ASHP REPORT

Clinical practice guidelines for antimicrobial prophylaxis in surgery

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These guidelines were developed jointly by the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA). This work represents an update to the previously published ASHP Therapeutic Guidelines on Antimicrobial Prophylaxis in Surgery,[1] as well as guidelines from IDSA and SIS.[2,3] The guidelines are intended to provide practitioners with a standardized approach to the rational, safe, and effective use of antimicrobial agents for the prevention of surgical-site infections (SSIs) based on currently available clinical evidence and emerging issues.

Prophylaxis refers to the prevention of an infection and can be characterized as primary prophylaxis, secondary prophylaxis, or eradication. Primary prophylaxis refers to the prevention of an initial infection. Secondary prophylaxis refers to the prevention of recurrence or reactivation of a preexisting infection. Eradication refers to the elimination of a colonized organism to prevent the development of an infection. These guidelines focus on primary perioperative prophylaxis.

Guidelines development and use

Members of ASHP, IDSA, SIS, and SHEA were appointed to serve on an expert panel established to ensure the validity, reliability, and utility of the revised guidelines. The work of the panel was facilitated by faculty of the University of Pittsburgh School of Pharmacy and University of Pittsburgh Medical Center Drug Use and Disease State Management Program who served as contract researchers and writers for the project. Panel members and contractors were required to disclose any possible conflicts of interest before their appointment and throughout the guideline development process. Drafted documents for each surgical procedural section were reviewed by the expert panel and, once revised, were available for public comment on the ASHP website. After additional revisions were made to address reviewer comments, the final document was

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approved by the expert panel and the boards of directors of the above-named organizations.

Strength of evidence and grading of recommendations. The primary literature from the previous ASHP Therapeutic Guidelines on Antimicrobial Prophylaxis in Surgery[1] was reviewed together with the primary literature published between the date of the previous guidelines, 1999, and June 2010, identified by searches of MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews. Particular attention was paid to study design, with greatest credence given to randomized, controlled, double-blind studies. There is a limited number of adequately powered randomized controlled trials evaluating the efficacy of antimicrobial prophylaxis in surgical procedures. Guidelines development included consideration of the following characteristics: validity, reliability, clinical applicability, flexibility, clarity, and a multidisciplinary nature as consistent with ASHP's philosophy on therapeutic guidelines.[4] The limitations of the evidence base are noted within each individual procedure section of the guidelines. Published guidelines with recommendations by experts in a procedure area (e.g., American College of Obstetricians and Gynecologists [ACOG]) and noted general guidelines (e.g., Centers for Disease Control and Prevention [CDC], Scottish Intercollegiate Guidelines Network, *Medical Letter*, SIS, SHEA/IDSA) were also considered.[2,3,5-11]

Recommendations for the use of antimicrobial prophylaxis are graded according to the strength of evidence available. The strength of evidence represents only support for or against prophylaxis and does not apply to the antimicrobial agent, dose, or dosage regimen. Studies supporting the recommendations for the use of antimicrobial therapy were classified as follows:

- Level I (evidence from large, well-conducted, randomized, controlled clinical trials or a meta-analysis),
- Level II (evidence from small, well-conducted, randomized, controlled clinical trials),
- Level III (evidence from well-conducted cohort studies),
- Level IV (evidence from well-conducted case–control studies),
- Level V (evidence from uncontrolled studies that were not well conducted),
- Level VI (conflicting evidence that tends to favor the recommendation), or
- Level VII (expert opinion or data extrapolated from evidence for general principles and other procedures).

This system has been used by the Agency for Healthcare Research and Quality, and ASHP, IDSA, SIS, and SHEA support it as an acceptable method for organizing strength of evidence for a variety of therapeutic or diagnostic recommendations.[4] Each recommendation was categorized according to the strength of evidence that supports the use or nonuse of antimicrobial prophylaxis as category A (levels I–III), category B (levels IV–VI), or category C (level VII).

When higher-level data are not available, a category C recommendation represents a consensus of expert panel members based on their clinical experience, extrapolation from other procedures with similar microbial or other clinical features, and available published literature. In these cases, the expert panel also extrapolated general principles and evidence from other procedures. Some recommendations include alternative approaches in situations in which panel member opinions were divided.

A major limitation of the available literature on antimicrobial prophylaxis is the difficulty in establishing significant differences in efficacy between prophylactic antimicrobial agents and controls (including placebo, no treatment, or other antimicrobial agents) due to study design and low SSI rates for most procedures. A small sample size increases the likelihood of a Type II error; therefore, there may be no apparent difference between the antimicrobial agent and placebo when in fact the antimicrobial has a beneficial effect.[12] A valid

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study is placebo controlled and randomized with a sufficient sample in each group to avoid a Type II error. Of note, prophylaxis is recommended in some cases due to the severity of complications of postoperative infection (e.g., an infected device that is not easily removable) necessitating precautionary measures despite the lack of statistical support.

Summary of key updates. These guidelines reflect substantial changes from the guidelines published in 1999.[1] Highlights of those changes are outlined here.

Preoperative-dose timing. The optimal time for administration of preoperative doses is within 60 minutes before surgical incision. This is a more-specific time frame than the previously recommended time, which was "at induction of anesthesia." Some agents, such as fluoroquinolones and vancomycin, require administration over one to two hours; therefore, the administration of these agents should begin within 120 minutes before surgical incision.

Selection and dosing. Information is included regarding the approach to weight-based dosing in obese patients and the need for repeat doses during prolonged procedures.[13-18] Obesity has been linked to an increased risk for SSI. The pharmacokinetics of drugs may be altered in obese patients, so dosage adjustments based on body weight may be warranted in these patients. For all patients, intraoperative redosing is needed to ensure adequate serum and tissue concentrations of the antimicrobial if the duration of the procedure exceeds two half-lives of the drug or there is excessive blood loss during the procedure (Table 1). Recommendations for selection of antimicrobial agents for specific surgical procedures and alternative agents (e.g., for patients with allergies to β-lactam antimicrobials) are provided in Table 2.

Duration of prophylaxis. New recommendations for a shortened post-

Table 1.
Recommended Doses and Redosing Intervals for Commonly Used Antimicrobials for Surgical Prophylaxis

Antimicrobial	Recommended Dose		Half-life in Adults With Normal Renal Function, hr[19]	Recommended Redosing Interval (From Initiation of Preoperative Dose), hr[c]
	Adults[a]	Pediatrics[b]		
Ampicillin–sulbactam	3 g (ampicillin 2 g/sulbactam 1 g)	50 mg/kg of the ampicillin component	0.8–1.3	2
Ampicillin	2 g	50 mg/kg	1–1.9	2
Aztreonam	2 g	30 mg/kg	1.3–2.4	4
Cefazolin	2 g, 3 g for pts weighing ≥120 kg	30 mg/kg	1.2–2.2	4
Cefuroxime	1.5 g	50 mg/kg	1–2	4
Cefotaxime	1 g[d]	50 mg/kg	0.9–1.7	3
Cefoxitin	2 g	40 mg/kg	0.7–1.1	2
Cefotetan	2 g	40 mg/kg	2.8–4.6	6
Ceftriaxone	2 g[e]	50–75 mg/kg	5.4–10.9	NA
Ciprofloxacin[f]	400 mg	10 mg/kg	3–7	NA
Clindamycin	900 mg	10 mg/kg	2–4	6
Ertapenem	1 g	15 mg/kg	3–5	NA
Fluconazole	400 mg	6 mg/kg	30	NA
Gentamicin[g]	5 mg/kg based on dosing weight (single dose)	2.5 mg/kg based on dosing weight	2–3	NA
Levofloxacin[f]	500 mg	10 mg/kg	6–8	NA
Metronidazole	500 mg	15 mg/kg	6–8	NA
		Neonates weighing <1200 g should receive a single 7.5-mg/kg dose		

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Table 1 (*continued*)

Antimicrobial	Recommended Dose		Half-life in Adults With Normal Renal Function, hr[19]	Recommended Redosing Interval (From Initiation of Preoperative Dose), hr[c]
	Adults[a]	Pediatrics[b]		
Moxifloxacin[f]	400 mg	10 mg/kg	8–15	NA
Piperacillin–tazobactam	3.375 g	Infants 2–9 mo: 80 mg/kg of the piperacillin component Children >9 mo and ≤40 kg: 100 mg/kg of the piperacillin component	0.7–1.2	2
Vancomycin	15 mg/kg	15 mg/kg	4–8	NA
Oral antibiotics for colorectal surgery prophylaxis (used in conjunction with a mechanical bowel preparation)				
Erythromycin base	1 g	20 mg/kg	0.8–3	NA
Metronidazole	1 g	15 mg/kg	6–10	NA
Neomycin	1 g	15 mg/kg	2–3 (3% absorbed under normal gastrointestinal conditions)	NA

[a]Adult doses are obtained from the studies cited in each section. When doses differed between studies, expert opinion used the most-often recommended dose.
[b]The maximum pediatric dose should not exceed the usual adult dose.
[c]For antimicrobials with a short half-life (e.g., cefazolin, cefoxitin) used before long procedures, redosing in the operating room is recommended at an interval of approximately two times the half-life of the agent in patients with normal renal function. Recommended redosing intervals marked as "not applicable" (NA) are based on typical case length; for unusually long procedures, redosing may be needed.
[d]Although FDA-approved package insert labeling indicates 1 g,[14] experts recommend 2 g for obese patients.
[e]When used as a single dose in combination with metronidazole for colorectal procedures.
[f]While fluoroquinolones have been associated with an increased risk of tendinitis/tendon rupture in all ages, use of these agents for single-dose prophylaxis is generally safe.
[g]In general, gentamicin for surgical antibiotic prophylaxis should be limited to a single dose given preoperatively. Dosing is based on the patient's actual body weight. If the patient's actual weight is more than 20% above ideal body weight (IBW), the dosing weight (DW) can be determined as follows: DW = IBW + 0.4(actual weight – IBW).

operative course of antimicrobials involving a single dose or continuation for less than 24 hours are provided. Further clarity on the lack of need for postoperative antimicrobial prophylaxis based on the presence of indwelling drains and intravascular catheters is included.

Common principles. A section addressing concepts that apply to all types of surgical procedures has been added. Expanded and new recommendations are provided for plastic, urology, cardiac, and thoracic procedures, as well as clarity on prophylaxis when implantable devices are inserted. The latest information on the use of mupirocin and on the role of vancomycin in surgical prophylaxis is summarized in these updated guidelines.

Application of guidelines to clinical practice. Recommendations are provided for adult (age 19 years or older) and pediatric (age 1–18 years) patients. These guidelines do not specifically address newborn (premature and full-term) infants. While the guidelines do not address all concerns for patients with renal or hepatic dysfunction, antimicrobial prophylaxis often does not need to be modified for these patients when given as a single preoperative dose before surgical incision.

The recommendations herein may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the judgment of the clinician and consideration of individual patient circumstances and available resources.

These guidelines reflect current knowledge of antimicrobial prophylaxis in surgery. Given the dynamic nature of scientific information and technology, periodic review, updating, and revisions are to be expected.

Special patient populations. *Pediatric patients.* Pediatric patients undergo a number of procedures similar to adults that may warrant antimicrobial prophylaxis. Although

Table 2.
Recommendations for Surgical Antimicrobial Prophylaxis

Type of Procedure	Recommended Agents[a,b]	Alternative Agents in Pts With β-Lactam Allergy	Strength of Evidence[c]
Cardiac			
Coronary artery bypass	Cefazolin, cefuroxime	Clindamycin,[d] vancomycin[d]	A
Cardiac device insertion procedures (e.g., pacemaker implantation)	Cefazolin, cefuroxime	Clindamycin, vancomycin	A
Ventricular assist devices	Cefazolin, cefuroxime	Clindamycin, vancomycin	C
Thoracic			
Noncardiac procedures, including lobectomy, pneumonectomy, lung resection, and thoracotomy	Cefazolin, ampicillin–sulbactam	Clindamycin,[d] vancomycin[d]	A
Video-assisted thoracoscopic surgery	Cefazolin, ampicillin–sulbactam	Clindamycin,[d] vancomycin[d]	C
Gastroduodenal[e]			
Procedures involving entry into lumen of gastrointestinal tract (bariatric, pancreaticoduodenectomy[f])	Cefazolin	Clindamycin or vancomycin + aminoglycoside[g] or aztreonam or fluoroquinolone[h-j]	A
Procedures without entry into gastrointestinal tract (antireflux, highly selective vagotomy) for high-risk patients	Cefazolin	Clindamycin or vancomycin + aminoglycoside[g] or aztreonam or fluoroquinolone[h-j]	A
Biliary tract			
Open procedure	Cefazolin, cefoxitin, cefotetan, ceftriaxone,[k] ampicillin–sulbactam[h]	Clindamycin or vancomycin + aminoglycoside[g] or aztreonam or fluoroquinolone[h-j] Metronidazole + aminoglycoside[g] or fluoroquinolone[h-j]	A
Laparoscopic procedure			
Elective, low-risk[l]	None	None	A
Elective, high-risk[l]	Cefazolin, cefoxitin, cefotetan, ceftriaxone,[k] ampicillin–sulbactam[h]	Clindamycin or vancomycin + aminoglycoside[g] or aztreonam or fluoroquinolone[h-j] Metronidazole + aminoglycoside[g] or fluoroquinolone[h-j]	A
Appendectomy for uncomplicated appendicitis	Cefoxitin, cefotetan, cefazolin + metronidazole	Clindamycin + aminoglycoside[g] or aztreonam or fluoroquinolone[h-j] Metronidazole + aminoglycoside[g] or fluoroquinolone[h-j]	A
Small intestine			
Nonobstructed	Cefazolin	Clindamycin + aminoglycoside[g] or aztreonam or fluoroquinolone[h-j]	C

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Table 2 (*continued*)

Type of Procedure	Recommended Agents[a,b]	Alternative Agents in Pts With β-Lactam Allergy	Strength of Evidence[c]
Obstructed	Cefazolin + metronidazole, cefoxitin, cefotetan	Metronidazole + aminoglycoside[g] or fluoroquinolone[h-j]	C
Hernia repair (hernioplasty and herniorrhaphy)	Cefazolin	Clindamycin, vancomycin	A
Colorectal[m]	Cefazolin + metronidazole, cefoxitin, cefotetan, ampicillin–sulbactam,[h] ceftriaxone + metronidazole,[n] ertapenem	Clindamycin + aminoglycoside[g] or aztreonam or fluoroquinolone[h-j], metronidazole + aminoglycoside[g] or fluoroquinolone[h-j]	A
Head and neck			
Clean	None	None	B
Clean with placement of prosthesis (excludes tympanostomy tubes)	Cefazolin, cefuroxime	Clindamycin[d]	C
Clean-contaminated cancer surgery	Cefazolin + metronidazole, cefuroxime + metronidazole, ampicillin–sulbactam	Clindamycin[d]	A
Other clean-contaminated procedures with the exception of tonsillectomy and functional endoscopic sinus procedures	Cefazolin + metronidazole, cefuroxime + metronidazole, ampicillin–sulbactam	Clindamycin[d]	B
Neurosurgery			
Elective craniotomy and cerebrospinal fluid-shunting procedures	Cefazolin	Clindamycin,[d] vancomycin[d]	A
Implantation of intrathecal pumps	Cefazolin	Clindamycin,[d] vancomycin[d]	C
Cesarean delivery	Cefazolin	Clindamycin + aminoglycoside[g]	A
Hysterectomy (vaginal or abdominal)	Cefazolin, cefotetan, cefoxitin, ampicillin–sulbactam[h]	Clindamycin or vancomycin + aminoglycoside[g] or aztreonam or fluoroquinolone[h-j] Metronidazole + aminoglycoside[g] or fluoroquinolone[h-j]	A
Ophthalmic	Topical neomycin–polymyxin B–gramicidin or fourth-generation topical fluoroquinolones (gatifloxacin or moxifloxacin) given as 1 drop every 5–15 min for 5 doses[o] Addition of cefazolin 100 mg by subconjunctival injection or intracameral cefazolin 1–2.5 mg or cefuroxime 1 mg at the end of procedure is optional	None	B
Orthopedic			
Clean operations involving hand, knee, or foot and not involving implantation of foreign materials	None	None	C
Spinal procedures with and without instrumentation	Cefazolin	Clindamycin,[d] vancomycin[d]	A

Continued on next page

Table 2 (*continued*)

Type of Procedure	Recommended Agents[a,b]	Alternative Agents in Pts With β-Lactam Allergy	Strength of Evidence[c]
Hip fracture repair	Cefazolin	Clindamycin,[d] vancomycin[d]	A
Implantation of internal fixation devices (e.g., nails, screws, plates, wires)	Cefazolin	Clindamycin,[d] vancomycin[d]	C
Total joint replacement	Cefazolin	Clindamycin,[d] vancomycin[d]	A
Urologic			
Lower tract instrumentation with risk factors for infection (includes transrectal prostate biopsy)	Fluoroquinolone,[h-j] trimethoprim–sulfamethoxazole, cefazolin	Aminoglycoside[g] with or without clindamycin	A
Clean without entry into urinary tract	Cefazolin (the addition of a single dose of an aminoglycoside may be recommended for placement of prosthetic material [e.g., penile prosthesis])	Clindamycin,[d] vancomycin[d]	A
Involving implanted prosthesis	Cefazolin ± aminoglycoside, cefazolin ± aztreonam, ampicillin–sulbactam	Clindamycin ± aminoglycoside or aztreonam, vancomycin ± aminoglycoside or aztreonam	A
Clean with entry into urinary tract	Cefazolin (the addition of a single dose of an aminoglycoside may be recommended for placement of prosthetic material [e.g., penile prosthesis])	Fluoroquinolone,[h-j] aminoglycoside[g] with or without clindamycin	A
Clean-contaminated	Cefazolin + metronidazole, cefoxitin	Fluoroquinolone,[h-j] aminoglycoside[g] + metronidazole or clindamycin	A
Vascular[p]	Cefazolin	Clindamycin,[d] vancomycin[d]	A
Heart, lung, heart–lung transplantation[q]			
Heart transplantation[r]	Cefazolin	Clindamycin,[d] vancomycin[d]	A (based on cardiac procedures)
Lung and heart–lung transplantation[r,s]	Cefazolin	Clindamycin,[d] vancomycin[d]	A (based on cardiac procedures)
Liver transplantation[q,t]	Piperacillin–tazobactam, cefotaxime + ampicillin	Clindamycin or vancomycin + aminoglycoside[g] or aztreonam or fluoroquinolone[h-j]	B
Pancreas and pancreas–kidney transplantation[r]	Cefazolin, fluconazole (for patients at high risk of fungal infection [e.g., those with enteric drainage of the pancreas])	Clindamycin or vancomycin + aminoglycoside[g] or aztreonam or fluoroquinolone[h-j]	A
	Cefazolin	Clindamycin or vancomycin + aminoglycoside[g] or aztreonam or fluoroquinolone[h-j]	A

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Table 2 (*continued*)

Type of Procedure	Recommended Agents[a,b]	Alternative Agents in Pts With β-Lactam Allergy	Strength of Evidence[c]
Plastic surgery			
Clean with risk factors or clean-contaminated	Cefazolin, ampicillin–sulbactam	Clindamycin,[d] vancomycin[d]	C

[a]The antimicrobial agent should be started within 60 minutes before surgical incision (120 minutes for vancomycin or fluoroquinolones). While single-dose prophylaxis is usually sufficient, the duration of prophylaxis for all procedures should be less than 24 hours. If an agent with a short half-life is used (e.g., cefazolin, cefoxitin), it should be readministered if the procedure duration exceeds the recommended redosing interval (from the time of initiation of the preoperative dose [see Table 1]). Readministration may also be warranted if prolonged or excessive bleeding occurs or if there are other factors that may shorten the half-life of the prophylactic agent (e.g., extensive burns). Readministration may not be warranted in patients in whom the half-life of the agent may be prolonged (e.g., patients with renal insufficiency or failure).

[b]For patients known to be colonized with methicillin-resistant *Staphylococcus aureus*, it is reasonable to add a single preoperative dose of vancomycin to the recommended agent(s).

[c]Strength of evidence that supports the use or nonuse of prophylaxis is classified as A (levels I–III), B (levels IV–VI), or C (level VII). Level I evidence is from large, well-conducted, randomized controlled clinical trials. Level II evidence is from small, well-conducted, randomized controlled clinical trials. Level III evidence is from well-conducted cohort studies. Level IV evidence is from well-conducted case–control studies. Level V evidence is from uncontrolled studies that were not well conducted. Level VI evidence is conflicting evidence that tends to favor the recommendation. Level VII evidence is expert opinion.

[d]For procedures in which pathogens other than staphylococci and streptococci are likely, an additional agent with activity against those pathogens could be considered. For example, if there are surveillance data showing that gram-negative organisms are a cause of surgical-site infections (SSIs) for the procedure, practitioners may consider combining clindamycin or vancomycin with another agent (cefazolin if the patient is not β-lactam allergic; aztreonam, gentamicin, or single-dose fluoroquinolone if the patient is β-lactam allergic).

[e]Prophylaxis should be considered for patients at highest risk for postoperative gastroduodenal infections, such as those with increased gastric pH (e.g., those receiving histamine H_2-receptor antagonists or proton-pump inhibitors), gastroduodenal perforation, decreased gastric motility, gastric outlet obstruction, gastric bleeding, morbid obesity, or cancer. Antimicrobial prophylaxis may not be needed when the lumen of the intestinal tract is not entered.

[f]Consider additional antimicrobial coverage with infected biliary tract. See the biliary tract procedures section of this article.

[g]Gentamicin or tobramycin.

[h]Due to increasing resistance of *Escherichia coli* to fluoroquinolones and ampicillin–sulbactam, local population susceptibility profiles should be reviewed prior to use.

[i]Ciprofloxacin or levofloxacin.

[j]Fluoroquinolones are associated with an increased risk of tendonitis and tendon rupture in all ages. However, this risk would be expected to be quite small with single-dose antibiotic prophylaxis. Although the use of fluoroquinolones may be necessary for surgical antibiotic prophylaxis in some children, they are not drugs of first choice in the pediatric population due to an increased incidence of adverse events as compared with controls in some clinical trials.

[k]Ceftriaxone use should be limited to patients requiring antimicrobial treatment for acute cholecystitis or acute biliary tract infections which may not be determined prior to incision, not patients undergoing cholecystectomy for noninfected biliary conditions, including biliary colic or dyskinesia without infection.

[l]Factors that indicate a high risk of infectious complications in laparoscopic cholecystectomy include emergency procedures, diabetes, long procedure duration, intraoperative gallbladder rupture, age of >70 years, conversion from laparoscopic to open cholecystectomy, American Society of Anesthesiologists classification of 3 or greater, episode of colic within 30 days before the procedure, reintervention in less than one month for noninfectious complication, acute cholecystitis, bile spillage, jaundice, pregnancy, nonfunctioning gallbladder, immunosuppression, and insertion of prosthetic device. Because a number of these risk factors are not possible to determine before surgical intervention, it may be reasonable to give a single dose of antimicrobial prophylaxis to all patients undergoing laparoscopic cholecystectomy.

