CAUTI prevention efforts may have the side benefit of also reducing testing and treatment for ASB, because cloudy urine or visible sediment in the urine is a stimulus for urine cultures among nursing personnel.[194,200] A recent national study of over 4 million hospital admissions documented that 47% had a urinalysis and 27% had a urine culture during hospitalization[201]; thus there is considerable room for improvement in the stewardship of urine testing as well as stewardship of antimicrobial use for ASB.

MANAGEMENT OF HEALTH CARE–ASSOCIATED URINARY TRACT INFECTION

The issues relevant to clinical management of health care–associated UTI, particularly CAUTI, include whether the catheter should be changed prior to urine collection for culture, whether the catheter should be changed during the course of treatment, choice of drugs, duration of therapy, and when to consider complicating factors that may impair response to antimicrobials. The wide variety of underlying conditions, diverse spectrum of possible etiologic agents, and paucity of controlled clinical trials with stratification according to specific complicating factors make generalizing about clinical management of CAUTI difficult. Antimicrobials alone may not be successful, if underlying anatomic, functional, or metabolic defects are not corrected.

Urine Culture and Catheter Replacement Before Treatment

CAUTIs, especially in patients with long-term catheterization, are often polymicrobial and caused by multidrug-resistant uropathogens, so urine cultures should be obtained prior to treatment to confirm that the empirical regimen provides appropriate coverage and to allow tailoring of the regimen based on antimicrobial susceptibility data.[40,202] The culture should be obtained from a freshly placed catheter if the catheter has been in place for a few days because the catheter biofilm may result in spurious culture results.[53,54] Moreover, clinical outcomes are improved if the catheter is replaced, as shown in a prospective, randomized, controlled trial in elderly nursing home residents with long-term indwelling catheters and CAUTI. This study demonstrated that patients whose catheters had been in place for longer than 2 weeks and who underwent catheter replacement before antimicrobial treatment had significantly shorter time to improved clinical status and significantly lower rates of polymicrobial catheter-associated bacteriuria and CAUTI after therapy, compared with those who did not undergo catheter replacement.[203] These study findings support replacing the catheter and obtaining a urine culture from a freshly placed catheter before antimicrobial treatment for CAUTI if the catheter has been in place for at least 2 weeks and cannot be permanently removed.

Choice of Antimicrobial Agent

The choice of antimicrobial for empirical treatment should take into account the facility antibiogram, the patient's specific risk factors for having a multidrug-resistant urinary pathogen, the severity of illness, and the patient's underlying comorbidities.[204] Risk factors for colonization with a multidrug-resistant organism, particularly an extended-spectrum β-lactamase–producing Enterobacteriaceae, include international travel to an area endemic for resistant Enterobacteriaceae, such as southern Asia, within the prior 12 months, and receipt of antibiotics to treat traveler's diarrhea during a prior international trip.[205,206] Microbiologic data from urine cultures within the prior 2 years can be used to guide empirical antibiotic choice and improve the likelihood of choosing an antimicrobial agent effective against the current urinary pathogen.[207] Health care exposure (such as hospitalization or stay in an LTCF) and receipt of antibiotics within the prior 6 months are also risk factors for colonization with resistant organisms.[208] In nursing home residents, indwelling devices such as urinary catheters or feeding tubes are risk factors for colonization with, and thus infection by, multidrug-resistant organisms.[209] Whether the patient is able to take oral agents is also a consideration in antimicrobial choice.

A general perspective on resistance trends in CAUTI-causing organisms can also be useful, particularly if a facility-specific antibiogram is not available. Data from the NHSN between 2011 and 2014 showed a

high prevalence of multidrug-resistant phenotypes among strains causing CAUTI.[19] Thus in 2014, 34.8% of *E. coli* strains tested were resistant to fluoroquinolones and 15.5% to extended-spectrum cephalosporins (e.g., cefepime); 9.5% of *Klebsiella* spp. were resistant to carbapenems and 22.5% to extended-spectrum cephalosporins. Global studies from 2003 to 2010 of urology patients with health care–associated bacteriuria, which included ASB, found that slightly over 50% of urinary isolates were resistant to fluoroquinolones (excluding *Candida* from the possible pathogens).[210]

Appropriate empirical treatment choices require that patients be categorized on a spectrum from mild illness and ability to take oral agents to severe illness and inability to take oral agents. In all patients a urine culture should be collected before starting antimicrobials so that the antimicrobial can be changed to a more appropriate agent if necessary. Outpatients who are not severely ill can be empirically treated with oral fluoroquinolones, cephalosporins, trimethoprim-sulfamethoxazole, or amoxicillin-clavulanate (Table 302.7). Consideration should be given to providing an initial dose(s) of a broader-spectrum parenteral agent, such as ceftriaxone, a carbapenem, or an aminoglycoside, if there is concern about antimicrobial resistance, while waiting for urine culture results. Patients at low risk for multidrug resistance and who are not critically ill but who require inpatient therapy can be treated with ceftriaxone or piperacillin-tazobactam. If a patient who is not critically ill has risk factors for an extended-spectrum β-lactamase–producing organism and no prior cultures with carbapenem-resistant Enterobacteriaceae, a carbapenem should be considered for empirical therapy. Patients who are critically ill should be empirically treated with an antipseudomonal carbapenem (meropenem, imipenem, or doripenem) and vancomycin or daptomycin. Patients with prior carbapenem-resistant Enterobacteriaceae cultures who are critically ill or unable to take an oral agent, may warrant, in consultation with an infectious diseases expert, empirical use of some of the newer, expensive, and very broad-spectrum agents such as ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, or plazomicin. The antimicrobial regimen should be tailored as appropriate when the infecting strain has been identified and antimicrobial susceptibilities are known.

TABLE 302.7 Empirical Management of Catheter-Associated Urinary Tract Infection

Antimicrobial Agent and Dosing
Mild to Moderate Illness, Can Tolerate Oral Therapy (Dosage Duration: 5–10 Days)[a]
Ciprofloxacin 500 mg PO twice daily or 1 g (extended release) PO once daily[c]
Levofloxacin 750 mg PO once daily[c]
Cefpodoxime 200 mg PO q12h[d] (or other third-generation cephalosporin)
Trimethoprim-sulfamethoxazole (TMP-SMX) 160/800 mg PO q8h[e]
Amoxicillin-clavulanate immediate release 875 mg orally twice daily[d]
Severe Illness or Unable to Tolerate Oral Therapy (Dosage Duration: 5–14 Days)[b]
Ciprofloxacin 400 mg IV twice daily[c]
Levofloxacin 750 mg IV once daily[c]
Ceftriaxone 1–2 g IV once daily[d]
Cefepime 1 g IV twice daily[d]
Piperacillin-tazobactam 3.375 g IV (as piperacillin) q6h[d]
Meropenem 1 g IV q8h[d]
Imipenem-cilastatin 500 mg IV q6h[c]
Doripenem 500 mg IV q8h[d]
Ertapenem 1 g IV once daily[d]
Gentamicin 5–7 mg/kg IV once daily[e] ± ampicillin 1–2 g IV q6h[d]
Ceftolozane-tazobactam 1.5 g IV (as both drugs) q8h[d]
Ceftazidime-avibactam 2.5 g IV (as both drugs) q8h[d]
Meropenem-vaborbactam 4 g IV (as both drugs) q8h (pregnancy category unknown)
Plazomicin 15 mg/kg IV once daily[e]
In Choosing an Empirical Agent, Consider the Following:
Collect a urine culture before beginning treatment to guide subsequent therapy
Severity of illness and comorbidities—choose a broader agent for more severely ill patients or those who are immunocompromised
Antimicrobial susceptibility of bacteriuria strains within past 2 years
Antibiotic exposure within prior 6 months
Local resistance data—in some locations, fluoroquinolones and/or TMP-SMX are no longer reasonable empirical choices given high resistance levels among *E. coli*
Hospitalization or stay in a long-term care facility within past 6 months
Travel to an area with high prevalence of drug resistance in prior 12 months
Consider adding vancomycin if gram-positive organism suspected
Use a carbapenem (meropenem, imipenem, doripenem, or ertapenem) if an extended-spectrum β-lactamase strain is known or suspected
Tailor regimen based on susceptibility data, and transition to oral medications as soon as condition allows

[a]Consider a concomitant single initial dose of ceftriaxone 1 mg IV/IM, ertapenem 1 g IV/IM, meropenem 1 g IV, gentamicin 5 mg/kg IV/IM, amikacin 15 mg/kg IV/IM, or tobramycin 5 mg/kg IV/IM, particularly in febrile patients or patients at risk for being unable to follow up. Duration of therapy can be 5 days in patients receiving fluoroquinolones. Other agents should be used for 7–10 days.
[b]Consider an initial intravenous dose of a broader-spectrum agent, such as meropenem, particularly if using fluoroquinolones in a severely ill patient. Duration of therapy can be shortened to 5 days in patients receiving fluoroquinolones who have a rapid response. Other agents should be used for 7–14 days, with longer courses for patients with a slow response to therapy or with complications, such as an abscess. Doses in the table are for adults with normal renal function.
[c]Pregnancy category C—animal studies have shown an adverse effect on the fetus; use only if potential benefit justifies the potential risk to the fetus.
[d]Pregnancy category B—no clear risk to fetus based on animal or human studies, or both.
[e]Pregnancy category D—associated with human fetal risk; use only if the potential benefit justifies the potential risk to the fetus.
Modified from Hooton et al.[2] and Johnson and Russo.[204]

Duration

Few studies have been performed that evaluate duration of treatment in populations with CAUTI or other complicated UTIs. Reviews of complicated UTI have recommended treatment durations from 7 to 10 days,[14] 7 to 14 days,[40] and 7 to 21 days,[202] depending on the severity of the infection. However, it is desirable to limit the duration of treatment, especially for milder infections, to reduce the selection pressure for drug-resistant flora, especially in patients on long-term catheterization. In one small trial of women with lower urinary tract CAUTI, cure rates were comparable with a single-dose and a 10-day regimen of trimethoprim-sulfamethoxazole.[181] However, single-dose therapy was ineffective in eradicating bacteriuria in institutionalized elderly men.[211] In a randomized, double-blind, placebo-controlled trial comparing 3-day and 14-day regimens of ciprofloxacin for the treatment of mild CAUTI in 60 patients with SCI, there was no difference in clinical outcomes at long-term follow-up.[212] Most recently, clinical and microbiologic success rates following treatment were almost identical in a noninferiority study of 619 patients with acute pyelonephritis or complicated UTI treated with a 5-day course of levofloxacin or a 10-day course of ciprofloxacin.[213] These data suggest that a 7-day regimen is reasonable for most patients with CAUTI, depending on their clinical response, and that shorter regimens, such as a 5-day regimen of a urinary fluoroquinolone, are likely to be sufficient in those patients who are less severely ill, are infected with uropathogens susceptible to the antimicrobial used, and have a rapid response to treatment.