[m]For most patients, a mechanical bowel preparation combined with oral neomycin sulfate plus oral erythromycin base or with oral neomycin sulfate plus oral metronidazole should be given in addition to i.v. prophylaxis.

[n]Where there is increasing resistance to first- and second-generation cephalosporins among gram-negative isolates from SSIs, a single dose of ceftriaxone plus metronidazole may be preferred over the routine use of carbapenems.

[o]The necessity of continuing topical antimicrobials postoperatively has not been established.

[p]Prophylaxis is not routinely indicated for brachiocephalic procedures. Although there are no data in support, patients undergoing brachiocephalic procedures involving vascular prostheses or patch implantation (e.g., carotid endarterectomy) may benefit from prophylaxis.

[q]These guidelines reflect recommendations for perioperative antibiotic prophylaxis to prevent SSIs and do not provide recommendations for prevention of opportunistic infections in immunosuppressed transplantation patients (e.g., for antifungal or antiviral medications).

[r]Patients who have left-ventricular assist devices as a bridge and who are chronically infected might also benefit from coverage of the infecting microorganism.

[s]The prophylactic regimen may need to be modified to provide coverage against any potential pathogens, including gram-negative (e.g., *Pseudomonas aeruginosa*) or fungal organisms, isolated from the donor lung or the recipient before transplantation. Patients undergoing lung transplantation with negative pretransplantation cultures should receive antimicrobial prophylaxis as appropriate for other types of cardiothoracic surgeries. Patients undergoing lung transplantation for cystic fibrosis should receive 7–14 days of treatment with antimicrobials selected according to pretransplantation culture and susceptibility results. This treatment may include additional antibacterial or antifungal agents.

[t]The prophylactic regimen may need to be modified to provide coverage against any potential pathogens, including vancomycin-resistant enterococci, isolated from the recipient before transplantation.

pediatric-specific prophylaxis data are sparse, available data have been evaluated and are presented in some of the procedure-specific sections of these guidelines. Selection of antimicrobial prophylactic agents mirrors that in adult guidelines, with the agents of choice being first- and second-generation cephalosporins, reserving the use of vancomycin for patients with documented β-lactam allergies.[19,20] While the use of a penicillin with a β-lactamase inhibitor in combination with cefazolin or vancomycin and gentamicin has also been studied in pediatric patients, the number of patients included in these evaluations remains small.[20-23] As with adults, there is little evidence supporting the use of vancomycin, alone or in combination with other antimicrobials, for routine perioperative antimicrobial prophylaxis in institutions that have a high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA). Vancomycin may be considered in children known to be colonized with MRSA and, in one retrospective historical cohort study, was shown to decrease MRSA infections.[21] Mupirocin use has been studied in and is efficacious in children colonized with MRSA, but there are limited data supporting its use perioperatively.[24-30] However, there is little reason to think that the impact and effect would be any different in children, so its use may be justified. Additional studies in this setting are needed to establish firm guidelines.

Unless noted in specific sections, all recommendations for adults are the same for pediatric patients, except for dosing. In most cases, the data in pediatric patients are limited and have been extrapolated from adult data; therefore, nearly all pediatric recommendations are based on expert opinion. In some sections, pediatric efficacy data do not exist and thus are not addressed in these guidelines. Fluoroquinolones should not be routinely used for surgical prophylaxis in pediatric patients because of the potential for toxicity in this population. The same principle of preoperative dosing within 60 minutes before incision has been applied to pediatric patients.[20-23] Additional intraoperative dosing may be needed if the duration of the procedure exceeds two half-lives of the antimicrobial agent or there is excessive blood loss during the procedure.[19,21] As with adult patients, single-dose prophylaxis is usually sufficient. If antimicrobial prophylaxis is continued postoperatively, the duration should be less than 24 hours, regardless of the presence of intravascular catheters or indwelling drains.[19,22,23,31,32] There are sufficient pharmacokinetic studies of most agents to recommend pediatric dosages that provide adequate systemic exposure and, presumably, efficacy comparable to that demonstrated in adults. Therefore, the pediatric dosages provided in these guidelines are based largely on pharmacokinetic data and the extrapolation of adult efficacy data to pediatric patients. Because few clinical trials have been conducted in pediatric surgical patients, strength of evidence criteria have not been applied to these recommendations. With few exceptions (e.g., aminoglycoside dosages), pediatric dosages should not exceed the maximum adult recommended dosages. Generally, if dosages are calculated on a milligram-per-kilogram basis for children weighing more than 40 kg, the calculated dosage will exceed the maximum recommended dosage for adults; adult dosages should therefore be used.

Patients with prosthetic implants. For patients with existing prosthetic implants who undergo an invasive procedure, there is no evidence that antimicrobial prophylaxis prevents infections of the implant. However, updated guidelines from the American Heart Association (AHA) suggest that prophylaxis may be justified in a limited subset of patients for the prevention of endocarditis.[11]

Common principles and procedure-specific guidelines. The Common Principles section has been developed to provide information common to many surgical procedures. These principles are general recommendations based on currently available data at the time of publication that may change over time; therefore, these principles need to be applied with careful attention to each clinical situation. Detailed information pertinent to specific surgical procedures is included in the procedure-specific sections of these guidelines.

In addition to patient- and procedure-specific considerations, several institution-specific factors must be considered by practitioners before instituting these guidelines. The availability of antimicrobial agents at the institution may be restricted by local antimicrobial-use policy or lack of approval for use by regulatory authorities. Medications that are no longer available or not approved for use by the Food and Drug Administration (FDA) are so noted. Local resistance patterns should also be considered in selecting antimicrobial agents and are discussed in the colonization and resistance patterns section of the Common Principles section.

Requirements for effective surgical prophylaxis

Appendix A lists the wound classification criteria currently used by the CDC National Healthcare Safety Network (NHSN) and Healthcare Infection Control Practices Advisory Committee (HICPAC).[33-35]

Criteria for defining an SSI have also been established by NHSN (Appendix B).[8,36] These definitions assist in evaluating the importance of providing antimicrobial prophylaxis and the potential consequences of infection, including the need for treatment. Some criteria vary slightly by procedure.

Although antimicrobial prophylaxis plays an important role in reduc-

ing the rate of SSIs, other factors such as attention to basic infection-control strategies,[37] the surgeon's experience and technique, the duration of the procedure, hospital and operating-room environments, instrument-sterilization issues, preoperative preparation (e.g., surgical scrub, skin antisepsis, appropriate hair removal), perioperative management (temperature and glycemic control), and the underlying medical condition of the patient may have a strong impact on SSI rates.[5,8] These guidelines recognize the importance of these other factors but do not include a discussion of or any recommendations regarding these issues beyond the optimal use of prophylactic antimicrobial agents. Patient-related factors associated with an increased risk of SSI include extremes of age, nutritional status, obesity, diabetes mellitus, tobacco use, coexistent remote body-site infections, altered immune response, corticosteroid therapy, recent surgical procedure, length of preoperative hospitalization, and colonization with microorganisms. Antimicrobial prophylaxis may be justified for any procedure if the patient has an underlying medical condition associated with a high risk of SSI or if the patient is immunocompromised (e.g., malnourished, neutropenic, receiving immunosuppressive agents).

Antimicrobial prophylaxis may be beneficial in surgical procedures associated with a high rate of infection (i.e., clean-contaminated or contaminated procedures) and in certain clean procedures where there are severe consequences of infection (e.g., prosthetic implants), even if infection is unlikely. While prophylactic antimicrobials are not indicated for some clean surgical procedures,[8] available data suggest that the relative risk reduction of SSI from the use of antimicrobial prophylaxis is the same in clean and in higher-risk procedures.[38] The decision to use prophylaxis depends on the cost of treating and the morbidity associated with infection compared with the cost and morbidity associated with using prophylaxis. Antimicrobial prophylaxis is justified for most clean-contaminated procedures. The use of antimicrobial agents for dirty procedures (Appendix A) or established infections is classified as treatment of presumed infection, not prophylaxis. See the procedure-specific sections for detailed recommendations.

Quality-improvement efforts. National, state, local, and institutional groups have developed and implemented collaborative efforts to improve the appropriateness of surgical antimicrobial prophylaxis. Various process and outcomes measures are employed, and results are disseminated. Institutional epidemiology and infection-control programs, state-based quality-improvement campaigns (e.g., the Michigan Surgical Quality Collaborative, the Washington State Surgical Clinical Outcomes Assessment Program[39,40]), CDC, NHSN, the National Surgical Quality Improvement Program, the Joint Commission, and the National Quality Forum have been instrumental in developing programs to prevent SSIs.

Over the past decade or more, several organizations, payers, and government agencies, including the Centers for Medicare and Medicaid Services (CMS), have established national quality-improvement initiatives to further improve the safety and outcomes of health care, including surgery.[41-47] One area of focus in these initiatives for patients undergoing surgical procedures is the prevention of SSIs. The performance measures used, data collection and reporting requirements, and financial implications vary among the initiatives. The Surgical Care Improvement Project (SCIP) began in 2002 as the Surgical Infection Prevention (SIP) project, focusing on the timing, selection, and duration of prophylactic antimicrobial agents.[41,42] The SIP project was expanded to SCIP to include additional process measures surrounding patient safety and care during surgical procedures, including glucose control, venous thromboembolism prophylaxis, hair removal, and temperature control. Similar measures have been adopted by the Joint Commission.[43] The Physicians Quality Reporting System was established in 2006 to provide financial incentives to physicians meeting performance standards for quality measures, including surgery-related measures similar to those reported for SCIP and the Joint Commission.[44] Data are required to be collected by institutions and reported to payers.[42,44,46] Data for CMS and the Physicians Quality Reporting System measures are displayed on public websites to allow consumers to compare performance among hospitals. Institutional data collection and reporting are required, with financial incentives tied to performance to varying degrees, including payment for reporting, payment increases for meeting or exceeding minimum levels of performance, payment reduction for poor performance, and lack of payment for the development of surgical complications, such as mediastinitis.

Quality-improvement initiatives and mandated performance reporting are subject to change, so readers of these guidelines are advised to consult their local or institutional quality-improvement departments for new developments in requirements for measures and data reporting that apply to their practice.

Cost containment. Few pharmacoeconomic studies have addresed surgical antimicrobial prophylaxis; therefore, a cost-minimization approach was employed in developing these guidelines. The antimicrobial agent recommendations are based primarily on efficacy and safety. Individual institutions must consider their acquisition costs when implementing these guidelines.

Additional cost savings may be realized through collaborative management by pharmacists and surgeons to select the most cost-effective agent and minimize or eliminate postoperative dosing.[48-50] The use of standardized antimicrobial order sets, automatic stop-order programs, and educational initiatives has been shown to facilitate the adoption of guidelines for surgical antimicrobial prophylaxis.[51-58]

Common principles

Ideally, an antimicrobial agent for surgical prophylaxis should (1) prevent SSI, (2) prevent SSI-related morbidity and mortality, (3) reduce the duration and cost of health care (when the costs associated with the management of SSI are considered, the cost-effectiveness of prophylaxis becomes evident),[51,52] (4) produce no adverse effects, and (5) have no adverse consequences for the microbial flora of the patient or the hospital.[53] To achieve these goals, an antimicrobial agent should be (1) active against the pathogens most likely to contaminate the surgical site, (2) given in an appropriate dosage and at a time that ensures adequate serum and tissue concentrations during the period of potential contamination, (3) safe, and (4) administered for the shortest effective period to minimize adverse effects, the development of resistance, and costs.[8,59,60]

The selection of an appropriate antimicrobial agent for a specific patient should take into account the characteristics of the ideal agent, the comparative efficacy of the antimicrobial agent for the procedure, the safety profile, and the patient's medication allergies. A full discussion of the safety profile, including adverse events, drug interactions, contraindications, and warnings, for each antimicrobial agent is beyond the scope of these guidelines. Readers of these guidelines should review the FDA-approved prescribing information and published data for specific antimicrobial agents before use. For most procedures, cefazolin is the drug of choice for prophylaxis because it is the most widely studied antimicrobial agent, with proven efficacy. It has a desirable duration of action, spectrum of activity against organisms commonly encountered in surgery, reasonable safety, and low cost. There is little evidence to suggest that broad-spectrum antimicrobial agents (i.e., agents with broad in vitro antibacterial activity) result in lower rates of postoperative SSI compared with older antimicrobial agents with a narrower spectrum of activity. However, comparative studies are limited by small sample sizes, resulting in difficulty detecting a significant difference between antimicrobial agents; therefore, antimicrobial selection is based on cost, safety profile, ease of administration, pharmacokinetic profile, and bactericidal activity.

Common surgical pathogens

The agent chosen should have activity against the most common surgical-site pathogens. The predominant organisms causing SSIs after clean procedures are skin flora, including *S. aureus* and coagulase-negative staphylococci (e.g., *Staphylococcus epidermidis*).[61] In clean-contaminated procedures, including abdominal procedures and heart, kidney, and liver transplantations, the predominant organisms include gram-negative rods and enterococci in addition to skin flora. Additional details on common organisms can be found in procedure-specific sections of these guidelines.

Recommendations for the selection of prophylactic antimicrobials for various surgical procedures are provided in Table 2. Adult and pediatric dosages are included in Table 1. Agents that are FDA-approved for use in surgical antimicrobial prophylaxis include cefazolin, cefuroxime, cefoxitin, cefotetan, ertapenem, and vancomycin.[62-67]

Trends in microbiology. The causative pathogens associated with SSIs in U.S. hospitals have changed over the past two decades. Analysis of National Nosocomial Infections Surveillance (NNIS) System data found that the percentage of SSIs caused by gram-negative bacilli decreased from 56.5% in 1986 to 33.8% in 2003.[68] *S. aureus* was the most common pathogen, causing 22.5% of SSIs during this time period. NHSN data from 2006 to 2007 revealed that the proportion of SSIs caused by *S. aureus* increased to 30%, with MRSA comprising 49.2% of these isolates.[61] In a study of patients readmitted to U.S. hospitals between 2003 and 2007 with a culture-confirmed SSI, the proportion of infections caused by MRSA increased significantly from 16.1% to 20.6% ($p < 0.0001$).[69] MRSA infections were associated with higher mortality rates, longer hospital stays, and higher hospital costs compared with other infections.

Spectrum of activity. Antimicrobial agents with the narrowest spectrum of activity required for efficacy in preventing infection are recommended in these guidelines. Alternative antimicrobial agents with documented efficacy are also listed herein. Individual health systems must consider local resistance patterns of organisms and overall SSI rates at their site when adopting these recommendations. Resistance patterns from organisms causing SSIs—in some cases procedure-specific resistance patterns—should take precedence over hospitalwide antibiograms.

Vancomycin. In 1999, HICPAC, an advisory committee to CDC and the Secretary of the Department of Health and Human Services, collaborated with other major organizations to develop recommendations for preventing and controlling vancomycin resistance.[70] The recommendations are echoed by these and other guidelines.[6,7,41,71] Routine use of vancomycin prophylaxis is not recommended for any procedure.[8] Vancomycin may be included in the regimen of choice when a cluster of

MRSA cases (e.g., mediastinitis after cardiac procedures) or methicillin-resistant coagulase-negative staphylococci SSIs have been detected at an institution. Vancomycin prophylaxis should be considered for patients with known MRSA colonization or at high risk for MRSA colonization in the absence of surveillance data (e.g., patients with recent hospitalization, nursing-home residents, hemodialysis patients).[5,41,72] In institutions with SSIs attributable to community-associated MRSA, antimicrobial agents with known in vitro activity against this pathogen may be considered as an alternative to vancomycin.

Each institution is encouraged to develop guidelines for the proper use of vancomycin. Although vancomycin is commonly used when the risk for MRSA is high, data suggest that vancomycin is less effective than cefazolin for preventing SSIs caused by methicillin-susceptible *S. aureus* (MSSA).[73,74] For this reason, vancomycin is used in combination with cefazolin at some institutions with both MSSA and MRSA SSIs. For procedures in which pathogens other than staphylococci and streptococci are likely, an additional agent with activity against those pathogens should be considered. For example, if there are surveillance data showing that gram-negative organisms are a cause of SSIs for the procedure, practitioners may consider combining vancomycin with another agent (cefazolin if the patient does not have a β-lactam allergy; an aminoglycoside [gentamicin or tobramycin], aztreonam, or single-dose fluoroquinolone if the patient has a β-lactam allergy). The use of vancomycin for MRSA prophylaxis does not supplant the need for routine surgical prophylaxis appropriate for the type of procedure. When vancomycin is used, it can almost always be used as a single dose due to its long half-life.

Colonization and resistance. A national survey determined that *S. aureus* nasal colonization in the general population decreased from 32.4% in 2001–02 to 28.6% in 2003–04 ($p < 0.01$), whereas the prevalence of colonization with MRSA increased from 0.8% to 1.5% ($p < 0.05$) during the same time periods.[75] Colonization with MRSA was independently associated with health care exposure among men, having been born in the United States, age of >60 years, diabetes, and poverty among women. Similarly, children are colonized with *S. aureus* and MRSA, but colonization varies by age. Children under 5 years of age have the highest rates, mirroring rates seen in patients over age 60 years.[76] The rates drop in children between 5 and 14 years of age and gradually increase to rates seen in the adult population. Lo et al.[77] reported that in a large cohort of children, 28.1% were colonized with *S. aureus* between 2004 and 2006. Between 2007 and 2009, 23.3% of children were colonized with *S. aureus*, but the proportion of children colonized with MRSA had increased from 8.1% in 2004 to 15.1% in 2009.

Surgical antimicrobial prophylaxis can alter individual and institutional bacterial flora, leading to changes in colonization rates and increased bacterial resistance.[78-84] Surgical prophylaxis can also predispose patients to *Clostridium difficile*-associated colitis.[81] Risk factors for development of *C. difficile*-associated colitis include longer duration of prophylaxis or therapy and use of multiple antimicrobial agents.[85] Limiting the duration of antimicrobial prophylaxis to a single preoperative dose can reduce the risk of *C. difficile* disease.

The question of what antimicrobial surgical prophylaxis to use for patients known to be colonized or recently infected with multidrug-resistant pathogens cannot be answered easily or in a manner that can be applied uniformly to all patient scenarios. Whether prophylaxis should be expanded to provide coverage for these pathogens depends on many factors, including the pathogen, its antimicrobial susceptibility profile, the host, the procedure to be performed, and the proximity of the likely reservoir of the pathogen to the incision and operative sites. While there is no evidence on the management of surgical antimicrobial prophylaxis in a patient with past infection or colonization with a resistant gram-negative pathogen, it is logical to provide prophylaxis with an agent active against MRSA for any patient known to be colonized with this gram-positive pathogen who will have a skin incision; specific prophylaxis for a resistant gram-negative pathogen in a patient with past infection or colonization with such a pathogen may not be necessary for a purely cutaneous procedure. Similarly, a patient colonized with vancomycin-resistant enterococci (VRE) should receive prophylaxis effective against VRE when undergoing liver transplantation but probably not when undergoing an umbilical hernia repair without mesh placement. Thus, patients must be treated on a case-by-case basis, taking into account multiple considerations.

Patients receiving therapeutic antimicrobials for a remote infection before surgery should also be given antimicrobial prophylaxis before surgery to ensure adequate serum and tissue levels of antimicrobials with activity against likely pathogens for the duration of the operation. If the agents used therapeutically are appropriate for surgical prophylaxis, administering an extra dose within 60 minutes before surgical incision is sufficient. Otherwise, the antimicrobial prophylaxis recommended for the planned procedure should be used. For patients with indwelling tubes or drains, consideration may be given to using prophylactic agents active against pathogens found in these devices before the procedure, even though therapeutic treatment for pathogens in drains is not indicated at other times. For patients with chronic renal failure receiving

vancomycin, a preoperative dose of cefazolin should be considered instead of an extra dose of vancomycin, particularly if the probable pathogens associated with the procedure are gram-negative. In most circumstances, elective surgery should be postponed when the patient has an infection at a remote site.

Allergy to β-lactam antimicrobials. Allergy to β-lactam antimicrobials may be a consideration in the selection of surgical prophylaxis. The β-lactam antimicrobials, including cephalosporins, are the mainstay of surgical antimicrobial prophylaxis and are also the most commonly implicated drugs when allergic reactions occur. Because the predominant organisms in SSIs after clean procedures are gram-positive, the inclusion of vancomycin may be appropriate for a patient with a life-threatening allergy to β-lactam antimicrobials.

Although true Type 1 (immunoglobulin E [IgE]-mediated) cross-allergic reactions between penicillins, cephalosporins, and carbapenems are uncommon, cephalosporins and carbapenems should not be used for surgical prophylaxis in patients with documented or presumed IgE-mediated penicillin allergy. Confusion about the definition of true allergy among patients and practitioners leads to recommendations for alternative antimicrobial therapy with the potential for a lack of efficacy, increased costs, and adverse events.[86,87] Type 1 anaphylactic reactions to antimicrobials usually occur 30–60 minutes after administration. In patients receiving penicillins, this reaction is a life-threatening emergency that precludes subsequent use of penicillins.[88] Cephalosporins and carbapenems can safely be used in patients with an allergic reaction to penicillins that is not an IgE-mediated reaction (e.g., anaphylaxis, urticaria, bronchospasm) or exfoliative dermatitis (Stevens-Johnson syndrome, toxic epidermal necrolysis), a life-threatening hypersensitivity reaction that can be caused by β-lactam antimicrobials and other medications.[88,89] Patients should be carefully questioned about their history of antimicrobial allergies to determine whether a true allergy exists before selection of agents for prophylaxis. Patients with allergies to cephalosporins, penicillins, or both have been excluded from many clinical trials. Alternatives to β-lactam antimicrobials are provided in Table 2 based mainly on the antimicrobial activity profiles against predominant procedure-specific organisms and available clinical data.

Drug administration

The preferred route of administration varies with the type of procedure, but for a majority of procedures, i.v. administration is ideal because it produces rapid, reliable, and predictable serum and tissue concentrations.

Timing of initial dose. Successful prophylaxis requires the delivery of the antimicrobial to the operative site before contamination occurs. Thus, the antimicrobial agent should be administered at such a time to provide serum and tissue concentrations exceeding the minimum inhibitory concentration (MIC) for the probable organisms associated with the procedure, at the time of incision, and for the duration of the procedure.[41,90] In 1985, DiPiro et al.[91] demonstrated that higher serum and tissue cephalosporin concentrations at the time of surgical incision and at the end of the procedure were achieved when the drugs were given intravenously at the time of anesthesia induction compared with administration in the operating room. The average interval between antimicrobial administration and incision was 17–22 minutes[91] (Dellinger EP, personal communication, 2011 May).