Nephrostomy Tubes and Ureteral Stents

Patients with obstruction of the ureter or ureteropelvic junction, often due to stones, malignancy, or benign strictures, may have a ureteral catheter (stent) or a percutaneous nephrostomy tube inserted. A ureteral catheter may be inserted from the bladder during cystoscopy or through a percutaneous nephrostomy into the renal pelvis and further down into the ureter, with a drainage hole at the level of the renal pelvis. J-shaped curls at catheter ends are used to keep the catheter in place. Nephrolithiasis at the at the time of tube placement can trigger either systemic inflammatory response syndrome or sepsis; the risk of both is low but higher in patients who have a preexisting UTI or infected stone.[214] Intraoperative cultures of urine from the renal pelvis and stone material can be useful to guide postprocedure antibiotics.[215] Once a percutaneous nephrostomy tube is in place, colonization of the tube and urine with bacteria and/or *Candida* occurs commonly, often with more than one organism. Usually this colonization is asymptomatic, but it can lead to fever, pyelonephritis, renal abscess, or bacteremia if drainage from the renal pelvis becomes obstructed or, less often, if instrumentation of an infected urinary tract introduces organisms into the blood stream.[216] A clinical definition of nephrostomy-associated pyelonephritis, to help distinguish an actual infection from the more

common asymptomatic colonization, is the presence of fever, costovertebral angle tenderness, or flank pain associated with a positive urine culture, or a combination of these.[217] An obstructed, infected renal pelvis can rapidly evolve into a pyonephrosis (infection of the kidney with pus in the upper collecting system), which can be complicated by renal papillary necrosis or perinephric abscess. Infected urine in the pelvis can track along the nephrostomy tube into the perinephric space and even extend down the iliacus muscle. Treatment involves immediate drainage and appropriate antimicrobial drugs. Consideration should be given to exchange of the nephrostomy tube during treatment,[218] analogous to the recommendation to change an indwelling urethral catheter during treatment of a CAUTI. Penetration of the drug into the urine is not imperative in treating pyonephrosis or perinephric abscess but is relevant to treating bacteriuria or candiduria prior to a planned urologic procedure.[219] Fluconazole and flucytosine obtain high urine concentrations, while intravenous conventional amphotericin B achieves low concentrations. Other antifungals, such as the echinocandins, may have insufficient urine concentrations to affect candiduria but are active within the renal parenchyma. Amphotericin B irrigation of the renal pelvis as 50 mg/L in sterile water has been used for prophylaxis.[219] Toxicity is minimal but efficacy is unclear. When used as prophylaxis, an antifungal or antibacterial should be begun prior to the procedure and discontinued shortly after an uncomplicated procedure (duration of 24 hours or less).[222]

FUNGAL URINARY TRACT INFECTION

Yeasts, mostly *Candida* species, are commonly isolated from the urine of catheterized patients.[223] NHSN data from 2011 to 2014 reported that *C. albicans* was the second most common organism identified in CAUTI, second only to *E. coli*; other *Candida* species (including all except *C. albicans*) ranked 10th, and *Candida glabrata* alone ranked 14th.[19] In January 2015 the NHSN surveillance definitions for CAUTI changed to exclude *Candida* species and other fungal organisms as causative agents of CAUTI, so nationwide estimates on the prevalence of fungal CAUTI will be difficult to obtain after this date.

Among patients with nosocomial funguria enrolled in a multicenter prospective surveillance study, 85% had concomitant nonfungal infections (urinary and nonurinary); 90%, previous exposure to antimicrobial agents; 83%, urinary tract drainage devices; 39%, diabetes; 38%, urinary tract abnormalities; and 22%, a malignancy—only 11% had no obvious underlying illness.[224] Although only 1.3% of the 530 patients with candiduria followed for 12 weeks had documented candidemia, the importance of comorbid conditions was reflected in the 20% mortality rate. Candiduria in itself may be a marker for severity of underlying illness, because multiple studies have shown that patients with candiduria have higher mortality rates, although not typically from *Candida* infection.[225]

Determination of the clinical significance of candiduria can be problematic because it can represent contamination of a voided specimen, colonization of catheters or stents, bladder infection, ascending kidney infection, or kidney infection associated with candidemia. Hematogenous dissemination is relatively much more likely to be the source of candiduria than is the case with bacteriuria.[226] Neither colony count thresholds nor the presence of pseudohyphae in the urine are helpful to distinguish contamination from bladder infection. In noncatheterized women with candiduria, a catheter specimen may be indicated to rule out contamination with perineal flora.[226] In the catheterized patient, pyuria is a nonspecific finding, but its absence suggests that candiduria is not causing tissue invasion.

Most health care–associated candiduria occurs in catheterized patients, and most episodes are asymptomatic. In the large prospective study of nosocomial funguria mentioned earlier, only 2% to 4% of patients had urinary symptoms,[224] although comorbidities and urinary catheterization may complicate assessment of symptoms. However, catheterized patients with candiduria may have symptoms or signs such as suprapubic or flank pain, lower abdominal discomfort associated with prostatitis, or an enlarged and tender scrotum associated with epididymo-orchitis.

Ascending infection of the kidney and disseminated candidiasis are rarely associated with candiduria and usually occur in the setting of obstruction of the urinary tract. In a retrospective study of 26 cases of candidemia associated with a well-defined urinary tract source, urinary tract abnormalities (mostly obstruction) were present in 88%, and 73% had undergone urinary tract procedures before the onset of candidemia.[227] Episodes of candidemia were brief and low grade in intensity, although two of five in-hospital deaths were attributable to candidiasis. Paired urine and blood strains of *Candida,* however, may not be the same strain, as demonstrated in a case-control study in which 52% of paired strains were different by molecular typing.[228] Other complications associated with fungal infections of the genitourinary tract include fever, fungus balls in the bladder or renal pelvis, renal and perirenal abscesses, emphysematous pyelitis or pyelonephritis, and papillary necrosis—many of these complications are more likely to occur in diabetics.

Few treatment studies have been performed in patients with candiduria,[229] and there remain questions as to whom to treat, when to treat, and how long to treat. Asymptomatic candiduria rarely requires treatment because it often resolves spontaneously, morbidity is low, and treatment is often followed by rapid recurrence and may select out for resistant organisms.[225,230] In the large prospective observational study mentioned previously, funguria cleared in 76% of 155 patients who had no specific therapy for funguria and in 35% of 116 patients who had their catheter removed as the only treatment.[224] Other studies have shown spontaneous clearance rates of candiduria ranging from 29% to 62%.[224] In a randomized, placebo-controlled trial of 316 hospitalized patients with asymptomatic or minimally symptomatic candiduria, a 2-week course of fluconazole resulted in significantly higher eradication rates than placebo (50% vs. 29%), but there was no significant difference in candiduria rates 2 weeks after completion of treatment.[230] In placebo recipients who had their catheters removed, 41% had eradication of candiduria, compared with only 20% who had their catheters replaced. Pyelonephritis, candidemia, and fungus-related death were not observed in this study. The possibility of disseminated candidiasis should be considered in all hospitalized patients with candiduria, especially in the ICU, where candidemia is common and up to 80% of persons with candidemia will have accompanying candiduria.[231] However, candidemia occurs in less than 5% of ICU patients and thus most such patients with candiduria do not have candidemia.[231] If candiduria fails to resolve despite changing the catheter or stopping antibiotics (if feasible), a more deep-seated infection should be suspected, especially in critically ill patients, and imaging of the kidneys and collecting system is indicated to look for a renal abscess, fungus ball, or other urologic abnormality that may require treatment.[231] Antifungal treatment of candiduria should be reserved for those patients who have solid evidence of infection of the kidney or collecting system or disseminated candidiasis.[231] Treatment is also indicated in asymptomatic patients with neutropenia, infants with low birth weight, and patients who will undergo urologic manipulations because these conditions have a higher association with upper tract infection or dissemination.[225,226] Recent data have raised questions as to whether asymptomatic candiduria in patients with renal transplants warrants treatment.[232] Of note, in 2000, a multicenter study in the United States reported that 43% of instances of candiduria were treated, likely reflecting overtreatment of funguria.[224]

Candiduria should be treated in symptomatic patients, and those with systemic signs or symptoms should be evaluated for disseminated infection with imaging and blood cultures. Oral fluconazole is the drug of choice for cystitis and pyelonephritis due to most species of *Candida* (but not resistant *C. glabrata, Candida krusei,* or other resistant yeasts); of note, doses adjusted for renal insufficiency may result in subtherapeutic concentrations.[229] Amphotericin B and flucytosine can be used for *C. glabrata* resistant to fluconazole, and amphotericin B is the recommended agent for *C. krusei.*[225] Other azoles that could serve as alternative choices for resistant isolates, including itraconazole, voriconazole, and posaconazole, are not recommended for *Candida* UTI because of minimal excretion into the urine, even though they achieve antifungal activity in renal parenchyma.[231] Systemic amphotericin B deoxycholate is no more effective than fluconazole for susceptible strains, and bladder irrigation with amphotericin B deoxycholate is rarely used. Lipid formulations of amphotericin B may not be the first choice for *Candida* UTI because of presumed low concentrations of the drug in renal tissue. Failure of the lipid complex formulation of amphotericin B therapy has

been described in the treatment of *Candida* pyelonephritis in experimental animals and patients.[225] Echinocandins are minimally excreted and should not be considered first-line agents for candiduria. However, case reports suggest that caspofungin and micafungin may be effective in patients with *C. glabrata*–associated UTI.[233,234] Even with apparently successful local or systemic antifungal therapy for candiduria, relapse is frequent, and this likelihood is increased by continued use of a urinary catheter. Persistent candiduria, especially in immunocompromised patients, warrants radiologic imaging of the kidneys to evaluate for hydronephrosis, fungal bezoars (common in critically ill neonates[224]), or perinephric abscesses associated with ascending infection.

SUMMARY

Health care–associated bacteriuria and candiduria are common, mostly associated with urinary catheterization, and usually asymptomatic. Whereas any symptomatic UTI should be treated, published data do not support routine screening to detect health care–associated bacteriuria or candiduria in asymptomatic patients because treatment does not appear to alter the natural course of infection and an increase in antimicrobial resistance often results. However, among asymptomatic patients with bacteriuria or funguria, we need a better understanding as to who has upper tract involvement or tissue invasion, how these affect the clinical course, and thus which patients, if any, might benefit from screening and treatment. The quality of clinical trials needs to be improved because many are nonrandomized and underpowered and use nonspecific terminology and poorly described methodology. Studies of interventions to prevent catheter-associated bacteriuria need to address whether they prevent not only CAUTI (which many have not), but also whether prevention of catheter-associated ASB reduces inappropriate antimicrobial use, bacteremia, and cross-infection.

Strategies that are effective for prevention of catheter-associated bacteriuria are likely to also prevent catheter-associated candiduria. The most effective way to reduce health care–associated UTIs is to reduce urinary catheterization by restricting use to patients who have clear indications and by removing the catheter as soon as it is no longer needed. Implementation of strategies to reduce catheterization is likely to have more impact on catheter-associated bacteriuria than implementation of other strategies addressed in this chapter. However, use of multiple infection control techniques and strategies simultaneously (called *bundling*) likely offers the best opportunity to reduce the morbidity and mortality related to health care–associated infections.[235] In those patients who do require urinary catheterization, an effective stewardship program for both urine testing and antimicrobial treatment in asymptomatic patients offers potential benefits to patients and the health care system. More research is needed in terms of how to best implement effective stewardship programs for bacteriuria.

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The complete reference list is available online at Expert Consult.

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303 Health Care–Acquired Hepatitis

Mini Kamboj and Kent A. Sepkowitz

SHORT VIEW SUMMARY

Definition
- Viral hepatitis can be acquired by patients or health care workers (HCWs) during the process of health care delivery.

Epidemiology
- Transmission between patients and from patient to HCW or HCW to patient is rare, but the risk remains. Dialysis patients and workers are at particular risk, especially for hepatitis C virus (HCV) and, if unvaccinated, for hepatitis B virus (HBV).
- Increasingly, transmissions to patients are seen in long-term care settings and can be traced to inappropriate use of blood glucose monitoring devices.
- Transfusion-based risk of hepatitis E varies by geographic region. Implementation of universal screening of blood products varies accordingly.

Diagnosis
- Identification of transmission is difficult unless a cluster of cases occurs.
- Most investigations are conducted in conjunction with public health authorities.
- Use of a genotype to determine homology is useful in investigation.

Postexposure Treatment
- Hepatitis A: Vaccine is the preferred approach for postexposure prophylaxis (PEP) of otherwise healthy individuals. Vaccine and immunoglobulin are recommended for those with immunocompromising or chronic liver conditions.
- Hepatitis B: Give hepatitis B immune globulin (HBIG) to all exposed nonimmune persons (patients or HCWs) with or without initiation of vaccine series. The role of antivirals has not been determined.
- Hepatitis C: Monitor and treat only if the exposed person develops evidence of acute infection. Use of direct-acting antiviral (DAA) therapy has not been studied in this context.

Vaccination
- Hepatitis A vaccine is not routinely recommended for HCWs.
- Hepatitis B vaccine or formal declination is mandated for HCWs in the United States. Rapid decrease in measured antibody levels within months of immunization can occur despite persistence of immune protection. Booster doses are not recommended.
- No vaccine is available for HCV.

HISTORICAL BACKGROUND

The potential for bloodborne transmission of hepatitis B first was noted in 1885, when Lurman described jaundice in factory workers who had received smallpox vaccine prepared from "human lymph."[1] More reports appeared in the subsequent decades as use of vaccines derived from human serum became more common.[2] In addition, more frequent use of phlebotomy equipment,[3] insulin therapy,[4] and intramuscular injection of antibiotics all led to small outbreaks of jaundice, which were ascribed to a transmissible "icterogenic" agent.

By the late 1940s, studies to clarify the modes of transmission were undertaken. Central to these was the use of human volunteers, who were given putatively infectious material intradermally, intranasally, or by ingestion of feces, and then observed for development of jaundice.[2,5–7] From these landmark reports arose our current understanding of the basic principles of transmission of infectious hepatitis (hepatitis A) and serum hepatitis (hepatitis B).

The first report of occupational disease in health care workers (HCWs) was provided by Leibowitz and colleagues,[8] who described jaundice in a blood bank nurse with numerous needle pricks on her hands and fingers. A spate of similar reports followed, describing occupationally acquired hepatitis among nurses, blood bank workers, phlebotomists, house staff, and others.[9,10] Soon, the workers' compensation boards of certain states ruled that viral hepatitis was a compensable occupational hazard. Improved understanding of routes of transmission, more comprehensive and rigorous infection control including needle disposal, and, for hepatitis B, vaccination of workers at risk have helped to decrease, but not eliminate, this occupational risk. A corollary risk, that of transmission of infection from infected HCWs, particularly surgeons, to nonimmune patients, has been described for hepatitis B[11,12] and hepatitis C.[13]

CURRENT EPIDEMIOLOGY OF HEALTH CARE–ASSOCIATED HEPATITIS B AND C OUTBREAKS IN THE UNITED STATES

A health care–associated outbreak of hepatitis is defined as two or more cases that are epidemiologically and/or genetically linked.[14,15] Since 2008, The Centers for Disease Control and Prevention (CDC) has maintained a Web-based inventory of health care–associated cases and outbreaks of hepatitis B and C.[16] This source described 59 outbreaks affecting more than 450 people that were investigated between 2008 and 2016 (Fig. 303.1). In addition, 18 (15 hepatitis C and 3 hepatitis B) sporadic cases of patient-to-patient health care–associated transmission of hepatitis B and C were recognized during this time.

Health care–associated outbreaks of hepatitis mostly have been recognized in nonhospital settings, with a growing trend in long-term care facilities[17] and ambulatory areas,[18] especially outpatient hemodialysis units.[16] Practices associated with transmission of hepatitis reveal a shift in etiology: syringe reuse and needlestick injuries have less commonly been the cause, and more cases have been traced to other health care exposures.[19] These include improper use of blood glucose monitoring fingerstick devices on multiple patients,[20,21] contamination of saline flush and multidose vials,[18] and breaches in disinfection and sterilization of medical equipment.[19,22]

Hemodialysis-related outbreaks of hepatitis C continue to occur, with most being attributed to environmental contamination or unsafe practices during vascular access or medication preparation or administration.[16,23] Diversion of medication, wherein a practitioner personally administers an intravenous narcotic and then reuses the remainder of the vial of medication or the needle in a patient or patients, is also increasingly recognized as a source of transmission.[24] At least five

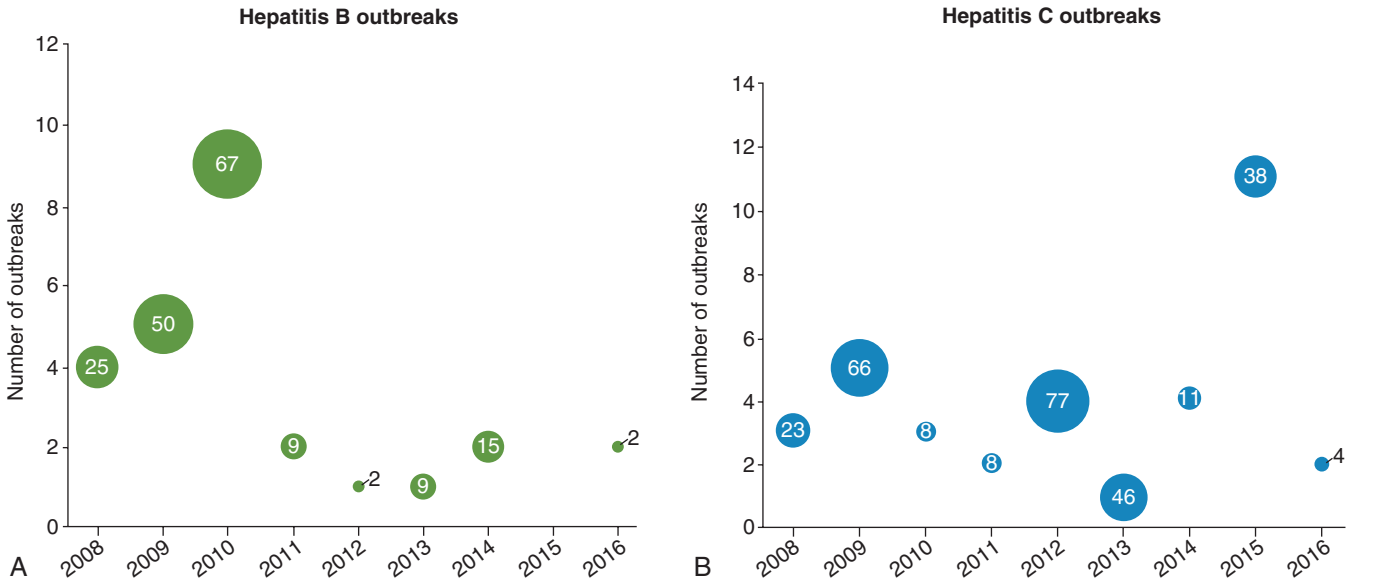

FIG. 303.1 (A and B) Hepatitis B and C outbreaks investigated between 2008 and 2016.