A prospective evaluation of 1708 surgical patients receiving antimicrobial prophylaxis found that preoperative administration of antimicrobials within 2 hours before surgical incision decreased the risk of SSI to 0.59%, compared with 3.8% for early administration (2–24 hours before surgical incision) and 3.3% for any postoperative administration (any time after incision).[92] In a study of 2048 patients undergoing coronary bypass graft or valve replacement surgery receiving vancomycin prophylaxis, the rate of SSI was lowest in those patients in whom an infusion was started 16–60 minutes before surgical incision.[93] This time interval (16–60 minutes before incision) was compared with four others, and the rates of SSIs were significantly lower when compared with infusions given 0–15 minutes before surgical incision ($p < 0.01$) and 121–180 minutes before incision ($p = 0.037$). The risk of infection was higher in patients receiving infusions 61–120 minutes before incision (odds ratio [OR], 2.3; 95% confidence interval [CI], 0.98–5.61) and for patients whose infusions were started more than 180 minutes before surgical incision (OR, 2.1; 95% CI, 0.82–5.62).[93]

In a large, prospective, multicenter study from the Trial to Reduce Antimicrobial Prophylaxis Errors (TRAPE) study group, the timing, duration, and intraoperative redosing of antimicrobial prophylaxis and risk of SSI were evaluated in 4472 patients undergoing cardiac surgery, hysterectomy, or hip or knee arthroplasty.[94] The majority of patients (90%) received antimicrobial prophylaxis per the SCIP guidelines.[41] Patients were assigned to one of four groups for analysis. Group 1 ($n = 1844$) received a cephalosporin (or other antimicrobial with a short infusion time) administered within 30 minutes before incision or vancomycin or a fluoroquinolone within one hour before incision. Group 2 ($n = 1796$) received a cephalosporin 31–60 minutes before incision or vancomycin 61–120 minutes before incision. Group 3 ($n = 644$) was given antimicrobials earlier than recommended, and group

4 (n = 188) received their initial antimicrobial doses after incision. The infection risk was lowest in group 1 (2.1%), followed by group 2 (2.4%) and group 3 (2.8%). The risk of infection was highest in group 4 (5.3%, p = 0.02 compared with group 1). When cephalosporins and other antimicrobials with short infusion times were analyzed separately (n = 3656), the infection rate with antimicrobials administered within 30 minutes before incision was 1.6% compared with 2.4% when antimicrobials were administered 31–60 minutes before incision (p = 0.13).

In a multicenter Dutch study of 1922 patients undergoing total hip arthroplasty, the lowest SSI rate was seen in patients who received the antimicrobial during the 30 minutes before incision.[95] The highest risk for infection was found in patients who received prophylaxis after the incision.

It seems intuitive that the entire antimicrobial dose should be infused before a tourniquet is inflated or before any other procedure that restricts blood flow to the surgical site is initiated; however, a study of total knee arthroplasties compared cefuroxime given 10–30 minutes before tourniquet inflation with cefuroxime given 10 minutes before tourniquet deflation and found no significant difference in SSI rates between the two groups.[96]

Overall, administration of the first dose of antimicrobial beginning within 60 minutes before surgical incision is recommended.[41,94,97] Administration of vancomycin and fluoroquinolones should begin within 120 minutes before surgical incision because of the prolonged infusion times required for these drugs. Because these drugs have long half-lives, this early administration should not compromise serum levels of these agents during most surgical procedures. Although the recent data summarized above suggest lower infection risk with antimicrobial administration beginning within 30 minutes before surgical incision, these data are not sufficiently robust to recommend narrowing the optimal window to begin infusion to 1–30 minutes before surgical incision. However, these data do suggest that antimicrobials can be administered too close to the time of incision. Although a few articles have suggested increased infection risk with administration too close to the time of incision,[93,96,97] the data presented are not convincing. In fact, all of these articles confirm the increased rate of SSI for antimicrobials given earlier than 60 minutes before incision. In one article, the infection rate for patients given an antimicrobial within 15 minutes of incision was lower than when antimicrobials were given 15–30 minutes before incision.[97] In another article, small numbers of patients were reported, and an assertion of high infection rates for infusion within 15 minutes of incision was made, but no numeric data or p values were provided.[98] In a third article, only 15 of over 2000 patients received antimicrobials within 15 minutes before incision.[93] Earlier studies found that giving antimicrobials within 20 minutes of incision and as close as 7 minutes before incision resulted in therapeutic levels in tissue at the time of incision.[41,90,91,94,97,98]

Dosing. To ensure that adequate serum and tissue concentrations of antimicrobial agents for prophylaxis of SSIs are achieved, antimicrobial-specific pharmacokinetic and pharmacodynamic properties and patient factors must be considered when selecting a dose. One of the earliest controlled studies of antimicrobial prophylaxis in cardiac surgery found a lower rate of infection in patients with detectable concentrations of the drug in serum at the end of surgery compared with patients in whom the drug was undetectable.[99] In another study, higher levels of antimicrobial in atrial tissue at the time of starting the pump for open-heart surgery were associated with fewer infections than were lower antimicrobial concentrations.[100] In patients undergoing colectomy, infection levels were inversely related to the serum gentamicin concentration at the time of surgical closure.[17] In general, it seems advisable to administer prophylactic agents in a manner that will ensure adequate levels of drug in serum and tissue for the interval during which the surgical site is open.

Weight-based dosing. The dosing of most antimicrobials in pediatric patients is based on body weight, but the dosing of many antimicrobials in adults is not based on body weight, because it is safe, effective, and convenient to use standardized doses for most of the adult patient population. Such standardized doses avoid the need for calculations and reduce the risk for medication errors. However, in obese patients, especially those who are morbidly obese, serum and tissue concentrations of some drugs may differ from those in normal-weight patients because of pharmacokinetic alterations that depend on the lipophilicity of the drug and other factors.[101] Limited data are available on the optimal approach to dosing of antimicrobial agents for obese patients.[102,103] If weight-based dosing is warranted for obese patients, it has not been determined whether the patient's ideal body weight or total (i.e., actual) body weight should be used. In theory, using the ideal body weight as the basis for dosing a lipophilic drug (e.g., vancomycin) could result in subtherapeutic concentrations in serum and tissue, and the use of actual body weight for dosing a hydrophilic drug (e.g., an aminoglycoside) could result in excessive concentrations in serum and tissue. Pediatric patients weighing more than 40 kg should receive weight-based doses unless the dose or daily dose exceeds the recommended adult dose.[104]

Conclusive recommendations for weight-based dosing for antimicrobial prophylaxis in obese patients cannot be made because data demonstrating

clinically relevant decreases in SSI rates from the use of such dosing strategies instead of standard doses in obese patients are not available in the published literature.

In a small, nonrandomized, two-phase study of morbidly obese adults undergoing gastroplasty and normal-weight adults undergoing upper abdominal surgery, blood and tissue concentrations of cefazolin after the administration of a 1-g preoperative dose were consistently lower in morbidly obese patients than in the normal-weight patients.[101] The concentrations in morbidly obese patients also were lower than the MICs needed for prophylaxis against gram-positive cocci and gram-negative rods. In the second phase of the study, adequate blood and tissue cefazolin concentrations were achieved in morbidly obese patients receiving preoperative doses of cefazolin 2 g, and the rate of SSIs was significantly lower in these patients compared with morbidly obese patients receiving 1-g doses during the first phase of the study.

While the optimal cefazolin dose has not been established in obese patients, a few pharmacokinetic studies have investigated the cefazolin concentrations in serum and tissue during surgical procedures.[13,105] Two small pharmacokinetic studies found that administering 1- or 2-g doses of cefazolin may not be sufficient to produce serum and tissue concentrations exceeding the MIC for the most common pathogens. In a small, single-center study, 38 adults undergoing Roux-en-Y gastric bypass surgery were classified by body mass index (BMI) in one of three groups.[13] All patients were given cefazolin 2 g i.v. 30–60 minutes before the incision, followed by a second 2-g i.v. dose three hours later. The mean serum drug concentration before the second dose of cefazolin was lower than the resistance breakpoint in all three BMI groups. Serum drug concentrations were lower in patients with a high BMI than in patients with lower BMI values. Tissue drug concentrations were lower than a targeted concentration of 8 μg/mL at all measurement times, except the time of skin closure in the patients with the lowest BMIs. These results suggest that a 1-g dose of cefazolin may be inadequate for obese patients undergoing gastric bypass surgery. A weakness of the literature on drug dosing in morbidly obese patients is the practice of reporting results by BMI rather than weight.

Doubling the normal dose of cephalosporins or making fewer adjustments based on renal dysfunction may produce concentrations in obese patients similar to those achieved with standard doses in normal-weight patients.[103] Considering the low cost and favorable safety profile of cefazolin, increasing the dose to 2 g for patients weighing more than 80 kg and to 3 g for those weighing over 120 kg can easily be justified.[41] For simplification, some hospitals have standardized 2-g cefazolin doses for all adult patients.

Gentamicin doses have been compared for prophylaxis only in colorectal surgery, where a single dose of gentamicin 4.5 mg/kg in combination with metronidazole was more effective in SSI prevention than multiple doses of gentamicin 1.5 mg/kg every eight hours.[16,17] In obese patients who weigh 20% above their ideal body weight, the dose of gentamicin should be calculated using the ideal body weight plus 40% of the difference between the actual and ideal weights.[106] If gentamicin will be used in combination with a parenteral antimicrobial with activity against anaerobic agents for prophylaxis, it is probably advisable to use 4.5–5 mg/kg as a single dose.[16] This dose of gentamicin has been found safe and effective in a large body of literature examining the use of single daily doses of gentamicin for therapeutic indications.[106-113] When used as a single dose for prophylaxis, the risk of toxicity from gentamicin is very low.

Obese patients are often underrepresented in clinical trials and are not currently considered a special population for whom FDA requires separate pharmacokinetic studies during antimicrobial research and development by the drug manufacturer. Obesity has been recognized as a risk factor for SSI; therefore, optimal dosing of antimicrobial prophylaxis is needed in these patients.[114] While a BMI of >30 kg/m^2 is commonly used to define obesity, the body fat percentage (>25% in men and >31% in women) may better predict SSI risk, because the BMI may not reflect body composition. In a recent prospective cohort study of 590 patients undergoing elective surgery, there was no significant difference in SSI rates in nonobese and obese patients when the BMI was used to define obesity (12.3% versus 11.6%, respectively).[115] However, when the body fat percentage (determined by bioelectrical impedance analysis) was used as the basis for identifying obesity (>25% in men and >31% in women), obese patients had a fivefold-higher risk of SSI than did nonobese patients (OR, 5.3; 95% CI, 1.2–23.1; $p = 0.03$). These findings suggest that body fat percentage is a more sensitive and precise measurement of SSI risk than is the BMI.

Redosing. Intraoperative redosing is needed to ensure adequate serum and tissue concentrations of the antimicrobial if the duration of the procedure exceeds two half-lives of the antimicrobial or there is excessive blood loss (i.e., >1500 mL).[17,41,94,116-121] The redosing interval should be measured from the time of administration of the preoperative dose, not from the beginning of the procedure. Redosing may also be warranted if there are factors that shorten the half-life of the antimicrobial agent (e.g., extensive burns). Redosing may not be warranted in patients in whom the half-life of the antimicrobial agent is prolonged (e.g., patients with renal insufficiency or renal failure). See Table

1 for antimicrobial-specific redosing recommendations.

Duration. The shortest effective duration of antimicrobial administration for preventing SSI is not known; however, evidence is mounting that postoperative antimicrobial administration is not necessary for most procedures.[6,7,41,122-124] The duration of antimicrobial prophylaxis should be less than 24 hours for most procedures. Cardiothoracic procedures for which a prophylaxis duration of up to 48 hours has been accepted without evidence to support the practice is an area that remains controversial. The duration of cardiothoracic prophylaxis in these guidelines is based on expert panel consensus because the available data do not delineate the optimal duration of prophylaxis. In these procedures, prophylaxis for the duration of the procedure and certainly for less than 24 hours is appropriate.

A 1992 meta-analysis of studies comparing first-generation cephalosporins and antistaphylococcal antimicrobials (e.g., penicillins) with second-generation cephalosporins in patients undergoing cardiothoracic surgery found a reduction in the rate of SSI with second-generation cephalosporins but no benefit from continuing surgical prophylaxis beyond 48 hours.[125] Reports published in 1980,[126] 1993,[127] 1997,[128] and 2000[129] involving seven studies that compared single-dose prophylaxis or prophylaxis only during the operation with durations of one to four days failed to show any reduction in SSIs with the longer durations of prophylaxis. In a more-recent observational four-year cohort study of 2641 patients undergoing coronary artery bypass graft (CABG) surgery, the extended use of antimicrobial prophylaxis (>48 hours) instead of a shorter duration of prophylaxis (<48 hours) failed to reduce the risk of SSI (OR, 1.2; 95% CI, 0.8–1.6).[130] Moreover, prolonged prophylaxis was associated with an increased risk of acquired antimicrobial resistance (cephalosporin-resistant Enterobacteriaceae and VRE) compared with short-term prophylaxis (OR, 1.6; 95% CI, 1.1–2.6).

There are no data to support the continuation of antimicrobial prophylaxis until all indwelling drains and intravascular catheters are removed.[19,31,32,41,131-134]

Topical administration of irrigations, pastes, and washes

I.V. and oral antimicrobial administration are the main focus of these guidelines, and these routes of administration are used for most surgical procedures addressed by these guidelines, with the exception of ophthalmic procedures, for which topical administration is the primary route of administration. Limited high-quality data are available regarding the use of antimicrobial irrigations, pastes, and washes that are administered topically. Studies published in the early 1980s demonstrated that prophylactic topical administration of antimicrobials in the surgical incision during various nonophthalmic procedures is superior to placebo but not superior to parenteral administration, and topical administration does not increase the efficacy of parenteral antimicrobials when used in combination for prophylaxis.[135-138] Additional high-quality data on the safety and efficacy of topical antimicrobial administration as an adjunct to i.v. administration are needed to determine the role of topical antimicrobial prophylaxis.

One area of interest for topical administration of antimicrobials, mainly gentamicin and vancomycin, is application to the sternum during cardiac procedures in combination with i.v. agents to prevent mediastinitis. This strategy has been evaluated in cohort and randomized controlled studies.[139-142] While the studies found a significantly lower rate of SSI with topical antimicrobials compared with standard prophylaxis,[140] placebo,[142] and a historical control,[139] a smaller, randomized, placebo-controlled study found no difference between groups.[141]

More recently, implantable gentamicin collagen sponges failed to show any efficacy in reducing SSIs in a large prospective study of patients undergoing cardiac surgery and resulted in an increased infection rate in patients undergoing colectomy.[143,144] The safety and efficacy of topical antimicrobials have not been clearly established; therefore, routine use of this route cannot be recommended in cardiac or other procedures.[145]

Preoperative screening and decolonization

S. aureus is the most common pathogen causing SSIs, accounting for 30% of SSIs in the United States. Colonization with *S. aureus*, primarily in the nares, occurs in roughly one in four persons and increases the risk of SSI by 2- to 14-fold.[146-152] A national survey assessing nasal colonization with *S. aureus* in the general population conducted from 2001 through 2004 found that while the rate of colonization with *S. aureus* decreased from 32.4% in 2001–02 to 28.6% in 2003–04 ($p < 0.01$), the rate of colonization with MRSA increased from 0.8% to 1.5% ($p < 0.05$).[75]

Preoperative screening for *S. aureus* carriage and decolonization strategies have been explored as means to reduce the rate of SSIs. Anterior nasal swab cultures are most commonly used for preoperative surveillance, but screening additional sites (pharynx, groin, wounds, rectum) can increase detection rates.[153] Such preoperative surveillance swabs that can be cultured on selective or nonselective media or sent for rapid polymerase chain reaction (PCR)-based screening can be used to identify colonized patients in the preoperative period. When properly used, all of these techniques can identify MSSA and MRSA. However, not all PCR-based systems will identify both MRSA

and MSSA so verification with the laboratory is needed. While many studies have focused specifically on MRSA screening in high-risk hospitalized patients in an effort to prevent MRSA SSI and hospital-acquired infections, the risk of developing an SSI remains elevated for any *S. aureus* carrier. While some authors advocate screening for MRSA carriage in the general population, the data supporting universal screening in the surgical population are more controversial.[154,155] Screening has been advocated to both identify candidates for *S. aureus* decolonization and inform the selection of optimal prophylactic antimicrobials, such as the addition of vancomycin for those colonized with MRSA.

FDA has approved intranasal mupirocin to eradicate MRSA nasal colonization in adult patients and health care workers.[156] It is noted in the prescribing information that there are insufficient data to support use in prevention of autoinfection of high-risk patients from their own nasal colonization with *S. aureus*. However, additional data have demonstrated that the use of intranasal mupirocin in nasal carriers of *S. aureus* decreases the rate of *S. aureus* infections.[157,158] One meta-analysis of seven studies focused on surgical patients only[157]; the other meta-analysis of nine studies included high-quality studies in dialysis patients.[158]

Recent studies have confirmed that *S. aureus* decolonization of the anterior nares decreases SSI rates in many surgical patients.[159] The data are most compelling in cardiac and orthopedic surgery patients. There are fewer data in general surgery patients. A large, randomized controlled trial of general, cardiac, and neurosurgical patients (n = 3864) revealed that prophylactic intranasal application of mupirocin did not significantly reduce the overall rate of *S. aureus* SSIs (2.3% in the mupirocin group versus 2.4% in the control group) but did decrease the rate of *S. aureus* SSI among *S. aureus* carriers (3.7% in the mupirocin group versus 5.9% in the control group).[160]

Another randomized controlled trial found no significant difference in the rate of postoperative *S. aureus* SSIs among cardiac surgery patients receiving intranasal mupirocin and those receiving placebo, but the study was limited by the small numbers of patients (n = 257) and reported SSIs (n = 5).[161] Among elective orthopedic patients undergoing implantation and other procedures, a randomized clinical trial demonstrated a nonsignificant reduction in the rate of postoperative *S. aureus* SSIs in patients receiving mupirocin (n = 315, 3.8%) compared with those receiving placebo (n = 299, 4.7%).[150]

A recent randomized, double-blind, placebo-controlled, multicenter study conducted in the Netherlands found that the use of mupirocin nasal ointment and chlorhexidine baths in identified *S. aureus* carriers reduced the risk of hospital-associated *S. aureus* infections.[162] In the study, a real-time PCR assay was used to rapidly identify *S. aureus* nasal carriers; all of the *S. aureus* isolates were susceptible to methicillin. Deep SSIs occurred in 0.9% of the mupirocin–chlorhexidine-treated group (4 of 441 patients) versus 4.4% of the placebo group (16 of 367 patients) (relative risk, 0.21; 95% CI, 0.07–0.62). The reduction in superficial SSIs was less marked (1.6% versus 3.5%; relative risk, 0.45; 95% CI, 0.18–1.11). It is plausible that this approach would be beneficial in a setting of MRSA, but it has not been proven.

Most studies conclude that the use of preoperative intranasal mupirocin in colonized patients is safe and potentially beneficial as an adjuvant to i.v. antimicrobial prophylaxis to decrease the occurrence of SSIs. However, the optimal timing and duration of administration are not standardized. In most studies, mupirocin was used for five days before the operation. While *S. aureus* resistance to mupirocin has been detected,[148,162] raising concerns about the potential for widespread problems with resistance from routine use of this agent, resistance has only rarely been seen in the preoperative setting. Low-level resistance is associated with an increased rate of failure of decolonization and has been seen in institutions that use standardized mupirocin decolonization protocols.[163] Therefore, when decolonization therapy (e.g., mupirocin) is used as an adjunctive measure to prevent *S. aureus* SSI, surveillance of susceptibility of *S. aureus* isolated from SSIs to mupirocin is recommended.[164] While universal use of mupirocin is discouraged, specific recommendations for the drug's use can be found in the cardiac and orthopedic sections of these guidelines.

Future research

Additional research is needed in several areas related to surgical antimicrobial prophylaxis. The risks and benefits of continuing antimicrobial prophylaxis after the conclusion of the operative procedure, including dosing and duration, need to be further evaluated. Insight is needed to make specific recommendations for intraoperative repeat dosing, weight-based dosing in obese patients, and timing of presurgical antimicrobials that must be administered over a prolonged period (e.g., vancomycin, fluoroquinolones). Additional clarification is needed regarding targeted antimicrobial concentrations and intraoperative monitoring of antimicrobial serum and tissue concentrations to optimize efficacy. The role of topical administration of antimicrobial agents as a substitute for or an adjunct to i.v. antimicrobial prophylaxis needs to be further evaluated. Additional data are needed to guide the selection of antimicrobial agents for prophylaxis, particularly combination regimens, for patients with allergies to β-lactam antimicro-

bials. Data are also needed to devise strategies to optimize antimicrobial prophylaxis in patients and facilities with a high risk or high prevalence of resistant organisms implicated in SSIs (e.g., MRSA). Optimal strategies for screening for *S. aureus* and decolonization for certain procedures need to be identified. Finally, outcomes studies are needed to assess the impact of using quality measures and pay-for-performance incentives designed to reduce surgical morbidity and mortality.

Cardiac procedures

Background. Cardiac procedures include CABG procedures, valve repairs, and placement of temporary or permanent implantable cardiac devices, including ventricular assist devices (VADs). SSIs, including mediastinitis and sternal wound infection, are rare but serious complications after cardiac procedures. In patients undergoing CABG, the mean frequency of SSIs depending on NHSN SSI risk index category ranges from 0.35 to 8.49 per 100 operations when donor sites are included.[165] The mean frequency of SSIs depending on NHSN SSI risk index category for patients undergoing CABG with only chest incisions ranges from 0.23 to 5.67 per 100 operations.[165] Most of these infections are superficial in depth. Patient-related and procedure-related risk factors for SSIs after cardiac procedures have been identified from several single-center cohort and case–control studies.[117,128,166-176] These include diabetes,[166,169,171-175] hyperglycemia,[177-182] peripheral vascular disease,[171,172,174] chronic obstructive pulmonary disease,[166,174,175] obesity (BMI of >30 kg/m^2),[166-168,171,173-176] heart failure,[171,172] advanced age,[117,128,166,172] involvement of internal mammary artery,[168-172] reoperation,[169-171] increased number of grafts,[171] long duration of surgery,[117,166,167,176] and *S. aureus* nasal colonization.[146,160]

Patients requiring extracorporeal membrane oxygenation (ECMO) as a bridge to cardiac or lung transplantation should be treated with a similar approach. If there is no history of colonization or previous infection, the general recommendations for SSI antimicrobial prophylaxis for the specific procedure should be followed. For ECMO patients with a history of colonization or previous infection, changing the preoperative antimicrobial prophylaxis to cover these pathogens must be considered, weighing whether the pathogen is relevant to SSIs in the planned procedure.