TABLE 303.1 Risk of Transmission, Prevention, and Postexposure Management of Health Care Workers With Occupational Exposure to Hepatitis Viruses

HEPATITIS	RATE[a]	PREVENTION	POSTEXPOSURE MANAGEMENT
A	10%–30%	Vaccine not recommended routinely for HCWs except in outbreak setting	Vaccine within 2 weeks of exposure. Immunoglobulin plus vaccine may be considered for HCWs with chronic liver or immunocompromising conditions.
B	HBeAg⁻ source: 3% HBeAg⁺ source: 22%–31%	HBV vaccination	HCWs with previous response to vaccine need no additional postexposure treatment regardless of level of exposure and time since vaccination. HCWs with no history of vaccination or nonresponders should receive HBIG and vaccine (for those with no history) as soon as possible after the exposure. HCWs with unknown response after primary series should have anti-HBs titers checked. • Levels <10 mIU/mL: Give HBIG × 1 and revaccinate • No further treatment for immune titers If anti HBs titers cannot be readily obtained, first dose of HBIG should be administered. The role of antivirals is not defined.
C	3%	Immune globulin not recommended; see Chapter 154 for treatment	No role for direct-acting antivirals. Immediate baseline testing for hepatitis C antibody, then HCV RNA if antibody positive. If source patient confirmed with HCV infection, or with unknown status, repeat HCV RNA three weeks after exposure.
Delta	Unknown; outbreaks described only in dialysis units	HBV vaccination	Segregate HBsAg⁺ dialysis patients by delta antibody status.
E	Unknown	Standard precautions	

[a]Rate of transmission from outbreak or needlestick exposure.
HBeAg, hepatitis B e antigen; *HBIG,* hepatitis B immune globulin; *HBsAg,* hepatitis B surface antigen; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HCWs,* health care workers.

diversion-related outbreaks have been recognized in the United States since 2009,[16] including one from a traveling medical technician that spread across eight states, resulting in over 11,000 exposed individuals with 45 confirmed infections. This outbreak led to a criminal conviction of the source HCW.[25]

Fecal-Oral Transmission

Hepatitis A

HCWs are not considered to be at a higher occupational risk for hepatitis A, because nosocomial outbreaks and transmission from patient to care provider have been infrequent. The Advisory Committee on Immunization Practices (ACIP) does not recommend routine vaccination of HCWs to protect against hepatitis A.[26] The rare reports of nosocomial transmission have largely occurred in pediatric units and nurseries.[27,28] The preponderance of hepatitis A outbreak reports in neonatal settings is due to the asymptomatic nature of infection in infants and young children and prolonged shedding[29]; the disease in index cases often goes unrecognized until secondary cases in adult contacts have occurred.[30] Rare outbreaks in adults have been related to high physical dependency or diarrhea or fecal incontinence.[31–35]

Although dominantly an enterically transmitted infection, hepatitis A can rarely be acquired via blood and platelet transfusion from donors with incubating infection[36]; in addition, a single transplant-associated case has also been described. Tertiary transmission of hepatitis A from a child who had initially contracted hepatitis A via multi–visceral organ transplant eventually led to infection in 2 of 42 home health nurses who provided direct care to the child.[37,38]

Postexposure prophylaxis (PEP) by administration of intramuscular immune globulin to contacts has been used effectively for many years (Table 303.1).[39] Although not specifically assessed in health care–related exposures, vaccination within 2 weeks has been shown to be 80% to 90% effective in preventing clinical hepatitis A among immunocompetent

TABLE 303.2 Country-Specific Rates of Hepatitis E RNA Prevalence Among Screened Blood Products and Associated Risk of Transmission

COUNTRY (YEAR)	UNIT SCREENED	SAMPLES SCREENED	HEV RNA PREVALENCE	POSTTRANSFUSION HEV IN RECIPIENT	COMMENT
Netherlands (2013)	Mini-pools	59,474	0.076%	NA	Estimated duration of viremia in donors = 68 days
Germany (2012)	Mini-pools	16,125	0.08%	NA	
Spain (2015)	Individual	9998	0.03%	NA	
Denmark (2016)	Individual	25,637	0.04%	7/11 recipients without detectable viremia	Low copy numbers in donors (13 IU/mL)
Ireland (2016)	Individual	24,985	0.02%	NA	Universal screening implemented
France (2014)	Mini-pools	53,234	0.045%	NA	
United Kingdom (2014)	Mini-pools	225,000	0.035%	42% attack rate	Universal screening implemented
Australia (2017)	Pools	74,131	0.001%		
United States (2013)	Individual	1930	0%	No transmission	
United States (2016)	Individual	18,829	0.01%	NA	Low copy numbers in positive donors
United States (2017)	Mini-pools	128,028	0.002%	NA	Type 3a infections with low copy numbers

HEV, Hepatitis E virus; *NA,* not applicable.

adults younger than 40 years.[40] Vaccine was successfully used in two eligible nurses in the transplant recipient–related outbreak.[37] Since 2000, Canadian guidelines have routinely recommended vaccine as the preferred PEP for nonimmunocompromised patients older than 1 year. In United Kingdom, immune globulin is recommended to be given in conjunction with vaccine only for healthy adults older than 50 years, and those with chronic liver disease or an immunocompromising condition, regardless of age.[41]

Hepatitis E

First identified as a cause of acute hepatitis in Kashmir, India, hepatitis E virus (HEV) is primarily transmitted via contaminated water. The virus has caused several large-scale outbreaks among refugees and other displaced populations. Person-to-person spread among household contacts has been demonstrated only in resource-constrained settings, where transmission is attributed to poor sanitation and to communal hand-washing and eating practices.[42–44]

In Europe, indigenous infection from zoonotic contact or acquisition via meat products (undercooked pork, pork liver sausage, game meat, and shellfish) is on the rise, with predominantly genotype 3a infections.[45] Currently in Europe, infections due to HEV are at least as common as hepatitis A among patients hospitalized with acute hepatitis.[46] Approximately half of all HEV cases are autochthonous in origin[45–47] because risk of acquisition is strongly influenced by regional farming and dietary practices. Certain areas in eastern Japan, southwestern France, and the Netherlands have exceedingly high seropositivity rates as a result of these factors. A detailed description of the epidemiology of hepatitis E can be found in Chapter 178.

Seroprevalence of Hepatitis E in Developed Countries and Risk of Bloodborne Transmission

Seroprevalence of hepatitis E in the United States is estimated to be around 6.25%, with the highest rates in the Midwest.[48] Genotypes 3 and 4 prevail among the sporadic locally acquired infections. Based on population estimates from the National Health and Nutrition Examination Survey (NHANES), seroprevalence rates in US adults older than 30 years declined from 20% (1988–1994) to 8.4% (2009–2010); a decrease in seropositivity was seen among all age groups within this time period. Overall, anti-HEV immunoglobulin G (IgG) prevalence decreased from 9.6% to 5.2%.[49,50]

Several assessments of blood donors in the United States have concluded that the transmission risk of HEV is minimal.[48,51,52] Screening of blood products for HEV is not currently recommended in the United States. Blood donor screening data from several European countries have also demonstrated variable rates of hepatitis E viremia, ranging from 0.02% to 0.08% with an associated transmission risk of 0.04% (Table 303.2).[53–56] Some European countries have adopted universal screening of blood products for hepatitis E. A detailed discussion on this topic can be found in Chapter 304.

Other Nosocomial Transmission

Non–transfusion-related nosocomial HEV transmission is rare; an outbreak in Pakistan attributed to sharing of parenteral equipment affected 18 individuals, with 7 confirmed cases.[57] A single case of patient-to-patient spread of hepatitis E via contaminated hospital environment was suspected in a French hospital in which the donor patient with detectable virus in blood and stool had an overlapping stay with the case patient, who developed acute infection 3 weeks later. The strains were closely related by genotypic analysis.[58]

Hepatitis B

Epidemiology

Hepatitis B was the first bloodborne disease recognized to pose an occupational hazard.[8–10] In the prevaccine era, the prevalence of hepatitis B virus (HBV) among HCWs was 10-fold greater than in the general population. An early review found a preponderance of cases among pathologists, laboratory workers, and blood bank workers.[10] Later studies added dentists, physicians, nurses, and laboratory and dialysis staff to the list of HCWs with increased risk.[9,10,59–62]

Vaccine to prevent HBV infection became available in the United States in 1982. Introduction of the currently used recombinant HBV vaccine improved vaccine acceptance. Since 1991, it has been recommended as a universal childhood vaccination. In 1987, concern about occupational acquisition of human immunodeficiency virus (HIV) led the US Department of Labor, in conjunction with the Department of Health and Human Services, to recommend universal precautions to protect against exposure to body fluids.[63] Four years later, the Occupational Safety and Health Administration published the federal Bloodborne Pathogens Standard, which went into effect in early 1992.[64] This document mandated that HCWs with potential exposure to blood or other potentially infectious materials should be offered the hepatitis B vaccine series free of charge, should demonstrate immunity to hepatitis B, or should formally decline vaccination. In order to identify nonresponders and to intervene early, postvaccination serologic testing is recommended for HCWs prone to blood and body fluid exposures. Compliance with these recommendations has resulted in a 98% reduction in occupationally acquired hepatitis B,[65,66] although rare cases continue to occur. Based on a survey conducted by the CDC between 2005 and 2010, 203 cases of hepatitis B were reported among HCWs; among these, only 40% were possibly related to occupational exposures. Complete vaccination

with three or more doses could be confirmed for 35 HCWs infected with hepatitis B, 1 had immune titers, and others were nonresponders or without additional information.[66]

Incidence After Exposure

The risk of transmission from a single needlestick exposure varies according to the hepatitis B e antigen (HBeAg) status of the source case. The risk of developing clinical hepatitis ranges from 1% to 6% for HBeAg-negative blood to 22% to 31% for HBeAg-positive blood (see Table 303.1).[66,67] In addition, transmission from a viremic hepatitis B surface antigen (HBsAg)–negative patient, even with low viral burden, may occur.[68]

Reported Transmissions

Worker-to-patient transmission. Over the past several decades, dozens of episodes involving HCW-to-patient transmission of hepatitis B have been described, resulting in hundreds of secondary cases (range, 1–55 secondary cases per source case).[11,12,66,68–73] In a series of 10 clusters reported from the United Kingdom, the transmission rate ranged from 0.3% to 9%.[12,69] At least 42 of the 47 HCWs involved were dentists or surgeons. In a majority of the cases, no obvious infection-control breaches or overt percutaneous exposures were recognized. Lack of glove use during oral surgery and chronic skin conditions on the surgeon's exposed hands have been proposed as contributing factors in some of the older reports. No cases of dentist-to-patient transmission have been reported since 1987, which suggests the effectiveness of standard precautions and routine vaccination of HCWs,[69] although lack of case clustering may prevent recognition of sporadic transmission events.[73]

In the United States, the last documented HBV transmission from a surgeon to patients occurred in 2009.[74] The source was an orthopedic surgeon with previously unrecognized infection and an HBV DNA level of almost 18 million IU/mL. Of note, he had twice received a three-dose HBV vaccination series but had not been evaluated for chronic HBV infection, despite failure to respond to the vaccine and recent immigration from a country with high rates of HBV. The last reported transmission during a surgical procedure occurred in Japan from an HBeAg-positive gynecologic surgeon with high level of virus in serum, sweat, and saliva.[75] In a classic outbreak from the 1990s,[11] 19 (13%) of 144 susceptible patients operated on by an HBeAg-positive thoracic surgery resident developed acute hepatitis B infection despite appropriate infection-control measures. Thirteen available isolates, including the surgeon's, were identical when compared by means of genetic analysis. Examination of the resident's surgical technique suggested that small cuts in his fingers, sustained while he tied sutures, resulted in entry of his blood into patients' wounds. Of note, the surgeon had declined hepatitis B vaccine 2 years earlier and then had become infected as the result of an occupational exposure.

In most but not all of the reported outbreaks, the source worker was HBeAg positive. However, in one series, four HBeAg-negative surgeons all transmitted disease.[12] The cases occurred in England, where restriction of HBeAg-positive surgeons (principally cardiothoracic, gynecologic, orthopedic, and abdominal) is strictly enforced. Confirmation of transmission was aided by HBV DNA sequencing of both the putative source and secondary cases.

In response to concerns around HCW-to-patient transmission, in 1991, the CDC promulgated recommendations for preventing transmission of HIV and HBV to patients during exposure-prone invasive procedures, which were modified by non-CDC experts in 2012 and are currently in revision.[66,68,76] These and other guidelines addressing infected HCWs have attempted to balance patient safety against a worker's right to privacy. Most US and European guidelines now recommend that workers performing exposure-prone procedures maintain a low HBV DNA level, usually less than 1000 IU/mL.[76]

Patient-to-worker transmission. Widespread transmission from a single patient to several HCWs is rare. In one instance, a patient in the preclinical window period for hepatitis B sustained severe trauma and underwent several operations.[77] At least four HCWs, including nurses and physicians, developed acute hepatitis temporally consistent with transmission from this patient. As with worker-to-patient transmission, clustered cases lead to the identification of transmission more readily than individual transmissions. Other instances of transmission may go undetected and unreported.

Dialysis setting. For many years, dialysis patients and staff were at high risk for occupational acquisition of hepatitis B, given their high frequency of sharps injury or mucocutaneous exposure (5 instances per 10,000 dialysis procedures[78]), the high titers of HBV in blood (≥10^9/mL), and the ability of HBV to survive well in the environment[16,79] However, with segregation of patients by room, staff, and machine according to surface antigen (HBsAg) status; institution of active vaccination programs; monthly serologic testing of susceptible patients; and attention to disinfection, equipment, and cleaning procedures, this rate has decreased sharply.[16,59,79–81] When rates were compared from a classic study conducted before the availability of vaccine,[59,81] the incidence of new HBsAg among patients was found to have decreased from 3% to 0.05%, and the prevalence from 7.8% to 0.9%. During the same period, vaccination coverage of staff increased to 90% and HCW HBV incidence decreased from 2.6% to less than 0.5%. In US dialysis centers in 2002, the prevalence and incidence of HBV among dialysis patients had remained steady at 1% and 0.12%, respectively; 56% of patients and 90% of staff had been vaccinated.[59]

Despite these gains, transmission continues in centers that fail to identify HBV-infected patients, share staff and equipment, or fail to vaccinate susceptible patients.[16,79] Medication preparation close to treatment areas, infection-control lapses during vascular access, and inability to separate clean and contaminated environments continue to provide reservoirs of health care–based transmission of HBV.[16,59,79] Nonimmune persons undergoing hemodialysis should be vaccinated with high-dose or double-dose vaccine formulations.[80] Serologic assessment of postvaccination titers 1 to 2 months after completion of the series is recommended. The determination for booster doses is made on an annual basis, after anti-HBs level assessment, and with the goal of maintaining titers over 10 mIU/mL. Clinically significant hepatitis has been reported in patients on dialysis who achieve a minimum protective antibody level but with subsequent decline.[82] The approach for nonresponders is similar to others (refer to section "Postexposure Management").

Other nosocomial transmissions. In some countries, nosocomial transmission due to unsafe practices continues to account for a substantial proportion of overall hepatitis B cases.[83,84] In US and UK health care settings, transmission related to blood glucose monitoring devices,[20,85] endoscopy equipment, reuse of single-dose vials in podiatry care, and jet injections has been increasingly reported,[a] especially in long-term care.[15,16] This group of exposures now account for up to 37% of all health care–associated acquisition of HBV among older adults in the United States.[86] In addition, patients (so-called medical tourists) who for financial or other reasons receive care in countries with a high prevalence of HBV may unknowingly invite the additional risk of virus acquisition.[88] Hepatitis B was transmitted to a patient operated on by the same oral surgeon and assistants who had performed tooth extraction in an HBeAg-positive patient 2 hours before. Thorough review of the case failed to disclose any overt infection-control breach.[14]

Vaccine Acceptance and Response Among Health Care Workers, and Duration of Immunity

The National Health Interview Survey (NHIS) estimated vaccination coverage of 63.8% for health care personnel in 2011.[89] Three out of every four HCWs with direct patient contact are vaccinated against hepatitis B. Approximately 88% of individuals achieve seroprotective titers after vaccination; suboptimal responses are related to older age, obesity, and smoking.[90] Among those who do not develop protective titers after the primary series (<10 mIU/mL), cumulative response on revaccination with additional three doses approaches 70%.[66] Preemployment serologic testing and HBsAg testing are recommended for HCWs from geographic regions with prevalence rates of ≥2% regardless of vaccination status, and for those with known nonresponse to vaccine previously.[66]

Knowledge of serostatus aids in decisions to revaccinate and postexposure management. Therefore, serologic testing is routinely recommended for those with an anticipated risk of occupational exposure.

[a]References 15, 16, 20, 21, 86, 87.

If protective levels are achieved 1 to 2 months after immunization, no further testing is necessary regardless of future exposures. For vaccinated HCWs with anti-HBs <10 mIU/mL immediately after completion, an additional dose or revaccination with the three-dose series is recommended. Any additional immunization beyond the sixth dose is not recommended for those without a response to two complete series. These individuals should be considered susceptible in the event of a significant exposure, and hepatitis B immune globulin (HBIG) administered promptly.[91,92]

It is well recognized that antibody response wanes after completion of primary immunization series, regardless of initial response.[93,94] The most precipitous drop in titers occurs in the years immediately after vaccination. In longitudinal reports spanning across at least 2 decades, persons with declining antibody level (to <10 mIU/mL) remain protected.[95,96] Age at the time of vaccination and higher anti-HBs titers after vaccination correlate with duration of measurable immune titers.[93] In the longest cohort of vaccinees, including children and adults from 12 Alaskan communities, followed over a period of 30 years after primary hepatitis B vaccination series, approximately half of the individuals showed loss of measured protective antibody. Despite this, anamnestic response after booster challenge could be elicited in the vast majority (89%), confirming a protective response on exposure to HBV.[95] For the vaccinees without demonstrable anamnestic response, future susceptibility to acute or chronic HBV disease remains unclear.

Other studies conducted in areas of high endemicity have demonstrated breakthrough infection among vaccine responders marked by the development of antibodies against hepatitis B core protein.[93,97] HCWs vaccinated as adults also demonstrate durable antibody response for up to 28 years after primary immunization.[98] Loss of protective titers was detected in 22% and did not correlate with interval since vaccination. Among those given a booster dose, 94% developed adequate levels. Immunized HCWs with occupational exposure to HBV have been shown to develop core and polymerase-specific CD8 (+) T-cell responses akin to acquired immunity after HBV infection.[99] These data collectively suggest that newly infected vaccinees typically develop subclinical disease and that vaccine-induced immunity confers protection from chronic HBsAg carriage and clinical hepatitis, but may not entirely prevent infection. Based on this, the CDC does not recommend routine revaccination of otherwise healthy HCWs.[66]

In November 2017 a recombinant HPV vaccine with a novel CpG adjuvant was marketed for persons at least 18 years of age and is given as two doses 1 month apart. Immunogenicity is reported at least as good as the earlier two recombinant HBV vaccines. The vaccine, Heplisav-B, was recommended as an option in 2018 by the ACIP and may offer convenience for HCWs over the prior three-dose 16 weeks schedule.[99a]

Postexposure Management

Management in exposed or susceptible workers has been well summarized elsewhere[26,66] (see Table 303.1 and Chapter 145). Treatment should ideally be administered within 24 hours after exposure. Intramuscular HBIG was the original intervention for PEP.[66,100] It is still used, in conjunction with initiation of a vaccine series, for management after exposure in unvaccinated persons and vaccine nonresponders. For vaccine responders, no postexposure intervention is required, regardless of the HBsAg or HBeAg status of the source. Vaccinated persons with an unknown response to vaccine should have their antibody titer checked immediately after exposure and should be treated according to the result (see Table 303.1). If HBIG and vaccine are indicated, titers should be checked at least 3 months after HBIG after antibody levels from passive immunization have waned, in order to accurately assess response to the vaccine. Nonresponders to hepatitis B vaccine should receive a second dose of HBIG 1 month later (HBIG dose, 0.06 mL/kg or 5.0 mL for adults).[66,100] Vaccines and HBIG may be given at the same time but should be administered with separate needles and syringes and at different anatomic sites. Plain immune globulin does not contain sufficient titers of HBIG and should not be considered an acceptable alternative. The role of antiviral agents such as lamivudine, entecavir, and tenofovir in the management of nosocomial exposure has not been determined.

The best long-term management for the hepatitis B vaccine nonresponder is not known. All nonresponders to the first three-dose series should be tested for evidence of HBsAg if not already done at the time of hire.