Organisms. Almost two thirds of organisms isolated in both adult and pediatric patients undergoing cardiac procedures are gram-positive, including *S. aureus*, coagulase-negative staphylococcus, and, rarely, *Propionibacterium acnes.* Gram-negative organisms are less commonly isolated in these patients and include *Enterobacter* species, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Acinetobacter* species.[93,139,146,183-192]

Efficacy. The SSI rate in cardiac procedures is low, but there are potential consequences if infection occurs. Multiple studies have found that antimicrobial prophylaxis in cardiac procedures lowers the occurrence of postoperative SSI up to fivefold.[125]

Choice of agent. Cephalosporins have been the most studied antimicrobials for the prevention of SSIs in cardiac procedures. Both first-generation (cefazolin) and second-generation (cefamandole and cefuroxime) cephalosporins have been shown to be effective in reducing SSI in cardiac surgery; however, the superiority of one class over another has not been proven.[125,127,193-199]

A meta-analysis comparing cephalosporins with glycopeptides (e.g., vancomycin) as antimicrobial prophylaxis regimens for cardiac procedures found a higher frequency of postoperative chest and deep-chest SSIs and a trend toward an increased risk of gram-positive SSI in the glycopeptide group but a lower frequency of SSIs caused by resistant gram-positive pathogens.[72] The routine use of vancomycin for the prevention of SSIs is not recommended, based on limited evidence of efficacy and concerns of increased glycopeptide resistance of microorganisms.[8,116] There is no clear evidence to support the use of vancomycin, alone or in combination with other antimicrobials, for routine antimicrobial prophylaxis in institutions that have a high prevalence of MRSA.[8,11,41,72,73,116,200] Vancomycin should be considered in patients who are colonized with MRSA.[41,116,201] The accepted alternative antimicrobial for β-lactam-allergic patients undergoing cardiac procedures is vancomycin or clindamycin for gram-positive coverage.[41,116,201,202] The addition of an aminoglycoside, aztreonam, or a fluoroquinolone may be prudent when gram-negative pathogens are a concern.[8,116]

Mupirocin. The proportion of infections related to *S. aureus* among patients undergoing cardiac surgery and the increase in MRSA as a cause of SSIs at some institutions have led to investigations of methods for preoperative eradication, particularly with intranasal mupirocin.[203] Readers are referred to the Common Principles section of these guidelines for discussion of the use of intranasal mupirocin. Of note, the data demonstrated a 45% reduction in *S. aureus* SSIs with the use of preoperative mupirocin among patients known to be colonized with *S. aureus* who undergo cardiac procedures.[157,193] Institutions should monitor for mupirocin resistance periodically.

Topical administration. Additional information on topical administration of antimicrobials can be found in the Common Principles section of these guidelines. Use of topical antimicrobials, mainly gentamicin or vancomycin, applied to the sternum during cardiac procedures in com-

bination with i.v. agents to prevent mediastinitis has been evaluated in both cohort[139] and randomized controlled studies.[140-142] While the studies found a significantly lower rate of SSIs with topical antimicrobials compared with standard prophylaxis,[140] placebo,[142] and a historical control,[139] a smaller randomized, placebo-controlled study found no difference between groups.[141] More recent studies of gentamicin collagen sponges failed to show any efficacy in a large prospective study of cardiac surgery.[143] The safety and efficacy of topical antimicrobials have not been clearly established and therefore cannot be recommended for routine use in cardiac procedures.[139-142]

Cardiopulmonary bypass. Cardiopulmonary bypass (CPB) is a common surgical technique in cardiac procedures that alters the volume of distribution and bioavailability of medications administered during the procedure.[116,204,205] Several small cohort or comparative studies[128,204-213] have evaluated the serum and tissue concentrations of several routinely used antimicrobial prophylactic agents (i.e., cefazolin, cefuroxime, gentamicin, and vancomycin) in patients undergoing CPB during cardiac procedures. Until further clinical outcomes data and well-designed studies become available to inform alternative dosing strategies, routinely used doses of common antimicrobial agents should be used in patients undergoing CPB during cardiac procedures.

Duration. The optimal duration of antimicrobial prophylaxis for cardiac procedures continues to be evaluated. Data support a duration ranging from a single dose up to 24 hours postoperatively.[41,99,131,191,214-217] No significant differences were found in several small studies in patients undergoing cardiac procedures between these dosing strategies in patients primarily receiving first- or second-generation cephalosporins. Although a recent meta-analysis suggested the possibility of increased efficacy with cardiac surgical prophylaxis extending beyond 24 hours, the authors noted that the findings were limited by the heterogeneity of antimicrobial regimens used and the risk of bias in the published studies.[218] The comparisons of varying durations were performed with different antimicrobials with differing efficacy and do not support longer durations. Consequently, this meta-analysis does not provide evidence to support changing the currently accepted prophylaxis duration of less than 24 hours, particularly given the evidence from studies involving noncardiac operations. The currently accepted duration of prophylaxis for cardiac procedures is less than 24 hours, but prophylaxis should be continued for the duration of the procedure.[41,59,126-129,131,201]

Two small studies did not support the continuation of antimicrobial prophylaxis until intravascular catheters or intraaortic balloon pumps were removed, due to a lack of influence on infections or catheter colonization compared with short-course (24 hours) cefazolin or cefuroxime.[219,220] The practice of continuing antimicrobial prophylaxis until all invasive lines, drains, and indwelling catheters are removed cannot be supported due to concerns regarding the development of drug-resistant organisms, superinfections, and drug toxicity.[41,131]

Pediatric efficacy. The rate of SSI in pediatric cardiac procedures is sometimes higher than in adult patients.[20,31,221] Significant risk factors in pediatric patients with a mediastinal SSI included the presence of other infections at the time of the procedure, young age (newborns and infants), small body size, the duration of the procedure (including CPB time), the need for an intraoperative blood transfusion, an open sternum postoperatively, the need for a reexploration procedure, the length of stay in the intensive care unit, an NNIS/NHSN risk score of 2, and the performance of emergency procedures.[20,31,221]

The organisms of concern in pediatric patients are the same as those in adult patients.[20,21,31,221] However, MRSA is rarely a concern in this population as a risk factor for SSI.[221] Pediatric patients considered at high risk for MRSA infection are those with preoperative MRSA colonization or a history of MRSA infection, neonates younger than one month of age, and neonates under three months of age who have been in the hospital since birth or have a complex cardiac disorder.[21] Strategies such as intranasal mupirocin and changes in antimicrobial prophylactic agent to vancomycin led to decreased rates of MRSA carriage and the absence of MRSA infections in one time-series evaluation; however, the overall clinical impact of these efforts is still unclear.[21,221]

No well-controlled studies have evaluated the efficacy of antimicrobial prophylaxis in pediatric patients undergoing cardiac procedures. Therefore, the efficacy of antimicrobial prophylaxis is extrapolated from adult studies and should be considered the standard of care for pediatric cardiac surgery patients.[19]

No well-designed studies or consensus has established the appropriate doses for common antimicrobial prophylactic agents for use in pediatric cardiac patients. Antibiotic doses have been extrapolated from guidelines for the prevention of bacterial endocarditis.[11] In recent evaluations, doses of cefazolin have ranged from 25 to 50 mg/kg,[19-21,31] and vancomycin doses have ranged from 10 to 20 mg/kg.[19-21,31,222-226] Gentamicin doses used in studies have included 2.5[20] and 5 mg/kg[22]; however, the study authors[22] felt that the higher dose was excessive. The expert panel recognizes that the usual total daily dose for pediatric patients older than six months can be 6.5–7.5 mg/kg and that dosing schedules for younger patients may be complicated.

Recommendations. For patients undergoing cardiac procedures, the recommended regimen is a single preincision dose of cefazolin or cefuroxime with appropriate intraoperative redosing (Table 2). Currently, there is no evidence to support continuing prophylaxis until all drains and indwelling catheters are removed. Clindamycin or vancomycin is an acceptable alternative in patients with a documented β-lactam allergy. Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. If organizational SSI surveillance shows that gram-negative organisms cause infections for patients undergoing these operations, practitioners should combine clindamycin or vancomycin with another agent (cefazolin if the patient is not β-lactam allergic; aztreonam, aminoglycoside, or single-dose fluoroquinolone if the patient is β-lactam allergic). Mupirocin should be given intranasally to all patients with documented *S. aureus* colonization. (Strength of evidence for prophylaxis = A.)

Cardiac device insertion procedures

Background. Antimicrobial prophylaxis is the standard of care for patients undergoing cardiac implantable device insertion (e.g., pacemaker implantation).[227] Based on available data and perceived infection risk, antimicrobial prophylaxis is not routinely recommended for cardiac catheterization or transesophageal echocardiogram.[228]

NHSN has reported a mean SSI rate after pacemaker placement of 0.44 per 100 procedures.[165] This rate may underestimate the risk of late SSI and complications.[229] Risk factors for device-related infection after implantation of cardioverter–defibrillator systems or pacemakers identified in two large, prospective, multicenter cohort studies[230,231] and a large case–control study[232] included fever within 24 hours before implantation, temporary pacing before implantation, and early reintervention for hematoma or lead replacement[230]; corticosteroid use for more than one month during the preceding year and more than two leads in place compared with two leads[232]; and development of pocket hematoma.[231] In all of the evaluations, antimicrobial prophylaxis was found to be protective against device-related infection.[230-232] Limited data are available on the efficacy and optimal dose and duration of antimicrobial prophylaxis in patients undergoing implantation of a new pacemaker, pacing system, or other cardiac device.

A meta-analysis of 15 prospective, randomized, controlled, mainly open-label studies evaluated the effectiveness of systemic antimicrobial prophylaxis compared with controls (no antimicrobials) on infection rates after pacemaker implantation.[227] Antibiotics included penicillins or cephalosporins with a duration ranging from a single preoperative dose to four days postoperatively. A consistent and significant protective effect of antimicrobial prophylaxis was found and encouraged the routine use of antimicrobial prophylaxis in patients undergoing permanent pacemaker implantation. A prospective, single-center cohort study found a low rate (1.7%) of SSI complications with a single 2-g dose of cefazolin in patients undergoing implantation of a new pacemaker, pulse-generator replacement, or upgrading of a preexisting pacing system.[233] A notable limitation of the study was the exclusion of patients with temporary percutanous cardiac stimulators who are at high risk of infection.

A large, randomized, double-blind, placebo-controlled study found a significantly lower rate of SSI with a single 1-g dose of cefazolin (0.64%) compared with placebo (3.28%) ($p = 0.016$) given immediately before device implantation or generator replacement in a permanent pacemaker, implantable cardioverter defibrillator, or cardiac resynchronization device in a surgical operating room.[231] The expert panel noted that the cefazolin dose was not adjusted for patient weight. Recently, AHA produced evidence-based guidelines that recommend the use of a single dose of a preoperative antimicrobial.[229]

VADs are increasingly used to bridge patients to transplantation or to support individuals who do not respond to medical therapy for congestive heart failure. Very limited data exist on infection rates, and there are no published studies that demonstrate the effectiveness of preoperative antimicrobial therapy. Using 2006–08 data from the Interagency Registry for Mechanically Assisted Circulatory Support, Holman and colleagues[234] reported that most infections related to mechanical cardiac support devices were bacterial (87%), with the remainder associated with fungal (9%), viral (1%), protozoal (0.3%), or unknown (2%) causes. Driveline infections are primarily caused by staphylococcal species from the skin. Fungal organisms also play an important role in VAD infections, most notably *Candida* species, and carry a high risk of mortality. A recent survey of antimicrobial surgical prophylaxis with VADs illustrates the variability and lack of consensus with regimens, using anywhere from one to four drugs for a duration of 24–72 hours.[235] Immediate postoperative infections are caused by gram-positive organisms. Complications from long-term infections should not be confused with immediate postprocedure SSIs.[236] Based on the consensus of the expert panel, antimicrobial prophylaxis for replacement of a VAD due to ongoing or recent infection should incorporate coverage directed at the offending organism or organisms. While many centers use vancomycin plus ciprofloxacin plus fluconazole, this practice is not based on the published evidence.

Recommendation. A single dose of cefazolin or cefuroxime is recommended for device implantation or generator replacement in a permanent pacemaker, implantable cardioverter defibrillator, or cardiac resynchronization device. (Strength of evidence for prophylaxis = A.) There is limited evidence to make specific recommendations for VADs, and each practice should tailor protocols based on pathogen prevalence and local susceptibility profiles. Clindamycin or vancomycin is an acceptable alternative in patients with a documented β-lactam allergy. Vancomycin should be considered for prophylaxis in patients known to be colonized with MRSA.

Thoracic procedures

Background. Noncardiac thoracic procedures include lobectomy, pneumonectomy, thoracoscopy, lung resection, and thoracotomy. In addition to SSIs, postoperative nosocomial pneumonia and empyema are of concern after thoracic procedures.[237]

NHSN has reported that the rate of infection associated with thoracic surgery ranges from 0.76% to 2.04%.[165] Studies have found that the reported rate of SSIs after thoracic procedures in patients receiving antimicrobial prophylaxis ranged from 0.42% to 4%.[238-241] One study found an SSI rate of 14% when prophylaxis was not used.[239] The reported rates of pneumonia and empyema with antimicrobial prophylaxis are 3–24% and 0–7%, respectively.[237,239-244]

Video-assisted thoracoscopic surgery (VATS) is commonly used for thoracic procedures. In some settings, VATS constitutes one third or more of all thoracic surgical procedures.[245] Since VATS uses small incisions, the rate of SSIs is lower compared with the rate associated with open thoracic surgical procedures.[246] A prospective cohort study ($n = 346$) confirmed a low rate of SSIs (1.7%) after minimally invasive VATS procedures.[240] An additional prospective study of 988 lung resection patients confirmed that the SSI rate was significantly lower (5.5%) in VATS patients than in open thoracotomy patients (14.3%).[247] Furthermore, SSI correlated with the duration of surgery, serum albumin, concurrent comorbidity, age, and forced expiratory volume in one second. Antimicrobial prophylaxis recommendations in this section refer to both open thoracotomy and VATS procedures. Based on available data and perceived infection risk, antimicrobial prophylaxis is not routinely recommended for chest tube insertion.

Results of a prospective cohort and case–control study revealed the following independent risk factors for pneumonia after thoracic procedures: extent of lung resection, intraoperative bronchial colonization, chronic obstructive pulmonary disease, BMI of >25 kg/m^2, induction therapy (chemotherapy, radiotherapy, or chemoradiotherapy), advanced age (≥75 years old), and stage III or IV cancer.[243,244]

Organisms. The organisms reported from SSIs in patients undergoing thoracic procedures were *S. aureus* and *S. epidermidis*.[237] Organisms isolated in patients with postoperative pneumonia included gram-positive (*Streptococcus* and *Staphylococcus* species), gram-negative (*Haemophilus influenzae*, *Enterobacter cloacae*, *K. pneumoniae*, *Acinetobacter* species, *P. aeruginosa*, and *Moraxella catarrhalis*), and fungal (*Candida* species) pathogens.[237,239-243]

Efficacy. Antimicrobial prophylaxis is the standard of care for patients undergoing noncardiac thoracic surgery, including pulmonary resection.[11,201,237] One randomized, double-blind, placebo-controlled, single-center study of patients in Spain undergoing pulmonary resection, persistent pneumothorax without thoracotomy tube before surgery, and nonpulmonary thoracic surgical procedures, excluding those involving the esophagus and exploratory thoracotomies, compared a single dose of cefazolin 1 g i.v. and placebo given 30 minutes before the procedure.[239] The study was stopped early due to the significant difference in SSI rates between groups (1.5% with cefazolin versus 14% with placebo, $p < 0.01$). No differences in the rates of pneumonia and empyema were seen between groups, but these were not endpoints of the study.

Choice of agent. There is no clear optimal choice for antimicrobial prophylaxis in thoracic procedures. The need to consider pneumonia and empyema as well as SSIs after thoracic procedures has been raised in the literature.[237,241-244] There are a limited number of small, single-center, randomized controlled or cohort studies that evaluated several antimicrobial agents. One small, randomized controlled study and one cohort study found that ampicillin–sulbactam was significantly better than cephalosporins (cefazolin and cefamandole) for preventing pneumonia.[242,243] No statistically significant difference was found between cefuroxime and cefepime in the rate of postoperative SSI, pneumonia, or empyema in a small, randomized controlled study in patients undergoing elective thoracotomy.[241] Lower rates of infections and susceptibility of all organisms were noted with cefuroxime compared with cefepime. Therefore, the study authors concluded that cefuroxime was marginally more effective and was more cost-effective than cefepime.

Duration. No clear consensus on the duration of antimicrobial prophylaxis has been established. Studies have evaluated different dosing strategies for cephalosporins or penicillins, with most studies using single doses given preoperatively within 60 minutes before surgical incision.[237,239,240,242,244] Studies found differing results when comparing agents given for 24 hours (cefepime, ampicillin–sulbactam) and 48 hours

(cefuroxime, cefamandole); however, these findings may be attributable to the different antimicrobials tested.[241,243] Additional discussion on dosing is provided in the Common Principles section of these guidelines.

Recommendations. In patients undergoing thoracic procedures, a single dose of cefazolin or ampicillin–sulbactam is recommended (Appendix B). Clindamycin or vancomycin is an acceptable alternative in patients with a documented β-lactam allergy. Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. If organizational SSI surveillance shows that gram-negative organisms are associated with infections during these operations or if there is risk of gram-negative contamination of the surgical site, practitioners should combine clindamycin or vancomycin with another agent (cefazolin if the patient is not β-lactam allergic; aztreonam, aminoglycoside, or single-dose fluoroquinolone if the patient is β-lactam allergic). (Strength of evidence for prophylaxis for VATS = C; strength of evidence for prophylaxis for other thoracic procedures = A.)

Gastroduodenal procedures

Background. The gastroduodenal procedures considered in these guidelines include resection with or without vagotomy for gastric or duodenal ulcers, resection for gastric carcinoma, revision required to repair strictures of the gastric outlet, percutaneous endoscopic gastrostomy (PEG) insertion, perforated ulcer procedures (i.e., Graham patch repair), pancreaticoduodenectomy (Whipple procedure), and bariatric surgical procedures (gastric bypass, gastric banding, gastroplasty, other restrictive procedures, biliopancreatic diversion). Studies specifically addressing antimicrobial prophylaxis for gastroesophageal reflux disease procedures (Nissen fundoplication) or highly selective vagotomy for ulcers (usually done laparoscopically) could not be identified. Antireflux procedures and highly selective vagotomy are clean procedures in contrast to essentially all other gastroduodenal procedures that are clean-contaminated. Other procedures that are generally performed using laparoscopic or endoscopic techniques (e.g., endoscopic retrograde cholangiopancreatography) are not specifically discussed in this document. Natural orifice transluminal endoscopic surgery (NOTES) is a developing operative technique using natural orifices (e.g., vagina, anus, mouth, stomach) for entry into the abdomen that leaves no visible scar.[248] No studies on antimicrobial prophylaxis using NOTES have been published. SSI rates reported in patients not receiving antimicrobial prophylaxis were 6% after vagotomy and drainage, 13% after gastric ulcer procedures, 6.8–17% after procedures for gastric cancer,[249-253] 8% for pancreaticoduodenectomy,[254] and 23.9–26% after PEG insertion.[255,256]

The stomach is an effective barrier to bacterial colonization; this is at least partially related to its acidity. The stomach and the duodenum typically contain small numbers of organisms ($<10^4$ colony-forming units [CFU]/mL), the most common of which are streptococci, lactobacilli, diphtheroids, and fungi.[257,258] Treatment with agents that increase gastric pH increases the concentration of gastric organisms.[259-261] Alterations in gastric and duodenal bacterial flora as a result of increases in gastric pH have the potential to increase the postoperative infection rate.[262,263]

The risk of postoperative infection in gastroduodenal procedures depends on a number of factors, including the gastroduodenal procedure performed. Patients who are at highest risk include those with achlorhydria, including those receiving pharmacotherapy with histamine H_2-receptor antagonists or proton-pump inhibitors,[264] gastroduodenal perforation, decreased gastric motility, gastric outlet obstruction, morbid obesity, gastric bleeding, or cancer.[265] Similar to other types of surgical procedures, risk factors for SSIs related to gastroduodenal procedures include long procedure duration,[252,266,267] performance of emergency procedures,[250,261] greater than normal blood loss,[251,252] American Society of Anesthesiologists (ASA) classification of ≥3, and late administration of antimicrobials.[268]

Organisms. The most common organisms cultured from SSIs after gastroduodenal procedures are coliforms (*E. coli, Proteus* species, *Klebsiella* species), staphylococci, streptococci, enterococci, and occasionally *Bacteroides* species.[101,269-276]

Efficacy. Randomized controlled trials have shown that prophylactic antimicrobials are effective in decreasing postoperative infection rates in high-risk patients after gastroduodenal procedures. The majority of available studies were conducted in single centers outside of the United States. Relative to other types of gastrointestinal tract procedures, the number of clinical trials evaluating antimicrobial prophylaxis for gastroduodenal procedures is limited. In placebo-controlled trials, infection rates ranged from 0% to 22% for patients receiving cephalosporins or penicillins and from 1.7% to 66% for patients receiving placebo.[270,271,273-275,277-284] The difference was significant in most studies.