Hepatitis C

Seroprevalence

Most[78,101] series suggest that many HCWs with increased risk for hepatitis B, including dialysis workers, laboratory workers, surgeons, nurses, and workers with the mentally impaired, have no increase in hepatitis C virus (HCV) seroprevalence. The overall prevalence of HCV among persons receiving dialysis is approximately 8% (nearly fivefold higher than the general population) and among dialysis center staff is around 1.7% (same as US general population).[59] Some studies, including a recent meta-analysis, have suggested that medical and laboratory staff and dental health workers may have an elevated risk.[102,103]

Incidence After Occupational Exposure

Percutaneous exposure is the most common mode of health care–associated transmission. Risk is greatest with deep injuries from a hollow-bore needle that has been used to access the source patient's artery or vein.[104] Rare cases of acquisition from blood splash on the conjunctiva have been reported. HCV after exposure to body fluids other than blood or via contaminated environment has not been conclusively documented. Seroconversion occurs in 0% to 10% of nonimmune HCWs who sustain needlesticks from a source patient with hepatitis C.[26,78,105–108] Maternal-fetal transmission rates are similar (5%–9%). Rates may vary because of differences in the diagnostic test used (antibody or HCV RNA) and nature of evaluated exposures. The highest transmission rate (10%) was from a study in which HCV RNA was used to detect infection in exposed workers.[106,108] This high rate has not been duplicated, and most studies have placed the transmission rate at less than 3%. In a large case series from the United Kingdom, 626 percutaneous HCV exposures to blood or bloodstained fluids occurred from 1997 to 2007, resulting in a seroconversion rate of 2.2%.[104] Existing evidence supports a correlation between HCV RNA level in the source patient's blood and higher risk of transmission.[109] This association has not been established for other body fluids. A report of simultaneous transmission of HCV and HIV from a single needlestick was remarkable for the delayed time to seroconversion against each virus and the fulminant, fatal course of the HCV infection.[110] This phenomenon appears to be extremely rare.

Reported Transmissions

Worker-to-patient transmission. HCWs have transmitted HCV to patients on several occasions, sometimes after acquiring their own infection from a different patient.[111–113] A cardiac surgeon transmitted HCV to at least 5 of 222 patients; all infected patients underwent valve replacement.[13] Molecular analysis showed significant homology between the surgeon's and the patients' viruses. The surgeon was treated until his HCV RNA level became undetectable. At that point, he was allowed to resume performing surgery.

Additional isolated cases of HCV transmission during thoracic, cardiac, and orthopedic surgery have been reported.[114] In the UK experience, look-back investigations covering exposure-prone procedures from an HCV-infected source have yielded a transmission rate of 0.13% among susceptible patients. In Germany, an anesthesiologist at an outpatient gynecology clinic transmitted HCV to three patients during minor procedures on the same day; the precise cause of this cluster could not be determined. Additional testing did not reveal transmission events originating from the anesthesiologist.[115]

HCV infection in two Scottish tourists was traced back to an HCW; the two patients had received hemodialysis during a holiday in Spain.[116] Most other transmissions involving nonsurgical personnel have occurred from drug diversion practices through cross-contamination of equipment and supplies by an HCV-infected HCW.[117] In the last decade, three separate outbreaks in the United States, two from different radiology technicians and one from a nurse anesthetist, led to spread of HCV infection in 68 individuals.[24,25,118] Ensuring secure access, tracking mechanisms, and safe administration of narcotics are

essential to eliminate HCV and other infection risks associated with drug diversion.

Transmission in dialysis setting. Despite improvements, transmission of HCV remains a substantial problem for dialysis patients throughout the world. In most series, HCV seroprevalence among dialysis patients is 2- to 10-fold higher than in the general population. The CDC reported regularly on dialysis-associated diseases in the United States through 2002. In their last survey, which included 96% of all US centers, representing more than 260,000 patients and 58,000 staff members, 63% of the institutions routinely tested patients for HCV, an increase from 39% in 1995.[59] HCV seroprevalence is even higher in South American, African, and Asian dialysis centers, exceeding 40% in some areas. Prevalence estimates have ranged from 5% to 10% in Europe and the United States.[59,119] The prevalence of HCV among peritoneal dialysis patients, in contrast, is not elevated.[120]

Because of their compromised immune response, dialysis patients may not mount a significant antibody response to HCV; therefore, concurrent testing with HCV RNA is recommended. Studies done among hemodialysis patients from Germany and France with an overall HCV prevalence of 7% found that 0.6% to 12.3% of HCV-infected patients were viremic without detectable antibody with third-generation assays.[121,122] Cost remains a prohibiting factor for the routine use of HCV RNA in resource-limited settings. Select hepatitis C core antigen assays have demonstrated comparable diagnostic performance to nucleic acid amplification testing (NAAT) at HCV RNA levels >3000 IU/mL and may become an affordable option for broader screening in these areas.[123] The current recommendation by the CDC, endorsed by the National Kidney Foundation, is monthly measurement of alanine aminotransferase (ALT) levels combined with semiannual anti-HCV testing for susceptible dialysis patients as a more cost-effective approach.

Early reports demonstrated that nosocomial spread was caused by overt interruptions in infection control,[124] and one more recent report suggested that HCV was transmitted by contaminated hands of HCWs, demonstrating that the problem persists.[125,126] In most newer reports, however, obvious breaches of infection control in dialysis centers and elsewhere have not been identified, suggesting that either subtle interruptions are responsible for spread or that HCV transmission is incompletely understood.[16] Supporting the latter interpretation, some studies using genotypic analysis have not demonstrated homology among persons treated in the same or adjacent beds; rather, linked cases have been located throughout the dialysis center, suggesting widely dispersed transmission by means of an uncertain mechanism.[127]

Recognized risk factors for acquisition of HCV include blood transfusion and the number of months for which a patient has required dialysis,[128] with the latter being more significant. The risk of blood transfusion has been reduced by the use of erythropoietin. Possible explanations for the association of acquisition of HCV with duration of dialysis include sharing of dialysis machines by HCV-infected and uninfected patients and reprocessing of dialyzers from HCV-infected patients.[129,130] However, the current cleaning standards are extremely high, and the CDC therefore does not recommend against sharing machines or against reusing dialysis filters.[59]

Some researchers have advocated keeping HCV-infected dialysis patients together, similar to the successful approach taken with HBV-infected patients. The CDC, however, does not advocate this approach because of the lack of sensitivity of the anti-HCV test, which means that not all infectious persons would be isolated, and because of the risk of superinfection or reinfection for those already infected.[59] Refer to Chapter 154 for further discussion.

Solid tumor transplantation. Transplantation of HCV-infected organs into HCV-infected or HCV-uninfected hosts is sometimes necessary.[131] However, almost all susceptible recipients of HCV-positive organs eventually develop HCV infection,[132] which may be severe.[132,133] In most series, however, no adverse effect on overall survival of patients or grafts has been found, although recipients of HCV-positive organs had a higher rate of liver-related morbidity and mortality.[132,133] Many organ banks now avoid using organs from HCV-positive donors except for lifesaving procedures such as heart, lung, and liver transplantation.[131] Transmission of HCV to eight organ or tissue recipients from a single, seronegative, and NAAT-positive organ donor has been described.[134] The donor died early in the HCV "window period." Introduction of tissue donor NAAT screening in conjunction with serologic testing has reduced the likelihood of undetected hepatitis C transmission; despite this, human error in interpreting results led to transmission in two kidney and a cardiopulmonary patch recipient from an antibody-negative, NAAT-positive donor.[135] In other transplant-related incidents, potential transmission via blood vessel conduit from a seropositive donor and through common use of perfusion machines has also been reported.[136] The use of active antivirals for organ recipients in these settings has not been studied.

Other nosocomial transmissions. As previously noted, in recent years more reports have described clustering of hepatitis C cases around various health care–related exposures, including transmissions related to endoscopy[137,138]; myocardial perfusion[139]; computed tomography scanning[140]; reuse of saline flushes,[141] needles and syringes,[16,142] and multidose vials[16,22,86,87,143]; and use of a spring-loaded fingerstick device.[144]

In a highly publicized report from Las Vegas, several patients seen at one endoscopy clinic were found to have hepatitis C.[137] The infection was thought to be related to inappropriate reuse of syringes and the use in multiple persons of medication vials intended only for single use. In other reports from endoscopy clinics, the transmission may have occurred as a result of inadequate cleaning of the biopsy suction channel of the colonoscope or failure to autoclave some equipment, such as biopsy forceps.[22,145] Hepatitis C transmission during a uterine dilation procedure was genotypically determined to have originated from a source patient who had undergone an operatation earlier on the same day. The only common link was an anesthesiologist who prepared medications on a cart that was rolled between operating rooms throughout the day without cleaning and disinfection in between.[146]

Transmission of hepatitis C between patients in a dental office has been documented.[147] The mechanism of transmission is unclear but might involve improperly sterilized instruments.

Several reports have suggested an association between development of HCV infection and hospitalization on an oncology or bone marrow transplant floor[18,148,149] or on a urology,[150] liver,[151] or general ward.[152] Although some studies are from relatively resource-poor countries, where reuse of needles may be the cause, the source of spread in other centers remains puzzling. Prolonged hospitalization is often a risk in these reports, and, in one large US outbreak, transmission was thought to be related to shared saline bags contaminated through syringe reuse.[148] Persistence of live HCV for several weeks on dried surfaces has been shown with use of a genetically engineered reporter strain.[153] Whether contact with contaminated surfaces can transmit hepatitis C is plausible but unproven.

Management

The CDC recommends determining the HCV serostatus of the source patient after any exposure.[154] For the exposed HCW, immediate anti-HCV testing within 48 hours is recommended. HCV RNA testing should be done if the initial testing result is positive. For those who are anti-HCV negative, an assessment for HCV RNA should be done at least 3 weeks after exposure to a source patient with HCV or unknown status. HCWs who test positive for HCV RNA at symptom onset or at postexposure testing at ≥3 weeks should be retested at 6 months for spontaneous clearance of infection.[154]

Optimal management of a needlestick exposure is unknown, but each exposure need not be managed with antivirals. For the small subset of HCWs who seroconvert and remain with detectable RNA, newer direct-acting antivirals (DAAs) are highly efficacious at achieving a sustained virologic response. The role of DAAs has not been evaluated in the context of PEP, and they are not currently recommended for this purpose (see Chapter 154). Interferon-α (IFN-α) remains the only drug that has been studied in early infection; in a single report, HCV resolved in all 14 HCWs who were treated with IFN soon after acute infection.[155]

Hepatitis D

Delta virus is a defective RNA virus that requires the presence of active HBV infection (acute HBV or HBsAg carrier state) to infect the liver. In a report from the 1980s,[72] an HBV- and delta-infected source patient

regularly shared a dialysis machine with an asymptomatic HBsAg carrier. The latter patient subsequently developed acute delta hepatitis. A surgeon may also have become dually infected after a deep needlestick sustained while operating on the same source patient. Review identified several additional possible instances of delta hepatitis transmission in dialysis centers. This review led to the current recommendation that patients and staff be vaccinated against HBV and that dialysis patients be separated according to delta virus status. An additional benefit of hepatitis B vaccination is that the incidence of hepatitis D has also substantially declined. Refer to Chapter 146.

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304 Transfusion- and Transplantation-Transmitted Infections

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SHORT VIEW SUMMARY

Definition
- Transfusion- and transplant-transmitted infections occur when a pathogen is spread from the donor to recipients through blood, organs, or other tissue.

Epidemiology
- Transfusion- and transplant-transmitted infections are unusual but occur when screening does not prevent transmission, or when a donation is not screened for a pathogen. The risk of infection transmitted through organ transplantation is likely greater than through blood or tissue owing to the lack of exclusion criteria for organ donors.

Microbiology
- Transfusion of blood product has transmitted infections caused by bacteria, viruses, parasites, and prions.
- Solid-organ transplantation has transmitted infections caused by viruses, bacteria, fungi, mycobacteria, and parasites.
- Encephalitis after solid-organ transplantation has resulted from transmission of West Nile virus, lymphocytic choriomeningitis virus, rabies, and *Balamuthia mandrillaris*.

Diagnosis
- Diagnosis is dependent on clinical recognition that a recipient has an infection that could have been acquired from a transfusion or transplant.

Therapy and Prevention
- Better donor screening, or prompt recognition when transfusion- or transplant-transmitted infection occurs, can improve recipient outcomes.

TRANSFUSION-ASSOCIATED INFECTIONS

Beeson reported the first cases of transfusion-associated hepatitis in 1943, describing seven patients who developed illness 1 to 4 months after having received a red blood cell (RBC) or plasma transfusion.[1] Later identified as transfusion-transmitted hepatitis B virus (HBV), the advent of the acquired immunodeficiency syndrome (AIDS) epidemic in the 1980s followed by recognition of transfusion transmission of hepatitis C virus (HCV) in the 1990s and, most recently, reports of transfusion-transmitted West Nile virus (WNV) and Zika virus (ZIKV) infections in the 21st century have continued to draw attention to the safety of the blood supply, particularly the potential risk from emerging infectious agents.[2–5]

Although infections with the human immunodeficiency virus (HIV), HBV, HCV, WNV, and ZIKV have been the most publicized, a wide spectrum of other organisms, including viruses, bacteria, parasites, and prions, have been transmitted by transfusion (Table 304.1).[6] Of these, transfusion transmission of bacterial infections is most common and earliest recognized in the history of transfusion, now is most often associated with platelet transfusions, and infrequently results in sepsis and death.[7] Recognition of the threat of *Trypanosoma cruzi* transmission via transfusion and the availability of suitable testing have led to screening for this pathogen, which is the cause of Chagas disease. In addition to WNV, mosquito-borne pathogens, such as dengue virus, chikungunya virus, and most recently, ZIKV, have shown potential for transfusion transmission, although the burden of disease is unknown. Tick-borne agents also are recognized to pose an increasing risk to transfusion safety, including transmission of babesiosis and, most recently, anaplasmosis and ehrlichiosis. Transmission of variant Creutzfeldt-Jakob disease (vCJD) via transfusion has occurred in the United Kingdom.

An ongoing dilemma of the blood-banking community is a mandate to ensure a maximally safe blood supply while giving consideration to the cost of such measures. The current questions for screening donors that have been adopted by most blood banks are presented in Fig. 304.1, and the laboratory screening measures currently in place are listed in Table 304.2. As of 2014, pathogens or diseases screened solely through donor interview include malaria and vCJD. Real or perceived threats to the blood supply occur regularly, as emerging or reemerging infectious diseases raise concern over potential transmission. A previously published review summarizes potential blood supply risks from pathogens, the majority of which are not screened for with laboratory testing.[8]

Pathogen reduction technology (PRT) is now available to reduce the need to develop screening measures for new infectious threats. In December 2014, the US Food and Drug Administration (FDA) approved a PRT method for plasma and apheresis platelets that uses chemicals activated by ultraviolet light to inactivate nucleic acid material comprising DNA and RNA.[9,10] However, there is no approved method for treatment of RBCs. Although this technology is likely to reduce the risk of transmitted infections of viruses, bacteria, and parasites, it will not likely eliminate it, because there are organisms occurring in high titers or that have structures (e.g., non–lipid-enveloped viruses, bacterial spores, prions) that resist or are not affected by the inactivation mechanism.[9,10]

SCOPE OF BLOOD TRANSFUSION

According to estimates from the World Health Organization (WHO), more than 112 million units of blood were collected in 2013.[11] Less than half of donated blood is collected in developing and transitional countries, which are home to about 80% of the world's population. Of the 156 countries providing data to WHO for 2013, 13 were not able to screen all of their donated blood for one or more of the four infections (HIV, HBV, HCV, and syphilis) that are most widely recognized to be transmitted through blood and are recommended by WHO to be screened at donation.[11] A total of 126 countries have national guidelines on the appropriate clinical use of blood, and 70 countries have a national hemovigilance system to monitor adverse events associated with transfusion.[11]

Surveys to determine blood product use in the United States, led by the National Heart and Lung Institute (now called the National Heart, Lung, and Blood Institute), began in 1971.[12] In the United States, surveys have reported the frequency of blood collection and utilization

[a]The findings and conclusions in this chapter are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

TABLE 304.1 List of Notable Infections Transmitted Through Blood Transfusion

Viruses

Colorado tick fever virus
Cytomegalovirus
Dengue virus
Epstein-Barr virus
Hepatitis A virus
Hepatitis B virus
Hepatitis C virus
Hepatitis E virus
Human herpesvirus 8
Human immunodeficiency virus 1 and 2
Human T-lymphotropic virus 1 and 2
Parvovirus B19
Tick-borne encephalitis virus
West Nile virus
Zika virus

Bacteria

Anaplasma phagocytophilum
Brucella spp.
Coxiella burnetii
Ehrlichia
Gram-positive organisms[a]
Gram-negative organisms[b]
Rickettsia rickettsii
Treponema pallidum[c]

Parasites

Babesia spp.
Leishmania spp.
Trypanosoma cruzi
Plasmodium spp.

Prions

Variant Creutzfeldt-Jakob disease

[a]Higher risk in platelets (see Table 304.3); in addition, *Streptococcus gallolyticus (bovis)* is notable for being associated with colon cancer in the donor.
[b]Noted in red blood cell units associated with cryophilic organisms, including *Pseudomonas fluorescens, Serratia liquefaciens,* and *Yersinia enterocolitica.*
[c]Not thought a current risk; last reported transfusion transmission of syphilis in the United States was in 1966.
Modified from Perkins HA, Busch MP. Transfusion-associated infections: 50 years of relentless challenges and remarkable progress. Transfusion. 2010;50:2080–2099; and Stramer SL, Hollinger FB, Katz LM, et al. Emerging infectious disease agents and their potential threat to transfusion safety. Transfusion. *2009;49:1S–29S.*

TABLE 304.2 Laboratory Screening Performed for Pathogens or Diseases by US Blood Collection Centers

Required or Recommended by US Food and Drug Administration

Hepatitis B surface antigen (HBsAg)
Hepatitis B core antibody (anti-HBcAb)
Hepatitis C virus antibody (anti-HCV)
HIV-1 and HIV-2 antibody (anti-HIV-1 and anti-HIV-2)
HIV p24 antigen
HTLV-1 and HTLV-2 antibody (anti-HTLV-1 and anti-HTLV-2)
Serologic test for syphilis
NAAT for HIV-1, HBV, and HCV
NAAT for West Nile virus
Serologic test for *Trypanosoma cruzi* (one-time donor testing)

Additionally Required by Accrediting Organizations[a]

Platelet screening for bacterial contamination[b]

Performed Voluntarily

Serologic test for cytomegalovirus (on request)

Performed Under Investigational Protocols

PCR and serologic test for *Babesia microti*
NAAT for Zika virus

[a]Including AABB (formerly known as the American Association of Blood Banks) and the College of American Pathologists.
[b]In general, liquid culture media for apheresis units and pH/glucose indicators or bacterial antigen point-of-use tests for whole-blood–derived pooled units.
HBV, Hepatitis B virus; *HCV,* hepatitis C virus; *HIV,* human immunodeficiency virus; *HTLV,* human T-cell lymphotropic virus; *NAAT,* nucleic acid amplification testing; *PCR,* polymerase chain reaction.

since the late 1980s, most recently through the National Blood Collection and Utilization Survey (NBCUS), which has been conducted biannually since 1998.[12–14] In the 2017 NBCUS report, reflecting data collected in 2015, there were nearly 11 million whole-blood and 3.7 million apheresis collections, with approximately 19 million blood components transfused.[14] In 2015, 11.33 million whole-blood and RBC units, 2.7 million units of plasma, 1.8 million units of apheresis platelets, 0.17 million units of whole-blood–derived platelets (measured in apheresis equivalent units), and 1.2 million units of cryoprecipitate were given.[14] The number of RBC transfusions has continued to decline since 2008, perhaps reflecting the growing adoption of more aggressive hospital blood management practices. The number of transfused platelets has remained approximately the same, but transfusion of apheresis platelets has continued to increase, while the amount of whole-blood–derived or pooled platelets has continued to decline. In addition to contributions from the voluntary donor pool, plasma units also are collected annually from paid donors and are used to prepare immune globulin, albumin, and various other plasma-derived products. By 1987, the cost of collecting, processing, and transfusing patients exceeded $3 billion; since then, costs have increased steadily with the addition of new screening tests and the implementation of leukoreduction.[12] In 2015, the mean price paid by a hospital was $217 for a unit of leukocyte-reduced RBCs, $60 for fresh-frozen plasma, and $537 for apheresis platelets, so current costs are likely to exceed $4 billion annually.[14,15]