Data support antimicrobial prophylaxis for patients undergoing PEG insertion.[264,285-287] A Cochrane review of systemic antimicrobial prophylaxis for PEG procedures that included 11 randomized controlled trials and 1196 patients found a statistically significant reduction in peristomal infections with antimicrobial prophylaxis (OR, 0.35; 95% CI, 0.23–0.48).[288] Two meta-analyses found statistically significant decreases in SSIs with antimicrobial prophylaxis compared with placebo or controls, from 23.9–26% to

6.4–8%, respectively.[255,256] Most well-designed, randomized controlled studies found a significant decrease in postoperative SSIs or peristomal infections with single i.v. doses of a cephalosporin or penicillin, ranging from 11% to 17%, compared with from 18% to 66% with placebo or no antimicrobials.[279-282,288] Conflicting results have been seen in studies evaluating the use of preoperative patient MRSA screening, decontamination washes and shampoos, five-day preoperative treatment with intranasal mupirocin, and single-dose teicoplanin preoperative prophylaxis to decrease postoperative MRSA infections during PEG insertion.[289,290]

While there have been no well-designed clinical trials of antimicrobial prophylaxis for patients undergoing bariatric surgical procedures, treatment guidelines support its use based on morbid obesity and additional comorbidities as risk factors for postoperative infections.[264,291] There is no consensus on the appropriate antimicrobial regimen; however, higher doses of antimicrobials may be needed for adequate serum and tissue concentrations in morbidly obese patients.[13,268,291]

A notable risk factor for SSIs after esophageal and gastroduodenal procedures is decreased gastric acidity and motility resulting from malignancy or acid-suppression therapy.[264,276] Therefore, antimicrobial prophylaxis is indicated for patients undergoing gastric cancer procedures (including gastrectomy) and gastroduodenal procedures related to gastric and duodenal ulcer disease or bariatric surgery or pancreaticoduodenectomy. Evaluations of practice for pancreaticoduodenectomy show that antimicrobials are typically given due to concerns of bile contamination. Prophylaxis for gastroduodenal procedures that do not enter the gastrointestinal tract, such as antireflux procedures, should be limited to high-risk patients due to lack of data supporting general use in all patients. Furthermore, laparoscopic antireflux procedures are associated with very low SSI rates (0.3%) compared with open antireflux procedures (1.4%), just as laparoscopic gastric bypass procedures are associated with lower rates than in open procedures (0.4% versus 1.2%).[292]

Choice of agent. The most frequently used agents for gastroduodenal procedures were first-generation[271,273,277,278,284,293-297] and second-generation[269,270,274,275,280,293,294,298] cephalosporins. No differences in efficacy between first- and second-generation cephalosporins were found. Amoxicillin–clavulanate[279,282,283,299] and ciprofloxacin[269,300] were also evaluated with similar results. Relatively few studies have compared the efficacy of different agents in reducing postoperative infection rates.

One meta-analysis recommended using a single dose of an i.v. broad-spectrum antimicrobial for SSI prophylaxis in these patients,[256] while another found no differences between penicillin- or cephalosporin-based regimens and three-dose or single-dose regimens.[255] In a comparative study, oral or i.v. ciprofloxacin and i.v. cefuroxime were similarly effective in upper gastrointestinal procedures, including gastrectomy, vagotomy, and fundoplication.[300] No differences in efficacy were seen between ceftriaxone and combination ceftriaxone and metronidazole for PEG insertion in pediatric patients.[301] An open-label study found a significant decrease in local peristomal and systemic infection (i.e., pneumonia) after PEG insertion after a single 1-g i.v. dose of ceftriaxone was given 30 minutes before surgery when compared with placebo (13.3% and 36.3%, respectively; $p < 0.05$).[281] No differences were noted between cefotaxime and piperacillin–tazobactam for PEG SSIs.[288] Ampicillin–sulbactam and cefazolin had equal efficacy in gastrectomy.[253] One study found that piperacillin–tazobactam in combination with ciprofloxacin or gentamicin was the most active regimen against bacteria recovered from bile in pancreatoduodenectomy patients.[302]

Duration. The majority of studies evaluated a single dose of cephalosporin or penicillin.[256,279-284,288,290,297] The available data indicate that single-dose and multiple-dose regimens are similarly effective. Three studies compared single- and multiple-dose regimens of cefamandole,[294] amoxicillin–cluvulanate,[299] and ampicillin–sulbactam and cefazolin.[253] There were no significant differences in SSI rates. Multiple-dose regimens of first-generation (cefazolin) or second-generation (cefotiam) cephalosporins of four days, operative day only, and three days in duration did not differ in overall SSI rates.[295]

Recommendations. Antimicrobial prophylaxis in gastroduodenal procedures should be considered for patients at highest risk for postoperative infections, including risk factors such as increased gastric pH (e.g., patients receiving acid-suppression therapy), gastroduodenal perforation, decreased gastric motility, gastric outlet obstruction, gastric bleeding, morbid obesity, ASA classification of ≥3, and cancer.

A single dose of cefazolin is recommended in procedures during which the lumen of the intestinal tract is entered (Table 2). (Strength of evidence for prophylaxis = A.) A single dose of cefazolin is recommended in clean procedures, such as highly selective vagotomy, and antireflux procedures only in patients at high risk of postoperative infection due to the presence of the above risk factors. (Strength of evidence for prophylaxis = C.) Alternative regimens for patients with β-lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone. Higher doses of antimicrobials are uniformly recommended in morbidly obese patients undergoing bariatric procedures. Higher doses of antimicrobials should be con-

sidered in significantly overweight patients undergoing gastroduodenal and endoscopic procedures.

Biliary tract procedures

Background. Biliary tract procedures include cholecystectomy, exploration of the common bile duct, and choledochoenterostomy. These guidelines pertain only to patients undergoing biliary tract procedures with no evidence of acute biliary tract infection and to patients with community-acquired acute cholecystitis of mild-to-moderate severity. As noted in the Common Principles section, patients receiving therapeutic antimicrobials for an infection before surgery should be given additional antimicrobial prophylaxis before surgery.

These guidelines do not address patients requiring biliary tract procedures for more-severe infections, including community-acquired acute cholecystitis with severe physiological disturbance, advanced age, or immunocompromised state; acute cholangitis; and health-care-associated or nosocomial biliary infections. These biliary tract infections are treated as complicated intraabdominal infections.[303] All patients with a suspected biliary tract infection who undergo biliary tract surgery should receive preoperative i.v. antimicrobials.

The majority of published literature regarding SSIs in biliary tract procedures focuses on cholecystectomy. The overall reported rate of postoperative infection in open biliary tract procedures with antimicrobial prophylaxis is 1–19%.[292,304-311] Infection rates after laparoscopic cholecystectomy range from 0% to approximately 4% in patients without antimicrobial prophylaxis[308,312-320] and from 0% to 7% with prophylaxis.[292,304-323] Several studies found that laparoscopic cholecystectomy SSI rates were significantly lower than those associated with open cholecystectomy.[292,306-311]

Risk factors associated with postoperative SSIs after biliary procedures include performance of emergency procedures,[305] diabetes,[305,306,311,315,317] longer procedure duration (over 120 minutes),[305,317,324] intraoperative gallbladder rupture,[305] age of >70 years,[6,311,315,317,325] open cholecystectomy,[7,311] conversion of laparoscopic to open cholecystectomy,[7] higher ASA classification (≥3),[306,310,317] episode of biliary colic within 30 days before the procedure,[315,316] reintervention in less than a month for noninfectious complications,[310] acute cholecystitis,[6,7,306] bile spillage,[7] jaundice,[6,7,306] pregnancy,[7] nonfunctioning gallbladder,[6] and immunosuppression.[7]

The biliary tract is usually sterile. Patients with bacteria in the bile at the time of surgery may be at higher risk of postoperative infection[305,326,327]; however, some studies have found no association between the presence of bacteria in the bile and infection.[305,315,316,319,321] Obesity (a BMI of >30 kg/m^2) was found to be a risk factor in some studies[306] but not in others.[315,319] Laparoscopic cholecystectomy was associated with a significantly decreased risk for SSI.[292,310,324,325]

Organisms. The organisms most commonly associated with infection after biliary tract procedures include *E. coli, Klebsiella* species, and enterococci; less frequently, other gram-negative organisms, streptococci, and staphylococci are isolated.[305,306,312,315,316,318,319,321,326,328-338] Anaerobes are occasionally reported, most commonly *Clostridium* species.

Recent studies have documented increasing antimicrobial resistance in the causative pathogens in biliary tract infections and other intraabdominal infections, with up to 40% of *E. coli* isolates resistant to ampicillin–sulbactam and fluoroquinolones.[339-341] Due to this increasing resistance of *E. coli* to fluoroquinolones and ampicillin–sulbactam, local population susceptibility profiles should be reviewed to determine the optimal antimicrobials for SSI prevention in biliary tract procedures.

Efficacy. Numerous studies have evaluated the use of prophylactic antimicrobials during biliary tract procedures, with a focus on laparoscopic cholecystectomy. Laparoscopic cholecystectomy has replaced open cholecystectomy as the standard of practice because of the reduction in recovery time and shorter hospital stay. The majority of studies of antimicrobial prophylaxis for laparoscopic cholecystectomy were underpowered and varied in control groups used (placebo, active, or no treatment), follow-up (from 30 to 60 days, while some studies did not clearly define length of time), and how SSIs were detected and reported.[308,312-316,318,319,321,322] Some studies included patients who were converted from laparoscopic to open cholecystectomy and others did not.

A large, multicenter, quality-assurance study in Germany assessed the effectiveness of antimicrobial prophylaxis in laparoscopic and open cholecystectomies.[308] This study included 4477 patients whose antimicrobial choice and dosage regimens were at the discretion of the medical center and surgeon. Antimicrobials used included first-, second-, and third-generation cephalosporins or penicillins alone or in combination with metronidazole, gentamicin, or both metronidazole and gentamicin. The most common cephalosporin used was ceftriaxone, allowing its data to be separated from data for other antimicrobials. Antimicrobial prophylaxis was administered to 2217 patients (ceftriaxone [n = 787 laparoscopic and n = 188 open] and other antimicrobials [n = 229 laparoscopic and n = 229 open]); none was given to 1328 laparoscopic and 932 open cholecystectomy patients. Significantly lower overall infectious complications occurred in patients receiving antimicrobial prophylaxis (0.8% ceftriaxone and 1.2% other antimicrobials), compared with 5%

of those who received no prophylaxis ($p < 0.05$). The overall rates of infectious complications were 0.6%, 0.8%, and 3.3% in patients undergoing laparoscopic cholecystectomy receiving ceftriaxone, other antimicrobials, and no prophylaxis, respectively, and 1.6%, 3.9%, and 7.4%, respectively, for patients undergoing open cholecystectomy. Significantly lower rates of SSIs and postoperative pneumonia were noted in patients receiving antimicrobials compared with those who did not receive prophylaxis ($p < 0.05$). SSI rates were significantly decreased in laparoscopic cholecystectomy patients who received ceftriaxone (0.1%) or other antimicrobials (0.2%) compared with those who received no antimicrobial prophylaxis (1.6%). SSI rates were significantly decreased in open cholecystectomy patients who received ceftriaxone (1.0%) or other antimicrobials (2.6%) compared with those who received no antimicrobial prophylaxis (4.4%). The study authors concluded that antimicrobial prophylaxis should be administered to all patients undergoing cholecystectomy, regardless of approach. The study had several limitations, including lack of randomization, lack of adequate controls, and lack of clear definition of patient selection for the antimicrobial regimens. The statistical analysis was not clearly defined. The study appears to have compared only the use and lack of use of antimicrobials (with ceftriaxone and other antimicrobials combined for analysis) and did not specifically compare the laparoscopic and open approaches.

The findings of this study contrast with those of several other published studies. A meta-analysis of 15 randomized controlled studies evaluated the need for antimicrobial prophylaxis in elective laparoscopic cholecystectomy for patients at low risk of infection.[313] Low risk was defined as not having any of the following: acute cholecystitis, a history of acute cholecystitis, common bile duct calculi, jaundice, immune suppression, and prosthetic implants. A total of 2961 patients were enrolled in the studies, including 1494 who received antimicrobial prophylaxis, primarily with cephalosporins, vancomycin, fluoroquinolones, metronidazole, and amoxicillin–clavulanate, and 1467 controls receiving placebo or no treatment. No significant difference was found in the rates of infectious complications (2.07% in patients receiving antimicrobial prophylaxis versus 2.45% in controls) or SSIs (1.47% in patients receiving antimicrobial prophylaxis versus 1.77% in controls). The authors of the meta-analysis concluded that antimicrobial prophylaxis was not necessary for low-risk patients undergoing elective laparoscopic cholecystectomy. An additional meta-analysis of 9 randomized controlled trials ($n = 1437$) also concluded that prophylactic antimicrobials do not prevent infections in low-risk patients undergoing laparoscopic cholecystectomy.[342]

A small, prospective, nonrandomized study compared the use of cefotaxime 1 g i.v. during surgery with an additional two i.v. doses given eight hours apart after surgery ($n = 80$) with no antimicrobial prophylaxis ($n = 86$) in patients undergoing elective laparoscopic cholecystectomy with accidental or incidental gallbladder rupture and spillage of bile.[317] Patients who had spillage of gallstone calculi or whose operations were converted to open operations were excluded from the study. The rate of SSIs did not significantly differ between treatment groups (2.5% with antimicrobials versus 3.4% without antimicrobial prophylaxis). Based on results of multivariate analysis, routine antimicrobial prophylaxis was not recommended for these patients unless they were diabetic, were older than 60 years, or had an ASA classification of ≥3 or the duration of the procedure exceeded 70 minutes.

Current data do not support antimicrobial prophylaxis for low-risk patients undergoing elective laparoscopic cholecystectomies or those with incidental or accidental gallbladder rupture. Antimicrobial prophylaxis should be considered for patients at high risk of infection, including those undergoing open cholecystectomy, as described above, or who are considered to be at high risk for conversion to an open procedure.

Choice of agent. The data do not indicate a significant difference among first-, second-, and third-generation cephalosporins. First-generation,[307,308,312,315,319,323,330,336,338,343,344] second-generation,[308,314,315,318,323,327-329,331,332,335,344-352] and third-generation[308,309,315-317,321,322,332,333,338,349,353,354] cephalosporins have been studied more extensively than other antimicrobials. Limited data are available for ampicillin with gentamicin,[355] piperacillin,[356] amoxicillin–clavulanate,[305,338,351,354] ciprofloxacin,[320,333,352,357] and cephalosporins or penicillins alone or in combination with metronidazole, gentamicin, or both metronidazole and gentamicin.[308]

Several studies have compared first-generation cephalosporins with second- or third-generation agents.[315,336,338,344-347,353,358] With one exception,[347] there was no significant difference in efficacy among agents. Other studies found no significant differences in efficacy between ampicillin and cefamandole,[335] ciprofloxacin and ceftriaxone,[333] amoxicillin–clavulanate and cefotaxime,[354] amoxicillin–clavulanate and cefamandole,[351] ceftriaxone and ceftazidime,[321] and oral and i.v. ciprofloxacin and i.v. cefuroxime.[352,357] One study found that i.v. ampicillin–sulbactam was associated with significantly lower rates of infection compared with cefuroxime[306] and that patients treated with oral ceftibuten had significantly lower infection rates than those who received amoxicillin–clavulanate.[338]

Duration. The effect of duration of prophylaxis on outcome has been evaluated. A single dose of a cephalosporin was compared with multiple doses in several studies; no significant differences in efficacy were found.[327,329,330,348,349,353,359] The largest study compared one dose of cefuroxime with three doses in 1004 patients with risk factors for infection who were undergoing biliary tract surgery.[327] There was no significant difference in the rates of minor or major SSIs between the single- and multiple-dose groups. In the majority of studies, one dose of an antimicrobial was administered at induction of anesthesia,[306,312,338,352,354] within 30 minutes before incision,[338] or 1[315,316,320,321] or 2[338] hours before incision. Additional doses were given as follows: one dose 12 hours after administration of the initial dose,[352] two doses 12 and 24 hours after administration of the initial dose,[338] two doses every 6[338] or 8[317,319] hours after surgery, and one dose 24 hours after surgery[315] and five days after surgery.[352] In one study, a second dose of amoxicillin–clavulanate or cefotaxime was administered for procedures lasting longer than 4 hours.[354]

Recommendations. A single dose of cefazolin should be administered in patients undergoing open biliary tract procedures (Table 2). (Strength of evidence for prophylaxis = A.) Alternatives include ampicillin–sulbactam and other cephalosporins (cefotetan, cefoxitin, and ceftriaxone). Alternative regimens for patients with β-lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone; or metronidazole plus gentamicin or a fluoroquinolone.

Antimicrobial prophylaxis is not necessary in low-risk patients undergoing elective laparoscopic cholecystectomies. (Strength of evidence against prophylaxis for low-risk patients = A.) Antimicrobial prophylaxis is recommended in patients undergoing laparoscopic cholecystectomy who have an increased risk of infectious complications. Risk factors include performance of emergency procedures, diabetes, anticipated procedure duration exceeding 120 minutes, risk of intraoperative gallbladder rupture, age of >70 years, open cholecystectomy, risk of conversion of laparoscopic to open cholecystectomy, ASA classification of ≥3, episode of biliary colic within 30 days before the procedure, reintervention in less than a month for noninfectious complications of prior biliary operation, acute cholecystitis, anticipated bile spillage, jaundice, pregnancy, nonfunctioning gallbladder, and immunosuppression. Because some of these risk factors cannot be determined before the surgical intervention, it may be reasonable to give a single dose of antimicrobial prophylaxis to all patients undergoing laparoscopic cholecystectomy. (Strength of evidence for prophylaxis for high-risk patients = A.)

Appendectomy procedures

Background. Cases of appendicitis can be described as complicated or uncomplicated on the basis of the pathology. Patients with uncomplicated appendicitis have an acutely inflamed appendix. Complicated appendicitis includes perforated or gangrenous appendicitis, including peritonitis or abscess formation. Because complicated appendicitis is treated as a complicated intra-abdominal infection,[303] it has not been addressed separately in these guidelines. All patients with a suspected clinical diagnosis of appendicitis, even those with an uncomplicated case, should receive appropriate preoperative i.v. antimicrobials for SSI prevention, which, due to the common microbiology encountered, requires similar antimicrobial choices to those used to treat complicated appendicitis.

Approximately 80% of patients with appendicitis have uncomplicated disease.[59] SSI has been reported in 9–30% of patients with uncomplicated appendicitis who do not receive prophylactic antimicrobials, though some reports suggest lower complication rates in children with uncomplicated appendicitis.[165,360-365] Mean SSI rates for appendectomy reported in the most recent NHSN report (2006–08) were 1.15% (60 of 5211) for NHSN risk index categories 0 and 1 versus 3.47% (23 of 663) for NHSN risk index categories 2 and 3.[165] Laparoscopic appendectomy has been reported to produce lower rates of incisional (superficial and deep) SSIs than open appendectomy in adults and children in multiple meta-analyses and several randomized clinical trials.[292,310,366-371] However, the rate of organ/space SSIs (i.e., intra-abdominal abscesses) was significantly increased with laparoscopic appendectomy.

Organisms. The most common microorganisms isolated from SSIs after appendectomy are anaerobic and aerobic gram-negative enteric organisms. *Bacteroides fragilis* is the most commonly cultured anaerobe, and *E. coli* is the most frequent aerobe, indicating that the bowel flora constitute a major source for pathogens.[59,372,373] Aerobic and anaerobic streptococci, *Staphylococcus* species, and *Enterococcus* species also have been reported. *P. aeruginosa* has been reported infrequently.

Efficacy. Antibiotic prophylaxis is generally recognized as effective in the prevention of postoperative SSIs in patients undergoing appendectomy when compared with placebo.[374]

Choice of agent. Randomized controlled trials have failed to identify an agent that is clearly superior to other agents in the prophylaxis of postappendectomy infectious complications. An appropriate choice for SSI prophylaxis in uncomplicated appendicitis would be any single agent or combination of agents that provides adequate gram-negative and anaerobic coverage. The second-generation cephalosporins with an-

aerobic activity and a first-generation cephalosporin plus metronidazole are the recommended agents on the basis of cost and tolerability. Given the relatively equivalent efficacy between agents, a cost-minimization approach is reasonable; the choice of agents should be based on local drug acquisition costs and antimicrobial sensitivity patterns.

A wide range of antimicrobials have been evaluated for prophylaxis in uncomplicated appendicitis. The most commonly used agents were cephalosporins. In general, a second-generation cephalosporin with anaerobic activity (cefoxitin or cefotetan) or third-generation cephalosporins with partial anaerobic activity (cefotaxime) were effective, with postoperative SSI rates of <5% in most studies.[364,375-381]

Piperacillin 2 g was comparable to cefoxitin 2 g in a well-controlled study.[381] Metronidazole used alone was less effective than cefotaxime, with infection rates above 10%.[376] However, when metronidazole was combined with cefazolin, ampicillin,[382] or gentamicin,[378,383] the postoperative SSI rates were 3–6%.

A double-blind, randomized, controlled trial was conducted at two hospitals to evaluate the effect of metronidazole, which is effective against most anaerobes, and cefazolin, which is effective against many aerobic organisms, singly and in combination, on the rate of sepsis after appendectomy.[384] Patients were randomized into one of four groups: metronidazole and placebo, cefazolin and placebo, metronidazole and cefazolin, or double placebo. Patients with generalized peritonitis were excluded for ethical reasons. Treatment was started before the procedure and continued every 8 hours for 24 hours. All patients in the trial were followed for about two weeks after discharge from the hospital, and their surgical sites were inspected. A total of 271 patients were assessed. Sepsis rates at the two hospitals were similar. Patients who received both cefazolin and metronidazole had a significantly lower infection rate compared with the other groups.[384] Consistent with the antibacterial spectrum of the agents, a prospective study of antimicrobial prophylaxis for colorectal procedures found that the combination of metronidazole with aztreonam did not show adequate coverage of gram-positive organisms.[385] The Common Principles section of these guidelines provides additional considerations for weight-based dosing.

Duration. In most of the studies of second- or third-generation cephalosporins or metronidazole combinations, a single dose[376-378,380,383] or two or three doses[364,379,382] were given. Although direct comparisons were not made, there was no discernible difference in postoperative SSI rates between single-dose and multidose administration in most studies. A randomized trial specifically comparing different durations of regimens found no statistical difference between a single preoperative dose, three doses (preoperative dose plus two additional doses), or a five-day regimen.[386] A large cohort study found that single doses of metronidazole and gentamicin in patients undergoing open appendectomy were effective and sufficient in decreasing the SSI rate.[387]

Pediatric efficacy. In pediatric patients, as with adults, preoperative determination of complicated versus uncomplicated appendicitis is difficult. A comprehensive review is not provided here, but this topic has been addressed by SIS.[388]

Two pediatric studies demonstrated no difference in SSI rates between placebo and several antimicrobials. The first study compared metronidazole, penicillin plus tobramycin, and piperacillin.[389] The second study compared single-dose metronidazole and single-dose metronidazole plus cefuroxime.[390] A meta-analysis including both adult and pediatric studies found that for pediatric patients, antimicrobial prophylaxis trended toward being beneficial, but the results were not statistically significant.[374] A retrospective chart review questioned the routine need for antimicrobial prophylaxis in children with simple appendicitis, due to relatively low infection rates in children not receiving prophylaxis.[365] However, these and other study authors have suggested antimicrobial prophylaxis may be considered due to the morbidity associated with infectious complications (e.g., prolonged hospitalization, readmission, reoperation) and due to the inability to preoperatively identify appendicitis.