It has been estimated that the annual likelihood of an individual's receiving a transfusion increases dramatically with age; in 2015, the transfusion rate in the US population was 35.3 units per 1000 people.[14] Because of concern about contracting an infectious disease, there has been historic interest in autologous and donor-directed blood donation. However, donor-directed units, usually given by family members for a specific patient, have been shown to have higher rates of various infectious agents. There has been movement away from donor-directed donation and toward building a dedicated, voluntary repeat donor population.[14,15] Viral infections are much less common among repeat donors compared with first-time whole-blood donors, and they may be even less common among donors associated with apheresis collection.[16,17]

A majority of, but not all, blood components transfused in the United States are leukoreduced, a modification that is performed to filter out the majority of white blood cells. Leukoreduction is performed to reduce nonhemolytic transfusion reactions, but it may also reduce the risk for infectious disease transmission through removal of infected white blood cells, particularly for cell-associated agents.[18]

In 2015, only about 0.42% of the donated allogeneic blood supply was discarded on testing, usually because of detection of a potentially transmissible infection.[14] This reflects a continued steady decline in units discarded owing to testing, perhaps indicating improved accuracy of screening tests and retention of repeat donors. The incidence of viral markers in donated units was increased among volunteers who donated after September 11, 2001, primarily owing to a large cohort of first-time and infrequent repeat donors.[19]

BLOODBORNE PATHOGENS

Transfusion-associated transmission risk has persisted for HIV, HBV, and HCV for two distinct reasons: (1) the incomplete sensitivity of the available screening tests, and (2) the "window" period, which is defined as the period between acute infection (and potential infectivity) and the point at which serologic tests can reliably detect infection.

The development and implementation of routine nucleic acid amplification testing (NAAT) has transformed blood bank screening for viral pathogens.[3,20–22] NAAT can detect viral RNA after the first 10 to 14 days of infection, narrowing the window period by 7 to 10 days for HIV and by 50 to 60 days for HCV compared with serology. NAAT for blood donor screening, in addition to HIV, HBV, and HCV, is now

additionally required for WNV and ZIKV, and is voluntarily performed by plasma manufacturers in pools for parvovirus B19.[23–26]

With introduction of NAAT, the risk of acquiring HIV or HCV per unit of blood transfused has plummeted from approximately 1 per 500,000 for HIV and 1 per 100,000 for HCV before NAAT to a current rate of 1 per 2 million for both viruses. Detected cases are so unusual that the incidence can only be estimated statistically.[27] As remarkable as this advance is, a small window period remains, meaning that the risk for receiving one of these viruses in a unit of blood is not zero. Four cases of HIV transmission and many more cases of HCV transmission through transfusion have been recognized and reported to public health authorities since NAAT was implemented; the modeling data estimate more cases than the number reported, so some cases likely go unrecognized.[28]

The advent of NAAT also has had a substantial impact on the choice of serologic tests. In addition to sensitivity, blood bankers seek optimal specificity: False-positive or indeterminate test results exclude otherwise appropriate donors from subsequent donations and create anxiety due to incorrect diagnosis of infection. The introduction of an extremely sensitive test such as NAAT allows blood banks to focus on the specificity of other screening tests, thereby limiting the number of persons potentially excluded from the donor pool because of misleading test results. Although sensitivity varies little between the second- and third-generation antibody tests, the third-generation assay has superior

Full-Length Donor History Questionnaire

	Yes	No	
Are you			
1. Feeling healthy and well today?	❑	❑	
2. Currently taking an antibiotic?	❑	❑	
3. Currently taking any other medication for an infection?	❑	❑	
Please read the Medication Deferral List.			
4. Are you now taking or have you ever taken any medications on the Medication Deferral List?	❑	❑	
5. Have you read the educational materials?	❑	❑	
In the past **48 hours**			
6. Have you taken aspirin or anything that has aspirin in it?	❑	❑	
In the past **6 weeks**			
7. Female donors: Have you been pregnant or are you pregnant now? (Males: check "I am male.")	❑	❑	❑ I am male
In the past **8 weeks have you**			
8. Donated blood, platelets or plasma?	❑	❑	
9. Had any vaccinations or other shots?	❑	❑	
10. Had contact with someone who had a smallpox vaccination?	❑	❑	
In the past **16 weeks**			
11. Have you donated a double unit of red cells using an apheresis machine?	❑	❑	
In the past **12 months have you**			
12. Had a blood transfusion?	❑	❑	
13. Had a transplant such as organ, tissue, or bone marrow?	❑	❑	
14. Had a graft such as bone or skin?	❑	❑	
15. Come into contact with someone else's blood?	❑	❑	
16. Had an accidental needle-stick?	❑	❑	
17. Had sexual contact with anyone who has HIV/AIDS or has had a positive test for the HIV/AIDS virus?	❑	❑	
18. Had sexual contact with a prostitute or anyone else who takes money or drugs or other payment for sex?	❑	❑	
19. Had sexual contact with anyone who has ever used needles to take drugs or steroids, or anything not prescribed by their doctor?	❑	❑	
20. Had sexual contact with anyone who has hemophilia or has used clotting factor concentrates?	❑	❑	
21. Female donors: Had sexual contact with a male who has ever had sexual contact with another male? (Males: check "I am male.")	❑	❑	❑ I am male
22. Had sexual contact with a person who has hepatitis?	❑	❑	
23. Lived with a person who has hepatitis?	❑	❑	
24. Had a tattoo?	❑	❑	
25. Had ear or body piercing?	❑	❑	

v.1.3 eff May 2008

FIG. 304.1 AABB (formerly American Association of Blood Banks) Blood Donor History Questionnaire, Version 1.3, May 2008. *(From AABB. Full-Length Donor History Questionnaire.* http://www.aabb.org/tm/questionnaires/Documents/dhq/v2/DHQ%20v2.0.pdf. *Accessed May 29, 2019.)*

Full-Length Donor History Questionnaire—cont'd

	Yes	No	
26. Had or been treated for syphilis or gonorrhea?	❑	❑	
27. Been in juvenile detention, lockup, jail, or prison for more than 72 hours?	❑	❑	
In the past **three years** have you			
28. Been outside the United States or Canada?	❑	❑	
From **1980 through 1996,**			
29. Did you spend time that adds up to three (3) months or more in the United Kingdom? (Review list of countries in the UK.)	❑	❑	
30. Were you a member of the U.S. military, a civilian military employee, or a dependent of a member of the U.S. military?	❑	❑	
From **1980 to the present,** did you			
31. Spend time that adds up to five (5) years or more in Europe? (Review list of countries in Europe.)	❑	❑	
32. Receive a blood transfusion in the United Kingdom or France? (Review list of countries in the UK.)	❑	❑	
From **1977 to the present,** have you			
33. Received money, drugs, or other payment for sex?	❑	❑	
34. Male donors: had sexual contact with another male, even once? (Females: check "I am female.")	❑	❑	❑ I am female
Have you **EVER**			
35. Had a positive test for the HIV/AIDS virus?	❑	❑	
36. Used needles to take drugs, steroids, or anything not prescribed by your doctor?	❑	❑	
37. Used clotting factor concentrates?	❑	❑	
38. Had hepatitis?	❑	❑	
39. Had malaria?	❑	❑	
40. Had Chagas disease?	❑	❑	
41. Had babesiosis?	❑	❑	
42. Received a dura mater (or brain covering) graft?	❑	❑	
43. Had any type of cancer, including leukemia?	❑	❑	
44. Had any problems with your heart or lungs?	❑	❑	
45. Had a bleeding condition or a blood disease?	❑	❑	
46. Had sexual contact with anyone who was born in or lived in Africa?	❑	❑	
47. Been in Africa?	❑	❑	
48. Have any of your relatives had Creutzfeldt-Jakob disease?	❑	❑	

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FIG. 304.1, cont'd

specificity, decreasing the proportion of persons with indeterminate antibody tests for HCV.[29] HBV NAAT has been adopted for blood donor screening.

Human Immunodeficiency Virus Type 1

More than 8000 persons in the United States have developed AIDS from receipt of blood or tissue.[30] In addition, at least 50% of all hemophiliacs in the United States and Europe became infected with HIV from 1978 to 1985, most from receipt of infected plasma factors, with the highest incidence in 1982, when there were 22 infections per 100 person-years.[31] The first HIV screening test was introduced in 1985, and since 1987 few new infections among hemophiliacs have been reported.[31] As noted, the introduction of NAAT screening has substantially lowered the risk for HIV transmission, with the last reported case occurring in 2008.[28]

Redundant methods of testing also have been useful in confirming the status of infection for blood donor follow-up. NAAT has been useful in clarifying the HIV serostatus of persons with indeterminate results of Western blot tests.[32] These reactions occur in about 1 of every 5000 donations and usually represent false-positive test results.[33]

Human Immunodeficiency Virus Type 2

In June 1992, the FDA mandated screening for HIV-2.[34] Since then, few HIV-2–positive donors have been identified, and no cases of transmission have occurred in the United States, although transfusion-related HIV-2 cases have occurred elsewhere.[35,36]

Human T-Cell Lymphotropic Virus Types 1 and 2

HTLV-1 and HTLV-2, unlike HIV-1 and HIV-2, are cell associated and therefore predominantly transmissible only with blood component transfusions.[37] Screening for both types is done with a single test. The rate of transmission of HTLV-1 decreased almost 10-fold (from 1 per 8,500 to 1 per 69,000) after introduction of the screening test.[38] Transplantation of solid organs from an HTLV-1–infected donor resulted in rapid progression to subacute myelopathy in three recipients; this phenomenon has not been described in transfusion recipients.[39]

Other Retroviruses

A short-lived perceived threat to the blood supply was raised when xenotropic murine leukemia virus–related virus (XMRV) was linked to prostate cancer and then chronic fatigue syndrome. Furthermore,