As a single agent, metronidazole was no more effective than placebo in two double-blind studies that included children 10 years of age or older[360] and 15 years of age or older.[363] In a randomized study that included pediatric patients, ceftizoxime and cefamandole were associated with significantly lower infection rates and duration of hospitalization than placebo.[391] Both cefoxitin and a combination of gentamicin and metronidazole were associated with a lower rate of postoperative infection in a randomized study that included pediatric patients younger than 16 years.[378] Second-generation cephalosporins with anaerobic activity (cefoxitin or cefotetan) and third-generation cephalosporins with anaerobic activity (cefotaxime) were effective, with postoperative infection rates of <5% in two studies that included pediatric patients younger than 12 years.[364,378,379] A single dose of gentamicin with clindamycin was found to be safe and effective in children with simple appendicitis.[392]

Recommendations. For uncomplicated appendicitis, the recommended regimen is a single dose of a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or a single dose of a first-generation cephalosporin (cefazolin) plus metronidazole (Table 2). For β-lactam-allergic patients, alternative regimens include (1) clindamycin plus gentamicin,

Appendicitis - Level A

aztreonam, or a fluoroquinolone and (2) metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin). (Strength of evidence for prophylaxis = A.)

Small intestine procedures

Background. Small intestine procedures, or small bowel surgery as defined by NHSN, include incision or resection of the small intestine, including enterectomy with or without intestinal anastomosis or enterostomy, intestinal bypass, and strictureoplasty; it does not include small-to-large bowel anastomosis.

The risk of SSI in small bowel surgery is variable. The Surgical Site Infection Surveillance Service in England (data collected by 168 hospitals in 13 categories of surgical procedures between 1997 and 2002) reported an SSI rate of 8.9% (94 of 1056).[393] Mean SSI rates for small bowel procedures reported in the most recent NHSN report (2006–08) were 3.44% for NHSN risk index category 0 versus 6.75% for NHSN risk index categories 1, 2, and 3. A study of 1472 patients undergoing bowel surgery (small bowel and colon) at 31 U.S. academic medical centers between September and December 2002 found an SSI rate of 8.7% for all wound categories. For patients with clean-contaminated wounds, the SSI rate was 7.9%; for those with contaminated or dirty-infected wounds, the SSI rates were 12.0% and 20.4%, respectively.[394]

In a study of 178 penetrating stomach and small bowel injuries, 94% of which were operated on within six hours of presentation, SSIs occurred in nearly 20% of cases. When associated colon injuries were excluded, SSIs occurred in 16% of gastric injuries and 13% of small bowel injuries. Although 74% of patients received antimicrobials, the specific timing of antimicrobial administration was not provided.[395] Other studies of small bowel injury confirm similar SSI rates.[396-400]

Antimicrobial prophylaxis is recommended for small bowel surgery, based on inferring effectiveness from other clean-contaminated procedures. No specific prospective randomized studies could be identified that addressed antimicrobial prophylaxis for small bowel surgery. Antimicrobial prophylaxis for small bowel surgical procedures related to a diagnosis of complicated intra-abdominal infection is not addressed separately in these guidelines, as antimicrobial therapy for established intraabdominal infection should be initiated preoperatively.

Organisms. The most common microorganisms isolated from SSIs after small bowel surgery are aerobic gram-negative enteric organisms. Among the species isolated from patients with SSI after small intestine surgery are gram-negative bacilli of gastrointestinal enteric origin (aerobic and anaerobic) and gram-positive species, such as streptococci, staphylococci, and enterococci, which is consistent with similar studies.[401] *E. coli* is the most frequently identified aerobe, indicating that the bowel flora constitute a major source of pathogens. Aerobic and anaerobic streptococci, *Staphylococcus* species, and *Enterococcus* species also have been reported.

The microbiology of 2280 SSIs after upper or lower abdominal surgery conducted from 1999 to 2006 was described in the Prevalence of Infections in Spanish Hospitals (EPINE) study.[402] The most frequent microorganisms isolated were *E. coli* (28%), *Enterococcus* species (15%), *Streptococcus* species (8%), *P. aeruginosa* (7%), and *S. aureus* (5%; resistant to methicillin, 2%). The microbiology of SSIs after upper abdominal tract surgery did not show any significant differences compared with SSIs of the lower tract, though there were relatively more staphylococci, *K. pneumoniae*, *Enterobacter* species, *Acinetobacter* species, and *Candida albicans* isolates and fewer *E. coli*, *B. fragilis,* and *Clostridium* species in the upper abdominal surgery group.[402]

Efficacy. Antibiotic prophylaxis is generally recognized as effective in the prevention of postoperative SSIs in patients undergoing small bowel surgery when compared with placebo. However, there are no prospective placebo-controlled trials to definitively establish the efficacy of prophylactic antimicrobials in this patient population.

Choice of agent. The antimicrobials selected for prophylaxis must cover the expected pathogens for the small intestine. The microbial ecology of the proximal small intestine (i.e., jejunum) is similar to that of the duodenum, whereas the microbial flora of the ileum are similar to those of the colon. In patients with small intestine obstruction, the microbial flora are similar to those of the colon.

No randomized controlled trials have confirmed that one antimicrobial agent is superior to other agents for SSI prophylaxis in small bowel surgery. An appropriate antimicrobial choice for SSI prophylaxis in small bowel surgery is any single agent or combination of agents that provides adequate coverage for the small intestinal microbes. In patients with small bowel obstruction, additional coverage of anaerobic bacteria is also desirable.

For small intestine procedures with no evidence of obstruction, a first-generation cephalosporin (cefazolin) is recommended. For patients with small intestine obstruction, a first-generation cephalosporin with metronidazole or a second-generation cephalosporin with anaerobic activity (cefoxitin or cefotetan) is the recommended agent. The choice of agents should be based on local drug acquisition costs and antimicrobial sensitivity patterns. The Common Principles section of these guidelines provides additional considerations for weight-based dosing.

Duration. Preoperative dosing of antimicrobials for SSI prevention, with

additional intraoperative antimicrobial dosing dependent on the duration of the operation and no postoperative dosing, is recommended for patients undergoing small bowel surgery.

Pediatric efficacy. In pediatric patients, as with adults, antimicrobial prophylaxis for SSI prevention in small bowel surgery is recommended.

Recommendations. For small bowel surgery without obstruction, the recommended regimen is a first-generation cephalosporin (cefazolin) (Table 2). For small bowel surgery with intestinal obstruction, the recommended regimen is a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or the combination of a first-generation cephalosporin (cefazolin) plus metronidazole. For β-lactam-allergic patients, alternative regimens include (1) clindamycin plus gentamicin, aztreonam, or a fluoroquinolone and (2) metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin). (Strength of evidence for prophylaxis = C.)

Hernia repair procedures (hernioplasty and herniorrhaphy)

Background. All patients who undergo hernioplasty (prosthetic mesh repair of hernia) or herniorrhaphy (suture repair of hernia) should receive appropriate preoperative i.v. antimicrobials for SSI prevention. The risk of SSIs is higher in hernioplasty compared with herniorrhaphy.[403] There is a significant risk of requiring prosthetic mesh removal in hernioplasty patients who develop an SSI, and determination of whether mesh placement will be required for hernia repair is not always possible in the preoperative period.

Mean SSI rates for herniorrhaphy reported in the most recent NHSN report (2006–08) were 0.74% (21 of 2852) for NHSN risk index category 0, 2.42% (81 of 3348) for NHSN risk index category 1, and 5.25% (67 of 1277) for NHSN risk index categories 2 and 3.[165]

A Cochrane meta-analysis of 17 randomized trials (n = 7843; 11 hernioplasty trials, 6 herniorrhaphy trials) in elective open inguinal hernia repair reported SSI rates of 3.1% versus 4.5% in the antimicrobial prophylaxis and control groups, respectively (OR, 0.64; 95% CI, 0.50–0.82).[404] The subgroup of patients with herniorrhaphy had SSI rates of 3.5% and 4.9% in the prophylaxis and control groups, respectively (OR, 0.71; 95% CI, 0.51–1.00). The subgroup of patients with hernioplasty had SSI rates of 2.4% and 4.2% in the prophylaxis and control groups, respectively (OR, 0.56; 95% CI, 0.38–0.81).

A meta-analysis of nine randomized trials of open hernioplasty for inguinal hernia documented SSI rates of 2.4% (39 of 1642) in the antimicrobial group and 4.2% (70 of 1676) in the control group. Antibiotics showed a protective effect in preventing SSI after mesh inguinal hernia repair (OR, 0.61; 95% CI, 0.40–0.92). Antibiotic prophylaxis did reduce the rate of SSI in hernia patients undergoing mesh hernioplasty.[405]

Based on the results of these two systematic reviews, preoperative antimicrobial prophylaxis for SSI prevention is recommended for both herniorrhaphy and hernioplasty. Compared with open hernia repair, laparoscopic hernia repair has been reported to produce lower rates of incisional (superficial and deep) SSIs in randomized clinical trials.[406-408] In a recent multicenter randomized trial of laparoscopic versus open ventral incisional hernia repair (n = 162), SSI was significantly less common in the laparoscopic group than in the open repair group (2.8% versus 21.9%; OR, 10.5; 95% CI, 2.3–48.2; $p = 0.003$).[409] A meta-analysis of eight randomized trials comparing laparoscopic and open incisional or ventral hernia repair with mesh revealed that laparoscopic hernia repair was associated with decreased SSI rates (relative risk, 0.22; 95% CI, 0.09–0.54) and a trend toward fewer infections requiring mesh removal.[410]

Organisms. The most common microorganisms isolated from SSIs after herniorrhaphy and hernioplasty are aerobic gram-positive organisms. Aerobic streptococci, *Staphylococcus* species, and *Enterococcus* species are common, and MRSA is commonly found in prosthetic mesh infections.[411]

Efficacy. Antibiotic prophylaxis is generally recognized as effective when compared with placebo in the prevention of postoperative SSIs in patients undergoing herniorrhaphy and hernioplasty.

Choice of agent. Randomized controlled trials have failed to identify an agent that is clearly superior to other agents for SSI prophylaxis in hernia repair. A first-generation cephalosporin is the recommended agent on the basis of cost and tolerability. The Common Principles section of these guidelines provides additional considerations for weight-based dosing.

Duration. Based on the evidence to date, a single preoperative dose of antimicrobial is recommended in hernioplasty and herniorrhaphy, with redosing as recommended in the Common Principles section of these guidelines (if the procedure duration exceeds the recommended redosing interval from the time of initiation of the preoperative dose or if there is prolonged or excessive bleeding).

Recommendations. For hernioplasty and herniorrhaphy, the recommended regimen is a single dose of a first-generation cephalosporin (cefazolin) (Table 2). For patients known to be colonized with MRSA, it is reasonable to add a single preoperative dose of vancomycin to the recommended agent. For β-lactam-allergic patients, alternative regimens include clindamycin and vancomycin. (Strength of evidence for prophylaxis = A.)

Colorectal procedures

Background. SSIs have been reported to occur in approximately

4–10% of patients undergoing colon procedures, 3–7% in small bowel procedures, and 3–27% in patients after rectal procedures, based on the risk index.[165] However, when patients are followed carefully in clinical trials, rates tend to be considerably higher (17–26%).[412] Other septic complications, such as fecal fistula, intra-abdominal abscesses, peritonitis, and septicemia, are serious concerns but are much less common.[413] Infectious complication rates range from 30% to 60% without antimicrobial prophylaxis[59,414] and are <10% with appropriate antimicrobial prophylaxis. A pooled analysis of clinical trials of antimicrobial prophylaxis in colon procedures demonstrated that antimicrobial use significantly reduced mortality rates (11.2% for control versus 4.5% for treatment) and SSI rates.[415]

The type and duration of the procedure can affect the risk of infection. Rectal resection is associated with a higher risk of infection than is intraperitoneal colon resection.[416-418] Other risk factors include extended procedure duration (e.g., >3.5 hours),[59,412,418,419] impaired host defenses,[418] age of >60 years,[418] hypoalbuminemia,[419,420] bacterial or fecal contamination of the surgical site,[418,420] inadvertent perforation or spillage,[412,421] corticosteroid therapy,[419] perioperative transfusion of packed red blood cells,[394,418] hypothermia,[422] hyperglycemia,[423,424] and obesity.[412,418]

Organisms. The infecting organisms in colorectal procedures are derived from the bowel lumen, where there are high concentrations of organisms. *B. fragilis* and other obligate anaerobes are the most frequently isolated organisms from the bowel, with concentrations 1,000–10,000 times higher than those of aerobes.[425] *E. coli* is the most common aerobe. *B. fragilis* and *E. coli* comprise approximately 20–30% of the fecal mass. They are the most frequently isolated pathogens from infected surgical sites after colon procedures.

Efficacy. Results from randomized controlled trials and a Cochrane review of 182 studies of over 30,000 patients support the routine use of prophylactic antimicrobials in all patients undergoing colorectal procedures.[426]

Choice of agent. The agent chosen for antimicrobial prophylaxis in colorectal procedures should have activity against the anaerobic and aerobic floras of the bowel. The most appropriate regimen for antimicrobial prophylaxis for colorectal procedure (e.g., oral, i.v, oral–i.v. combination) and the optimal choice of antimicrobial agent have not been fully resolved.

Oral regimens. The efficacy of oral prophylactic antimicrobial agents has been established in studies only when used with mechanical bowel preparation (MBP). A variety of oral agents administered after MBP have been evaluated for prophylaxis for colorectal procedures. The most common combinations include an aminoglycoside (neomycin and, less often, kanamycin, which is only available in injectable form in the United States) plus a medication with anaerobic activity, usually erythromycin[427-434] or metronidazole.[432,433,435-439] In placebo-controlled studies, the oral combination was significantly more effective than placebo in reducing SSIs.[427,433,434,439,440] Postoperative SSI rates were 0–11% with neomycin plus erythromycin[427-432] and 2–13% with neomycin and metronidazole.[436-438] Combinations of neomycin and tetracycline,[440] neomycin and clindamycin,[436] and neomycin and tinidazole[441] have also been used successfully, with postoperative SSI rates of <10%. The use of metronidazole as a single agent appears to be less effective, with reported SSI rates of 12–15%.[442-444]

Oral antimicrobials have been compared with i.v. agents in a few studies. Oral neomycin plus oral erythromycin was similarly effective as i.v. cefoxitin in one study[429] but inferior in another[445] and was similarly effective as i.v. ceftriaxone plus i.v. metronidazole in patients undergoing elective colorectal procedures.[431] The addition of i.v. cefamandole to oral neomycin plus oral erythromycin did not improve efficacy.[430] In one of these studies, oral neomycin and erythromycin were more effective than i.v. cefoxitin for procedures lasting longer than 4 hours.[445] A randomized controlled study was stopped early due to the significantly higher rate of infection in the oral neomycin and erythromycin group (41%) compared with the single-dose i.v. metronidazole and ceftriaxone group (9.6%) ($p < 0.01$).[446] Similarly, a study of oral metronidazole and kanamycin compared with the same medications given intravenously found an increased rate of postoperative sepsis (36% versus 6.5%, respectively) ($p < 0.001$), greater numbers of *E. coli* resistant to kanamycin, more bacterial overgrowth, and antimicrobial-associated pseudomembranous colitis in the oral group.[447] However, the oral antimicrobials were not given on a schedule expected to be effective, as they were discontinued 36 hours before the procedure. The fact that oral antibiotics were given for three days rather than less than one day, as is the current practice, was suggested as a possible reason for the resistance and colitis observed.

I.V. regimens. A wide range of i.v. antimicrobials have been evaluated for prophylaxis in colorectal procedures. Cephalosporins are the most common agents, usually administered as a single agent. The majority of studies found that single-agent first-generation cephalosporins (cefazolin and cephalothin)[445,448-451] were ineffective, with postoperative SSI rates ranging from 12% to 39%.[448,449] The lack of efficacy is likely due to their lack of *B. fragilis* activity. The combination of cefazolin and metronidazole provides adequate coverage of pathogens and may be a cost-effective prophylaxis strategy.[6,41]

Second-generation cephalosporins with anaerobic activity, such as cefoxitin and cefotetan, have been widely evaluated. In single-agent therapy, SSI rates ranged from 0% to 17%[91,417,445,452-459]; however, more than half of the studies found SSI rates of >10%.

Third-generation agents, cefotaxime and ceftriaxone, have been evaluated in a few trials; postoperative SSI rates were 8–19% with single-agent use.[456,460,461] In some studies, second- or third-generation cephalosporins were combined with other i.v. agents, most commonly metronidazole.[452,459-462] However, in all but one of these studies, a combination of a second- or third-generation cephalosporin plus metronidazole was no more effective than the cephalosporin alone. The use of third- or fourth-generation cephalosporins for routine antimicrobial prophylaxis is not recommended as use may lead to development of resistant organisms.[6,41,444,463] However, in institutions where there is increasing gram-negative resistance from isolates to first- and second-generation cephalosporins, a single dose of ceftriaxone plus metronidazole may be preferred over routine use of carbapenems.

Three small studies, with under 200 patients each, found i.v. ampicillin–sulbactam or amoxicillin–clavulanate to be as effective as i.v. combinations of gentamicin and metronidazole,[464] gentamicin and clindamycin,[465] and cefotaxime and metronidazole for preventing SSIs in elective colorectal procedures.

A randomized controlled study of adult patients undergoing elective colon or rectal procedures evaluated the use of a single high dose of gentamicin 4.5 mg/kg i.v. plus metronidazole 500 mg i.v. in sequential order over 30 minutes compared with multiple standard doses of gentamicin 1.5 mg/kg plus metronidazole given preoperatively and every 8 hours for 24 hours postoperatively.[16] All patients underwent MBP before surgery. Patients with a serum creatinine concentration exceeding 1.7 mg/L were excluded from the study. No statistically significant differences were seen in deep and superficial incisional SSI rates between groups. Significantly fewer superficial SSIs were seen in the single-dose group compared with the multidose group in procedures lasting longer than 3.5 hours (22.2% versus 55%, $p = 0.021$). A pharmacodynamic study of these patients found the gentamicin concentration at the time of surgical-site closure as the strongest independent factor for infection.[17] Of note, the infection rate was 80% in 10 patients with gentamicin concentrations of <0.5 mg/L.

Other i.v. agents that have been evaluated either alone or in combination include aminoglycosides,[464,466-469] clindamycin,[466] ampicillin,[467,469-471] penicillins plus β-lactamase inhibitors,[464,465,468,472,473] doxycycline,[470,474-476] piperacillin,[91,473] imipenem,[462] and ciprofloxacin.[300]

Ertapenem, a broad-spectrum carbapenem, is approved by FDA for the prophylaxis of SSIs after elective colorectal procedures.[67] Cefotetan is also FDA approved for surgical prophylaxis in clean-contaminated procedures (e.g., gastrointestinal procedures) in adult patients undergoing elective colon or rectal procedures.[62] A large, multicenter, randomized controlled study compared a single 1-g i.v. dose of ertapenem with cefotetan 2 g i.v. infused within 60 minutes before surgical incision.[412] All patients received MBP preoperatively. SSI rates were significantly lower in the ertapenem group versus cefotetan in the per-protocol (18.1% and 31.1%, respectively) and the modified intent-to-treat (17.1% and 50.9%) populations. Ertapenem was found to be superior to cefotetan for SSI prevention. Although not statistically significant, higher rates of skin-related events (i.e., pruritis and rash), gastrointestinal events, and *C. difficile* infection were seen in the ertapenem group. The study authors concluded that ertapenem is an acceptable alternative to cefotetan and cefoxitin. Routine use of ertapenem for surgical prophylaxis remains controversial due to theoretical concerns regarding increases in resistant organisms and a potential increase in adverse events.[477]

Alternative agents for patients with a high likelihood of past serious adverse event or allergy to β-lactams include (1) clindamycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone.[41]

Combination oral and i.v. regimens. Combinations of oral and i.v. antimicrobials have been used in an attempt to further reduce postoperative infection rates. Regimens include oral neomycin and erythromycin plus i.v. administration of a cephalosporin,[416,417,429,445,449,478,479] metronidazole,[480,481] and gentamicin plus clindamycin.[466] Postoperative SSI rates in these studies ranged from 0% to 7%. With one exception,[416] there was no significant difference between oral neomycin–erythromycin plus an i.v. antimicrobial and oral neomycin–erythromycin alone.[429,449,466,478] When combination oral and i.v. agents were compared with i.v. agents alone, combination therapy was favored in five of six studies[417,429,445,449,480,482]; the difference was significant in three.[417,449,482] The most recent Cochrane review found that the infection rate was significantly lower with the combination of oral plus i.v. prophylaxis when compared with i.v. alone (relative risk, 0.55; $p = 0.000084$) or with oral prophylaxis alone (relative risk, 0.34; $p = 0.024$).[426] A recent report of over 2000 patients recorded prospectively in the Michigan Surgical Quality Collaborative—Colectomy Best Practices Project and analyzed retrospectively revealed a signifi-

cantly lower rate of postoperative infections when 370 colectomy patients received MBP and oral antimicrobial prophylaxis compared with propensity-matched patients receiving i.v. prophylaxis alone.[483]

A multicenter, randomized, controlled study of 491 patients who received MBP plus oral antimicrobials (kanamycin and erythromycin) with i.v. cefmetazole (not available in the United States but noted by the expert panel to have a similar spectrum of activity as cefotetan) or i.v. cefmetazole alone found no difference in SSI between groups for colon procedures.[484] However, the combination of oral and i.v. antimicrobials was significantly better than i.v. alone for rectal procedures, particularly abdominoperineal excision. Another study found the postoperative SSI rates after rectal resection were 23% and 11%, respectively, for patients receiving i.v. cefoxitin and cefoxitin plus oral neomycin and erythromycin.[417]

The safety and tolerability of oral antimicrobials have been investigated in two studies. One case–control study found an increased incidence of *C. difficile* colitis among patients with oral plus i.v. antimicrobials and MBP compared with i.v. antimicrobials and MBP alone.[485] However, another case–control study found a lower rate (not statistically significant) of *C. difficile* infection in patients who had received oral antimicrobials compared with those who had not (1.6% versus 2.9%, $p = 0.09$).[486] A randomized controlled study of 300 patients undergoing elective colorectal procedures found significantly higher rates of nausea and vomiting among patients receiving three doses of oral antimicrobials (neomycin and metronidazole, 44% and 31%, respectively) in combination with i.v. cefoxitin and MBP compared with regimens including one dose of oral antimicrobials (18% and 11%, respectively) and no oral antimicrobials (13% and 9%, respectively).[487] No difference was noted between groups for rates of abdominal pain, SSIs, or intraabdominal abscesses. An increased number of gastrointestinal adverse events was also reported in another comparative study in the combination oral and i.v. group (2.9%) compared with the i.v.-only group (2.1%), although the results were not statistically significant.[484] Overall, the evidence suggests that the combination of oral antimicrobials with MBP in addition to i.v. prophylactic antimicrobials reduces the rate of postoperative infections compared with i.v. antimicrobials alone without MBP, although the addition of oral antimicrobials increases gastrointestinal symptoms.

Duration. Single and multiple doses were compared in several studies.[454-456,461,471,475] However, only two of these studies compared single doses with multiple doses of the same antimicrobial.[471,475] There was no significant difference in infection rates between single-dose and multidose administration. One study found a single dose of cefotaxime plus metronidazole was significantly more effective than three doses of cefotaxime alone.[461] The most recent Cochrane review found no benefit to extending the duration of prophylaxis ($p = 0.58$).[426] Generally, antimicrobial prophylaxis should be continued for no more than 24 hours and can typically be stopped when the procedure is completed and the surgical site is closed.[6,41,444] No evidence supports greater efficacy for doses given after the completion of the procedure. Additional discussion on this topic is found in the Common Principles section of these guidelines.

Consideration should be given to an additional dose of the i.v. antimicrobial if an agent with a short half-life is used and the procedure duration exceeds the recommended redosing interval (starting from the time of initiation of the preoperative dose) and if intraoperative blood loss occurs.[6,41,120,418,444,445] No significant difference was seen in SSI rates with single-dose cefazolin, single-dose cefotetan, and cefazolin given as one preoperative dose and a second dose three hours later for procedures with a duration of less than three hours.[118] SSI rates were significantly higher with a single dose of cefazolin for procedures with a duration of greater than three hours. Using an agent with a longer half-life can decrease the necessity to redose the antimicrobial during long procedures.

Pediatric efficacy. No well-controlled studies have evaluated the efficacy of antimicrobial prophylaxis in pediatric patients undergoing colorectal procedures. However, there is no reason to suspect that prophylaxis efficacy would be different. The safety, efficacy, tolerability, and cost-effectiveness of intestinal lavage have been demonstrated in two studies of 20 and 21 pediatric patients.[488,489]

Recommendations. A single dose of second-generation cephalosporin with both aerobic and anaerobic activities (cefoxitin or cefotetan) or cefazolin plus metronidazole is recommended for colon procedures (Table 2). In institutions where there is increasing resistance to first- and second-generation cephalosporins among gram-negative isolates from SSIs, the expert panel recommends a single dose of ceftriaxone plus metronidazole over routine use of carbapenems. An alternative regimen is ampicillin–sulbactam. In most patients, MBP combined with a combination of oral neomycin sulfate plus oral erythromycin base or oral neomycin sulfate plus oral metronidazole should be given in addition to i.v. prophylaxis. The oral antimicrobial should be given as three doses over approximately 10 hours the afternoon and evening before the operation and after the MBP. Alternative regimens for patients with β-lactam allergies include (1) clindamycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a

fluoroquinolone. Metronidazole plus aztreonam is not recommended as an alternative because this combination has no aerobic gram-positive activity.[385] (Strength of evidence for prophylaxis = A.)

Head and neck procedures

Background. Elective procedures of the head and neck are predominantly clean or clean-contaminated.[490] Clean procedures include thyroidectomy and lymph node excisions. Clean-contaminated procedures include all procedures involving an incision through the oral or pharyngeal mucosa, ranging from parotidectomy, submandibular gland excision, tonsillectomy, adenoidectomy, and rhinoplasty to complicated tumor-debulking and mandibular fracture repair procedures requiring reconstruction. The frequency of SSIs reported for clean procedures without antimicrobial prophylaxis is <1%.[491,492] In contrast, infection rates in patients undergoing complicated head and neck cancer surgery are quite high, with infection occurring in 24–87% of patients without antimicrobial prophylaxis.[493-497] While many of these head and neck cancer procedures are clean-contaminated, these procedures can fall into different wound classifications. Head and neck cancer patients often have many of the risk factors for infection mentioned below.[498]

Postoperative SSI rates are affected by age, nutritional status, and the presence of concomitant medical conditions such as diabetes mellitus, anemia, and peripheral vascular disease.[496,499-504] Use of tobacco,[498,505] alcohol,[505,506] or drugs of abuse[507] has also been associated with a higher risk of postoperative infection, particularly in patients with mandibular fracture. The hospital course, including length of hospitalization before operation, duration of antimicrobial use before operation, length of operation, presence of implants, and previous tracheotomy can also affect postoperative SSI rates.[496,497,501-504,508] In patients with cancer, preoperative radiation and chemotherapy as well as the stage of the malignancy may also affect infection risk.[497,498,502-504] Procedure-related risk factors for infection include radical or bilateral neck dissections[501,508] and reconstruction with myocutaneous flaps or microvascular-free flaps.[497-499,508]

Organisms. The normal floras of the mouth and the oropharynx are responsible for most infections that follow clean-contaminated head and neck procedures.[6,8,496,498,499,506,509-519] Anaerobic and aerobic bacteria are abundant in the oropharynx. As a result, postoperative SSIs are usually polymicrobial and involve both aerobic and anaerobic bacteria. The predominant oropharyngeal organisms include various streptococci (aerobic and anaerobic species), other oral anaerobes including *Bacteroides* species (but not *B. fragilis*), *Peptostreptococcus* species, *Prevotella* species, *Fusobacterium* species, *Veillonella* species, Enterobacteriaceae, and staphylococci. Nasal flora includes *Staphylococcus* species and *Streptococcus* species.

Efficacy. *Clean procedures.* Systemic administration of prophylactic antimicrobials has not been proven effective in reducing SSI rates in patients undergoing clean procedures of the head and neck and are not recommended for routine use.[6-8,497,520] One randomized, double-blind, multicenter study of 500 patients undergoing thyroid procedures for goiter or carcinoma found no difference in postoperative SSI rates in those who received antimicrobial prophylaxis (0.8%) and those who did not (0.4%).[491]

Clean-contaminated procedures. Based on the best available evidence, current guidelines and review articles recommend the use of antimicrobial prophylaxis for the majority of clean-contaminated procedures.[6-8,497,520,521] However, antimicrobial prophylaxis did not lower infection risk in randomized controlled trials of patients undergoing adenoidectomy, tonsillectomy,[522,523] and septoplasty,[524] and systematic reviews have not recommended prophylaxis for these procedures.[7,525,526]

The efficacy of antimicrobial prophylaxis is best established for head and neck cancer surgery. Several small randomized, controlled trials found high infection rates in placebo groups (24–78%) and markedly lower infection rates in the prophylaxis groups (5.8–38%) using a variety of regimens, including cefazolin, third-generation cephalosporins, and ampicillin plus cloxacillin. Although these studies were small, the results are concordant, and the high infection rates allowed the studies to reach statistical significance despite the small sample sizes. Similar results were reported in several additional small, uncontrolled studies.[500,527-529]

Choice of agent. Several randomized, single-center studies have compared antimicrobial regimens for clean-contaminated procedures. In one study, 189 patients undergoing head and neck cancer procedures were randomized to receive cefazolin 1 g (n = 92) or amoxicillin–clavulanate (n = 97), both given within one hour of incision and every eight hours postoperatively for three doses.[511] The postoperative SSI rates were 24% with cefazolin and 21% with amoxicillin–clavulanate; there was no statistically significant difference in infection rates in this underpowered study. Two studies have compared ampicillin–sulbactam to clindamycin and yielded discordant results. One study of 242 patients (169 evaluable) undergoing head and neck cancer procedures compared ampicillin–sulbactam 1.5 g (n = 119) and clindamycin 600 mg (n = 123) given within one to two hours of incision and every six hours postoperatively for a total of four doses.[510] No difference in SSIs was found, with 15 infections reported in each group (13% for the ampicillin–sulbactam

group and 12% for the clindamycin group). There was no significant difference in adverse events between groups. There was a higher rate of *C. difficile*-positive patients in the clindamycin group ($n = 7$) than in the ampicillin–sulbactam group ($n = 1$), with no reported statistical analysis. Another study of 212 patients undergoing clean-contaminated head and neck oncology surgery found significantly fewer infections in the ampicillin–sulbactam group (13.3%) compared with the clindamycin group (27.1%) ($p = 0.02$).[530] A greater number of gram-negative pathogens were recovered from patients randomized to the clindamycin group. The combination of gentamicin and clindamycin was superior to cefazolin in one older clinical trial.[531]

Duration. Studies of clean-contaminated head and neck procedures found no difference in efficacy between regimens of 24 hours and longer regimens of three, five, or seven days.[499-501,505,507,512,524,531-534] Limited data exist on single-dose prophylaxis in these procedures.

One study of patients undergoing free-flap reconstruction after head and neck procedures found a significantly lower rate of acquisition and infection with MRSA in patients receiving short-term cefuroxime and metronidazole (one dose during induction of anesthesia and one dose eight hours postoperatively) compared with long-term therapy (same antimicrobials with additional doses every eight hours for up to five days) ($p = 0.005$ and $p = 0.01$, respectively, for acquisition and infection).[535]

Recommendations. *Clean procedures.* Antimicrobial prophylaxis is not required in patients undergoing clean surgical procedures of the head and neck. If there is placement of prosthetic material, a preoperative dose of cefazolin or cefuroxime is reasonable, though there are few data supporting the efficacy of prophylaxis in this setting (Table 2). A reasonable alternative for patients with β-lactam allergies is clindamycin. (Strength of evidence against prophylaxis without prosthesis placement = B; strength of evidence for prophylaxis with prosthesis placement = C.)

Clean-contaminated procedures. Antimicrobial prophylaxis has not been shown to benefit patients undergoing tonsillectomy or functional endoscopic sinus procedures. The preferred regimens for patients undergoing other clean-contaminated head and neck procedures are (1) cefazolin or cefuroxime plus metronidazole and (2) ampicillin–sulbactam. Clindamycin is a reasonable alternative in patients with a documented β-lactam allergy. The addition of an aminoglycoside to clindamycin may be appropriate when there is an increased likelihood of gram-negative contamination of the surgical site. (Strength of evidence for prophylaxis in cancer surgery patients = A; strength of evidence for prophylaxis for other clean-contaminated procedures except tonsillectomy and functional endoscopic sinus procedures = B.)

Neurosurgery procedures

Background. Nosocomial central nervous system (CNS) infections do not often occur but have potentially serious consequences and poor outcomes, including death.[536] One of the greatest risks for these infections in children and adults is undergoing a neurosurgical procedure. A classification system for neurosurgery, validated by Narotam et al.,[537] divides procedures into five categories: clean, clean with foreign body, clean-contaminated, contaminated, and dirty. Risk factors for postoperative infections after neurological procedures include an ASA classification of ≥2,[538] postoperative monitoring of intracranial pressure[538,539] or ventricular drains[536,538] for five or more days, cerebrospinal fluid (CSF) leak,[539-541] procedure duration of more than two to four hours,[540,542-544] diabetes,[544] placement of foreign body,[536] repeat or additional neurosurgical procedures,[538,541-543] concurrent (remote, incision, or shunt) or previous shunt infection,[536,539,545,546] and emergency procedures.[542,545]

Organisms. Data from most published clinical trials indicate that SSIs are primarily associated with gram-positive bacteria, *S. aureus,* and coagulase-negative staphylococci.[6,8,537-545,547-554] Several cohort studies revealed high rates (up to 75–80% of isolates) of MRSA[540-543,548-552] and coagulase-negative staphylococci among patients undergoing a variety of neurosurgical procedures.[539,540,543,549] Other skin organisms such as *P. acnes* may be seen after CSF shunt placement, craniotomy, and other procedures.[536,555,556] Gram-negative bacteria have also been isolated as the sole cause of postoperative neurosurgical SSIs in approximately 5–8% of cases and have been isolated in polymicrobial infections.[537-539,541-545,547-550,552,553]

Efficacy. *Clean procedures.* Antimicrobial prophylaxis is recommended for adult and pediatric patients undergoing craniotomy and spinal procedures.[7,520] One meta-analysis of six studies found decreased odds of meningitis in patients undergoing craniotomy who received antimicrobial prophylaxis (1.1%) versus no prophylaxis (2.7%) ($p = 0.03$).[557] Two cohort studies[540,543] in patients undergoing craniotomy at the same institution found that antimicrobial prophylaxis with cloxacillin or amoxicillin–clavulanate, clindamycin for β-lactam-allergic patients, and other antimicrobials (not detailed) had a significantly lower infection rate (5.8%) than no prophylaxis (9.7%) ($p < 0.0001$).[543] A significantly lower infection rate of 4.6% was seen in low-risk patients (clean craniotomy, no implant) with antimicrobial prophylaxis compared with those without prophylaxis (4.6% versus 10%, $p < 0.0001$). A significantly lower rate of scalp infections, bone flap osteitis, and abscess

or empyema was seen with antimicrobial prophylaxis compared with no prophylaxis. Antimicrobial prophylaxis demonstrated no difference in postoperative meningitis[540,543] and infection rates in high-risk patients (those undergoing emergency, clean-contaminated, and dirty procedures or reoperation or with operative times exceeding four hours).[543]

Prospective studies involving large numbers of patients have also demonstrated lower neurosurgical postoperative infection rates when antimicrobial prophylaxis is used.[558-561] One such study of patients undergoing craniotomy, spinal, or shunting procedures was stopped early because of an excessive number of SSIs in the placebo group.[562]

Choice of agent. Studies of clean neurosurgical procedures reported antimicrobial regimens including clindamycin,[540,543,557] vancomycin,[542,557] cefotiam (not marketed in the United States),[557] piperacillin,[557] cloxacillin,[540,543,557] oxacillin,[542,557] cefuroxime,[547] cefotaxime,[548] sulfamethoxazole–trimethoprim,[548] cefazolin,[542,544] penicillin G,[542] and amoxicillin–clavulanate.[540,542,543] A meta-analysis found no significant difference in the rates of postcraniotomy meningitis with various antimicrobial regimens (single-dose regimens of clindamycin, vancomycin, or cefotiam; three doses of piperacillin; four doses of cloxacillin; and six doses of oxacillin).[557]

A randomized, open-label, multicenter study of 613 adult patients undergoing elective craniotomy, shunt, or stereotactic procedures found no difference in single doses of cefotaxime and trimethoprim–sulfamethoxazole in postoperative abscess formation, SSIs, and shunt infections.[548]

Duration. The majority of studies included single doses of antimicrobials; therefore, the use of single-dose antimicrobial prophylaxis given within 60 minutes before surgical incision in patients undergoing neurosurgery is generally recommended.[6,7,520,540,543,547,548,557,563]

Efficacy for CSF-shunting procedures. Antimicrobial prophylaxis is recommended for adults undergoing placement of a CSF shunt.[7] Prophylaxis in patients undergoing ventriculostomy or intraventrical prophylaxis at the time of ventriculoperitoneal shunt insertion has shown some benefit in reducing infection but remains controversial due to limited evidence.[6,7]

Because CNS infections after shunting procedures are responsible for substantial mortality and morbidity, especially in children, the possible role of prophylactic antimicrobials in such procedures has been studied in numerous small, well-conducted, randomized controlled trials.[564-571] Meticulous surgical and aseptic techniques and short procedure times were determined to be important factors in lowering infection rates after shunt placement. Although the number of patients studied in each trial was small, two meta-analyses of these data demonstrated that antimicrobial prophylaxis use in CSF-shunting procedures reduced the risk of infection by approximately 50%.[572,573]

Intrathecal pump placement involves the implantation of a permanent intrathecal catheter to allow instillation of medication. CNS infections may occur after these procedures, which are performed in both pediatric and adult populations. Several retrospective series have reported infection rates of 4.5–9% after intrathecal baclofen pump placement.[574-576] There are minimal published trial data regarding appropriate prophylaxis for intrathecal pump procedures. It has been suggested that prophylaxis for intrathecal pump procedures be managed similarly to prophylaxis for CSF-shunting procedures.[577]

There is no consensus on the use of antimicrobial prophylaxis in patients with extraventricular drains (EVDs) or intracranial pressure monitors.[134] An international survey of neurosurgeons and critical care medicine and infectious diseases specialists illustrates the difference in practices. The majority of neurosurgeons used or recommended the use of antimicrobial prophylaxis with EVDs (73.5%) and other monitoring devices (59%), compared with rates of 46–59% for critical care medicine specialists and 35% for infectious diseases specialists. The majority of specialists did not recommend or use antimicrobial-coated EVD catheters.

Two randomized controlled studies comparing antimicrobial-impregnated shunts to standard, non-antimicrobial-impregnated shunts along with antimicrobial prophylaxis with i.v. cephalosporin found a decrease in rates of shunt infections[549] and a significant decrease in CSF infection with antimicrobial-impregnated shunts.[545] At this time, routine use of antimicrobial-impregnated devices is not recommended; additional well-designed studies are needed to establish their place in therapy.[7,578]

Choice of agent. In CSF-shunting procedures, no single antimicrobial agent has been demonstrated to have greater efficacy than others.[546,548,551-554,579] There is a lack of data on the necessity of antimicrobials with CNS penetration relating to prevention of infection in CNS shunting procedures.

Duration. The majority of studies support the use of single-dose prophylaxis regimens or regimens with a duration of 24–48 hours postoperatively.[6-8,520,539,546,549-552,579] There is a lack of data evaluating the continuation of EVDs with and without antimicrobial prophylaxis. The international survey mentioned above asked respondents to indicate their recommended duration for antimicrobial prophylaxis with EVDs as either periprocedural, for 24 hours, for the first three days, for the entire time the device is in place, or other.[135] The respondents from the specialties

of neurosurgery, neurocritical care, and critical care had similar results, with 28–31% using or recommending periprocedural antimicrobials, 4–10% for 24 hours, 2–4% for the first three days, 43–64% for the entire time the device is in place, and 0–14% for other. The infectious diseases specialists reported rates of 62%, 19%, 4%, 12%, and 4%, respectively.

One retrospective single-center cohort study of 308 patients with EVDs placed for three days or more received antimicrobial prophylaxis for the duration of EVD use (n = 209) compared with patients receiving cefuroxime 1.5 g i.v. every eight hours for three doses or less frequently periprocedurally (timing not clearly defined in article) (n = 99).[580] The overall rate of bacterial ventriculitis was 3.9%, with 8 patients (3.8%) in the extended-use group and 4 patients (4%) in the short-term prophylaxis group, the difference of which was not significant. The study authors concluded that there was no benefit to the use of a prolonged duration of antimicrobial prophylaxis.

Pediatric efficacy for CSF-shunting procedures. Antimicrobial prophylaxis is recommended for children undergoing a CSF-shunting procedure.[7] The efficacy of antimicrobial prophylaxis is extrapolated from adult studies.

A retrospective pediatric study of 384 CSF-shunting procedures found a lower infection rate in patients who received antimicrobials (2.1%) compared with those who did not (5.6%), but this difference failed to reach statistical significance.[581] Two randomized, prospective studies that included pediatric patients did not demonstrate a significant difference in infection rates between the control group and the groups that received cefotiam[571] (not available in the United States) or methicillin.[568] A randomized, double-blind, placebo-controlled study that included pediatric patients undergoing ventriculoperitoneal shunt surgeries failed to demonstrate that the use of perioperative sulfamethoxazole–trimethoprim reduced the frequency of shunt infection.[564]

Other studies have demonstrated efficacy for prophylactic antimicrobials.[566,582] A single-center, randomized, double-blind, placebo-controlled trial of perioperative rifampin plus trimethoprim was performed in pediatric patients.[582] Among patients receiving rifampin plus trimethoprim, the infection rate was 12%, compared with 19% in patients receiving placebo. The study was ended because of the high infection rates before significance could be achieved. Infection rates at the study institution had been 7.5% in the years before the study. An open-label randomized study, including pediatric patients, demonstrated a lower infection rate in a group receiving oxacillin (3.3%) than in a control group (20%).[566]

Recommendations. A single dose of cefazolin is recommended for patients undergoing clean neurosurgical procedures, CSF-shunting procedures, or intrathecal pump placement (Table 2). Clindamycin or vancomycin should be reserved as an alternative agent for patients with a documented β-lactam allergy (vancomycin for MRSA-colonized patients). (Strength of evidence for prophylaxis = A.)

Cesarean delivery procedures

Background. Approximately 1.2 million infants are born by cesarean delivery in the United States annually.[583] The infection rate after cesarean delivery has been reported to be 4–15%,[583] though recent NHSN data showed an infection rate of 2–4%.[165]

Postpartum infectious complications are common after cesarean delivery. Endometritis (infection of the uterine lining) is usually identified by fever, malaise, tachycardia, abdominal pain, uterine tenderness, and sometimes abnormal or foul-smelling lochia.[584] Fever may also be the only symptom of endometritis.

Endometritis has been reported to occur in up to 24% of patients in elective cesarean delivery and up to approximately 60% of patients undergoing nonelective or emergency section.[584,585] Risk factors for endometritis include cesarean delivery, prolonged rupture of membranes, prolonged labor with multiple vaginal examinations, intrapartum fever, and low socioeconomic status.[585,586] Patients with low socioeconomic status may have received inadequate prenatal care.

The factor most frequently associated with infectious morbidity in postcesarean delivery is prolonged labor in the presence of ruptured membranes. Intact chorioamniotic membranes serve as a protective barrier against bacterial infection. Rupture of the membrane exposes the uterine surface to bacteria from the birth canal. The vaginal fluid with bacterial flora is drawn into the uterus when it relaxes between contractions during labor. Women undergoing labor for more than six to eight hours in the presence of ruptured membranes should be considered at high risk for developing endometritis.[587] Other risk factors for SSIs after cesarean delivery include systemic illness, poor hygiene, obesity, and anemia.[587,588]

Organisms. The normal flora of the vagina include staphylococci, streptococci, enterococci, lactobacilli, diphtheroids, *E. coli,* anaerobic streptococci (*Peptococcus* species and *Peptostreptococcus* species), *Bacteroides* species (e.g., *Bacteroides bivius, B. fragilis*), and *Fusobacterium* species.[584,587,589-592] Endometritis infections are often polymicrobial and include aerobic streptococcus (particularly group B β-hemolytic streptococcus and enterococci), gram-negative aerobes (particularly *E. coli*), gram-negative anaerobic rods (particularly *B. bivius*), and anaerobic cocci (*Peptococcus* species and *Peptostreptococcus* species). *Ureaplasma urealyticum* has been com-

monly isolated from endometrial and surgical-site cultures. Additional commonly isolated organisms from SSIs include *Staphylococcus* species and enterococci.

Efficacy. While the use of antimicrobial prophylaxis in low-risk procedures (i.e., those with no active labor and no rupture of membranes) has been brought into question by the results of several randomized, placebo-controlled studies that found no reduction in infectious complications (fever, SSI, urinary tract infection, or endometritis) with the use of prophylaxis, the majority of these evaluations were underpowered and included administration of antimicrobial prophylaxis at cord clamping.[593-599] However, the efficacy of antimicrobial prophylaxis in cesarean delivery has been shown in several studies and two meta-analyses for both elective and nonelective procedures. Therefore, prophylaxis is recommended for all patients undergoing cesarean delivery.[584,592]

One meta-analysis that reviewed 7 placebo-controlled randomized trials in low-risk elective cesarean delivery found that prophylaxis was associated with a significant decrease in endometritis and fever.[592] A larger meta-analysis of 81 randomized trials with 11,937 women undergoing both elective and nonelective cesarean delivery found that antimicrobial prophylaxis was associated with a significant reduction in risk of fever, endometritis, SSI, urinary tract infection, and serious infection.[585] The relative risk for endometritis in elective cesarean section was 0.38 (95% CI, 0.22–0.64) in those receiving antimicrobial prophylaxis compared to those receiving no prophylaxis.

Choice of agent. Although several different antimicrobials used alone or in combination for antimicrobial prophylaxis during cesarean delivery have been evaluated, the use of first-generation cephalosporins (specifically cefazolin) has been advocated by ACOG and the American Academy of Pediatrics (AAP), based on their efficacy, narrow spectrum of activity, and low cost.[584] This recommendation is supported by a meta-analysis of 51 randomized controlled trials comparing at least two antimicrobial regimens that concluded that ampicillin and first-generation cephalosporins have similar efficacy.[600]

Newer prospective randomized controlled and cohort studies have evaluated the addition of metronidazole, azithromycin,[601-603] or doxycycline[601] to a first- or second-generation cephalosporin to extend the spectrum of activity against common organisms isolated from endometrial and surgical-site cultures, specifically *U. urealyticum* and *Mycoplasma* species. These studies found significantly lower rates of postoperative infections (including endometritis and SSI) and a shorter duration of hospital stay compared with prophylaxis with a first- or second-generation cephalosporin alone.[601-604] Antibiotic administration occurred either postoperatively or after cord clamping in these studies. Further study, particularly with preoperative antimicrobial administration, is needed to confirm these preliminary findings and establish a place in therapy for this practice.

Timing. Historically, administration of antimicrobials in cesarean delivery was delayed until after cord clamping.[600,605,606] The principal reasons were to avoid suppression of the neonate's normal bacterial flora that could promote the selection of resistant organisms and concern that the antimicrobials could potentially mask neonatal infection, complicating evaluation of neonatal sepsis. However, more contemporary data support the administration of antimicrobial prophylaxis before surgical incision to protect against bacterial contamination of the surgical site and decrease the risk of infection. The practice of antimicrobial prophylaxis administration before surgical incision is endorsed by ACOG and AAP.[584,607] See the Common Principles section of these guidelines for additional discussion on antimicrobial timing.

A meta-analysis of three randomized controlled trials and two nonrandomized controlled studies provided evidence that preoperative antimicrobial administration significantly decreased the rate of endometritis compared with administration after cord clamping (3.9% and 8.9%, respectively; $p = 0.012$).[605] A lower SSI rate was also seen with preoperative antimicrobial administration (3.2% versus 5.4%), though this difference was not significant. The overall rate of infection-related morbidity was also significantly lower. No differences between the groups were seen in neonatal outcomes, including sepsis, sepsis workups, and neonatal intensive care unit admissions. The largest study included in this meta-analysis was a prospective, randomized, controlled, double-blind, single-center, double-dummy study of 357 patients comparing cefazolin 1 g i.v. given preoperatively and after cord clamping, which had results consistent with the overall meta-analysis.[606]

In a recent randomized trial of more than 1100 women undergoing cesarean section between 2004 and 2010, Witt and colleagues[608] found no difference in SSI rates for patients having antimicrobial administration before surgical incision compared with those who received antimicrobial prophylaxis at the time of cord clamping. All patients received a single dose of cefazolin 2 g.

Duration. A meta-analysis of 51 studies found that multidose regimens provided no apparent benefit over single-dose regimens.[600] The use of single-dose prophylaxis is supported by ACOG and AAP for procedures lasting less than two hours.[584] Additional intraoperative doses may be warranted for patients with excessive blood loss or for whom the duration of the procedure is extended.

For additional discussion of dosing, see the Common Principles section of these guidelines.

Recommendation. The recommended regimen for all women undergoing cesarean delivery is a single dose of cefazolin administered before surgical incision (Table 2). (Strength of evidence for prophylaxis = A.) For patients with β-lactam allergies, an alternative regimen is clindamycin plus gentamicin.

Hysterectomy procedures

Background. Hysterectomy is second only to cesarean delivery as the most frequently performed major gynecological procedure in the United States, with over 600,000 hysterectomies performed annually.[609] Uterine fibroid tumors account for 40% of all presurgical diagnoses leading to hysterectomy.[609] Other common diagnoses are dysfunctional uterine bleeding, genital prolapse, endometriosis, chronic pelvic pain, pelvic inflammatory disease, endometrial hyperplasia, and cancer.

Hysterectomy involves the removal of the uterus and, occasionally, one or two fallopian tubes, the ovaries, or a combination of ovaries and fallopian tubes.[610] Radical hysterectomy entails removal of the uterus, fallopian tubes, and ovaries and extensive stripping of the pelvic lymph nodes in patients with extension of their cancer. Hysterectomies are performed by a vaginal or abdominal approach using a laparoscopic- or robot-assisted method. During a vaginal hysterectomy, the procedure is completed through the vagina with no abdominal incision. Abdominal hysterectomy involves an abdominal incision. Laparoscopic and robotic methods involve small incisions and require additional equipment, increased operator experience, and increased length of procedures.[611,612] In the United States, between 2000 and 2004, the abdominal approach for hysterectomy was used in 67.9% of surgical procedures and the vaginal approach in 32.1%. Of hysterectomies performed via the vaginal approach, 32.4% also used laparoscopy.[609] The ACOG Committee on Gynecologic Practice recommends vaginal hysterectomy as the approach of choice for benign disease, based on evidence of better outcomes and fewer complications.[613] Laparoscopic abdominal hysterectomy is an alternative when the vaginal route is not indicated or feasible.[613,614] Of note, ACOG has stated that the supracervical approach—removal of the uterus with preservation of the cervix—should not be recommended as a superior technique for hysterectomy due to the lack of advantage in postoperative complications, urinary symptoms, or sexual function and the increased risk of future trachelectomy to remove the cervical stump.[615]

Infections after hysterectomy include superficial and organ/space (vaginal cuff infection, pelvic cellulitis, and pelvic abscess) SSIs.[589] The reported SSI rates between January 2006 and December 2008 in the United States, based on NNIS risk index category, were 0.73–1.16 per 100 procedures for vaginal hysterectomy and 1.10–4.05 per 100 procedures for abdominal hysterectomy.[165] A multicenter surveillance study found a mean infection rate of 2.53% associated with all types of hysterectomy and a significantly lower mean rate of infection with laparoscopic versus abdominal hysterectomies (1.15% versus 3.44%, respectively).[325]

Risk factors for infection after vaginal or abdominal hysterectomy include longer duration of surgery, young age, diabetes, obesity, peripheral vascular disease, collagen disease, anemia, transfusion, poor nutritional status, and previous history of postsurgical infection.[590,616-622] The depth of subcutaneous tissue is also a significant risk factor for infection after abdominal hysterectomy.[623] Additional risk factors for infection after radical hysterectomy for cervical cancer include the presence of malignancy, prior radiation therapy, and the presence of indwelling drainage catheters.[619,620]

Organisms. The vagina is normally colonized with a wide variety of bacteria, including gram-positive and gram-negative aerobes and anaerobes. The normal flora of the vagina includes staphylococci, streptococci, enterococci, lactobacilli, diphtheroids, *E. coli,* anaerobic streptococci, *Bacteroides* species, and *Fusobacterium* species.[589,624] Postoperative vaginal flora differs from preoperative flora; the amount of enterococci, gram-negative bacilli, and *Bacteroides* species increases postoperatively. Postoperative changes in flora may occur independently of prophylactic antimicrobial administration and are not by themselves predictive of postoperative infection.[589,625,626] Postoperative infections associated with vaginal hysterectomy are frequently polymicrobial, with enterococci, aerobic gram-negative bacilli, and *Bacteroides* species isolated most frequently. Postoperative SSIs after abdominal and radical hysterectomies are also polymicrobial; gram-positive cocci and enteric gram-negative bacilli predominate, and anaerobes are frequently isolated.[626,627]

Efficacy. A meta-analysis of 25 randomized controlled trials demonstrated the efficacy of antimicrobial prophylaxis, including first- and second-generation cephalosporins and metronidazole, in the prevention of infections after abdominal hysterectomy.[628] The infection rates were 21.1% with placebo or no prophylaxis and 9.0% with any antimicrobial. Another meta-analysis found that the rate of postoperative infection (surgical and pelvic sites) in women undergoing vaginal hysterectomy who received placebo or no prophylactic antimicrobial ranged from 14% to 57%, which was significantly higher than the 10% rate reported with antimicrobials.[629]

Malignant disease as the reason for hysterectomy is a common ex-

clusion from studies of antimicrobial prophylaxis. Older, prospective, placebo-controlled studies found a lower rate of SSIs with antimicrobial prophylaxis after radical hysterectomy.[619,630-633] The applicability of these results is limited by small sample size and the inclusion of antimicrobials not available in the United States. Radical hysterectomy is primarily completed through an abdominal approach but can also be performed by a vaginal approach and using laparoscopic or robotic methods.[634] Therefore, antimicrobial prophylaxis would be warranted, regardless of approach. No placebo-controlled studies have been conducted to evaluate the efficacy of antimicrobial prophylaxis when used for laparoscopic hysterectomy.

Choice of agent. Cephalosporins are the most frequently used and studied antimicrobials for prophylaxis in vaginal and abdominal hysterectomies. Studies directly comparing different cephalosporins have found no significant differences in rates of infection in vaginal hysterectomy and have indicated that first-generation cephalosporins (primarily cefazolin) are equivalent to second- and third-generation agents.[635-644] In abdominal hysterectomy, no significant differences in the rates of serious infections were noted between second- and third-generation cephalosporin regimens.[641,645-649] Few comparisons have been made between second-generation cephalosporins and cefazolin. Cefazolin has been at least as effective in preventing infectious complications as second- and third-generation cephalosporins.[636,650-652] However, one double-blind controlled study of 511 women undergoing abdominal hysterectomy found that the risk of major SSIs requiring antimicrobial therapy was significantly higher in the group receiving preoperative cefazolin 1 g (11.6%; relative risk, 1.84; 95% CI, 1.03–3.29) than in those treated with cefotetan 1 g (6.3%).[617] A multicenter, randomized, double-blind, active- and placebo-controlled study compared single doses of ampicillin, cefazolin, and placebo administered to women undergoing elective total abdominal hysterectomy at two centers in Thailand.[653] The study found a significantly lower rate of infection, including superficial and deep SSIs, urinary tract infections, vaginal cuff infection, and pneumonia, with cefazolin (10.3%) compared with placebo (26.9%) and ampicillin (22.6%). No difference was seen between ampicillin and placebo. The study authors concluded that cefazolin was more effective than ampicillin for elective total abdominal hysterectomy.

A randomized controlled study of 511 patients undergoing laparoscopic gynecological procedures at one center in Italy compared single doses of amoxicillin–clavulanate 2.2 g and cefazolin 2 g i.v. administered 20–30 minutes before the procedure.[654] A second dose was given if the surgery lasted over three hours or there was extensive blood loss (>1500 mL). No significant differences in the rates of any postoperative infection, including SSIs, were found between groups. The statistical power of the study was not stated.

In light of the organisms encountered in the vaginal canal and comparative studies conducted among different classes of cephalosporins, cefazolin, cefotetan, cefoxitin, cefuroxime, and ampicillin–sulbactam have been supported as appropriate first-line choices for prophylaxis during vaginal or abdominal hysterectomy.[6,9,41] Alternative agents for patients with a history of immediate hypersensitivity to penicillin include either clindamycin or metronidazole plus an aminoglycoside or a fluoroquinolone (ciprofloxacin, levofloxacin, or moxifloxacin) or aztreonam (with clindamycin only).

Duration. Studies comparing single doses of one antimicrobial with multidose regimens of a different antimicrobial have shown the two regimens to be equally effective in reducing the postoperative infection rate in women undergoing vaginal and abdominal hysterectomies.[635-643,645-650,655-663] The limited comparative trials involving single-dose cefazolin[637,654,655,664] or ampicillin–sulbactam[654,663] indicate that a single dose of antimicrobial is sufficient prophylaxis for SSIs for vaginal hysterectomy. Single doses of cefotetan, ceftizoxime, or cefotaxime appear to be as effective as multiple doses of cefoxitin.[644-649,665] A second dose of antimicrobial is warranted when the procedure lasts three hours or longer or if blood loss exceeds 1500 mL.[9,654]

Recommendation. The recommended regimen for women undergoing vaginal or abdominal hysterectomy, using an open or laparoscopic approach, is a single dose of cefazolin (Table 2). Cefoxitin, cefotetan, or ampicillin–sulbactam may also be used. Alternative agents for patients with a β-lactam allergy include (1) either clindamycin or vancomycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone. (Strength of evidence for prophylaxis = A.)

Ophthalmic procedures

Background. Ophthalmic procedures include cataract extractions, vitrectomies, keratoplasties, intraocular lens implantation, glaucoma procedures, strabotomies, retinal detachment repair, laser in situ keratomileusis, and laser-assisted subepithelial keratectomy. Most of the available data regarding antimicrobial prophylaxis involve cataract procedures. The goal of prophylaxis is primarily to reduce acute postoperative endophthalmitis, defined as severe intraocular inflammation due to infection, which can lead to loss of vision if untreated.[666] Since 2000, the reported frequency of endophthalmitis after ophthalmic

procedures is low worldwide, ranging from 0% to 0.63%.[667-680] The reported time from procedure to diagnosis of endophthalmitis ranges from one day to six weeks, with the majority of infections identified within one week.[666,669,671,673,674,681-683]

Potential risk factors for postoperative ophthalmic infections include preoperative factors such as diabetes,[666] active ocular infection or colonization,[666,684] lacrimal drainage system infection or obstruction, age of >85 years,[685] and immunodeficiency.[684] Procedure-related risk factors include clear corneal incisions (as opposed to scleral tunnel incisions),[680,686] any surgical complication, vitreous loss,[684] posterior capsule tear,[681,684,685] silicone intraocular lens implantation,[677,680] and the nonuse of facemasks in the operating theater.[681]

Organisms. Among organisms isolated from patients developing postoperative endophthalmitis after cataract procedure, approximately 25–60% were coagulase-negative *Staphylococcus* species, primarily *S. epidermidis.*[668,670,671,673,674,678,683,684,686] Other gram-positive organisms identified included *S. aureus, Streptococcus* species, *Enterococcus* species, *P. acnes,* and *Corynebacterium* species. Gram-negative organisms isolated included *Serratia* species, *Klebsiella* species, *P. mirabilis,* and *P. aeruginosa.* These organisms represent the normal flora isolated preoperatively in a number of studies.[675,687-693]

Efficacy. Data on antimicrobial prophylaxis efficacy in ophthalmic procedures to prevent endophthalmitis are limited; however, prophylaxis is common.[684] The low rate of postoperative endophthalmitis makes it difficult to complete an adequately powered study to show efficacy of antimicrobial prophylaxis in ophthalmic procedures; therefore, surrogate markers of eradication of normal flora bacteria and reduction of bacterial count on the conjunctiva, lower and upper eyelids, eyelashes, and inner canthus (corner of the eye) preoperatively and postoperatively are used. Many of the available studies are flawed with retrospective or uncontrolled design, inadequate follow-up, variations in surgical techniques (including disinfection, antimicrobial prophylaxis strategies, and methods for performing procedures), and limited reporting of clinical outcomes.

The large, randomized, partially-masked, placebo-controlled, multinational, multicenter study conducted by the European Society of Cataract and Refractive Surgeons (ESCRS) compared the rate of postoperative endophthalmitis in over 16,600 patients undergoing routine cataract procedures at 24 centers in Europe randomized to one of four perioperative prophylaxis groups.[679,680,694] Patients received no antimicrobial prophylaxis, intracameral cefuroxime at the end of the procedure alone, perioperative levofloxacin 0.5% ophthalmic solution given within the hour before the procedure, or both intracameral cefuroxime and perioperative levofloxacin. All patients had the eye area disinfected with povidone–iodine 5% preoperatively and received topical levofloxacin postoperatively. The study was stopped after an interim analysis due to results of a multivariate analysis indicating that patients not receiving intracameral cefuroxime were approximately five times more likely to develop endophthalmitis. The study has been questioned for its high rate of endophthalmitis, selection of cefuroxime due to gaps in gram-negative coverage, unknown drug concentrations in the aqueous humor, risks of hypersensitivity, the lack of a commercially available preparation, the lack of a subconjunctival cefuroxime treatment group, selection of topical levofloxacin, and methods for statistical analysis.[695-697]

Two single-center, historical-controlled studies in hospitals in Spain reported decreases in acute postoperative endophthalmitis among patients undergoing cataract procedure with intracameral cefazolin added to the previous routine prophylaxis of preoperative eyelid cleansing with soap for three days[670] and povidone–iodine eye area preparation,[670,674] topical antimicrobial, and corticosteroid preparations given at the end of the procedure and postoperatively. One study found a significant decrease and a relative risk reduction of 88.7% in postoperative endophthalmitis with intracameral cefazolin.[670] The other found a decrease from 0.63% to 0.055% in postoperative endophthalmitis with intracameral cefazolin.[674] No statistical analysis was performed in this study.

A retrospective cohort study of patients undergoing cataract procedure at one center in Canada between 1994 and 1998 found no significant difference in the rate of postoperative endophthalmitis with preoperative topical antimicrobials compared with none.[668] A significant decrease in endophthalmitis was seen with subconjunctival administration of antimicrobials at the end of the procedure compared with no antimicrobials.

Several prospective studies have shown decreases in ocular flora, measured by bacterial isolate and CFU counts, with preoperative antimicrobial irrigation,[675] topical antimicrobials,[687,688,691,692,698-700] and intracameral antimicrobials.[682] These studies did not report rates of endophthalmitis, limiting the application of the results.

Choice of agent. Along with careful site preparation and disinfection, the ideal antimicrobial prophylaxis agent should be bactericidal against common pathogens of postoperative endophthalmitis and be used safely in the eye.[6,8,684] There is no consensus on the agent of choice for antimicrobial prophylaxis in ophthalmic procedures, and no agent is FDA-approved for this indication. There are limited studies evaluating the efficacy of a particular choice of antimicrobial prophylaxis for ophthalmic surger-

ies. The most efficacious antimicrobial cannot be determined from the available data due to study flaws and a lack of direct comparisons. Local ocular flora resistance patterns should be monitored to aid in the selection of appropriate agents for prophylaxis.[683,689,701]

Based on the available literature, use of povidone–iodine as a preoperative antiseptic agent is recommended to decrease ocular microbes and thereby prevent endophthalmitis.[6,684,702] Povidone–iodine 5% or 10% is instilled in the conjunctival sac and applied topically to the ocular skin surface.[703] The most effective protocol has not been established, as povidone–iodine is frequently used in combination with other antimicrobials.[670,674,675,678,687,704] Chlorhexidine has been used as an effective alternative to povidone–iodine, particularly in patients who are iodine allergic.[682,703]

Ophthalmic surgeons surveyed in the United Kingdom reported that commonly used antimicrobial prophylactic agents included cephalosporins, aminoglycosides, vancomycin, chloramphenicol, neomycin alone or in combination with polymyxin, and fluoroquinolones.[695,703] A similar survey of members of the American Society of Cataract and Refractive Surgery found that over 90% of respondents used fluoroquinolones (mainly fourth-generation agents), vancomycin, and cephalosporins.[697] These antimicrobials have been recommended in practice guidelines.[6]

Cephalosporins, specifically cefazolin, cefuroxime, and ceftazidime, have been shown to be safe and effective in decreasing postoperative endophthalmitis when added to regimens of povidone–iodine and topical antimicrobials.[670,674,677,679,680,699] Vancomycin has been shown to decrease cultures and reach adequate concentrations to prevent and treat most corneal pathogens.[675,705] Aminoglycosides alone[687] or in combination with an antiseptic agent (chlorhexidine)[682] showed no significant difference in the reduction of culture results compared with an antiseptic alone (povidone–iodine or chlorhexidine)[682,690] and no antimicrobial prophylaxis.

A randomized controlled study compared the antimicrobial activity and safety of trimethoprim 0.1%–polymyxin B sulfate 10,000 units/mL ophthalmic solution and tobramycin 0.3% ophthalmic solution in patients undergoing cataract procedures.[692] All patients received one drop and a subconjunctival injection of corticosteroids and gentamicin postoperatively followed by one drop of study medication four times daily for five to seven days. No significant differences were seen between groups for positive culture results from conjunctiva at baseline, at procedure, or at postoperative days 5–7 or in lid margin culture at baseline and postoperative days 5–7. A higher rate of positive cultures at procedure was seen in the trimethoprim–polymyxin group (37 of 59 cultures, 63%) compared with 13 (41%) of 32 cultures in the tobramycin group ($p = 0.043$). Both medications eradicated the majority of bacteria on the day of procedure and postoperative days 5–7. Aqueous humor concentrations did not achieve the MICs of *S. aureus* or *S. epidermidis* and were undetectable for polymyxin B sulfate. The adverse events of irritation and allergic reaction were experienced by three patients in the trimethoprim–polymyxin group. The study authors concluded that there was no difference between trimethoprim and tobramycin in ocular flora reduction.

A randomized controlled study compared conjunctiva and contact lens culture results after treatment with tobramycin 0.3% versus ofloxacin 0.3% ophthalmic solutions in patients undergoing photorefractive keratectomy.[693] No differences were seen among preoperative, postoperative, or contact lens cultures between treatment groups. Although not statistically significant, logistic regression found that cultures from patients treated with tobramycin were two times more likely to be positive than those treated with ofloxacin. The study had low power and did not compare baseline and posttreatment culture results for any treatment group.

Fluoroquinolones have been found in studies to significantly decrease the ocular culture results from baseline[667,673,691,698,700,706]; achieve aqueous humor, vitreal, and corneal tissue concentrations adequate to prevent and treat common ocular pathogens[705,707-710]; and result in improved ocular measurements (i.e., visual acuity, epithelial cell counts, and epithelial healing).[711-716] A retrospective multicenter case series of 20,013 patients who underwent uncomplicated cataract surgeries and received fourth-generation fluoroquinolones preoperatively and postoperatively reported the rates of postoperative endophthalmitis.[673] Endophthalmitis occurred in 9 (0.06%) of 16,209 surgeries in patients treated with gatifloxacin 0.3% ophthalmic solution (95% CI, 0.03–0.1%) and in 5 (0.1%) of 3,804 surgeries in patients treated with moxifloxacin 0.5% ophthalmic solution (95% CI, 0.05–0.3%). There were no significant differences in efficacy between agents.

In a retrospective cross-sectional study conducted over a 10-year period with third- and fourth-generation fluoroquinolones, significantly lower rates of endophthalmitis were reported for the fourth-generation agents moxifloxacin and gatifloxacin (0.56 per 1000 cataract surgeries) than for the third-generation agents ciprofloxacin and ofloxacin (1.97 per 1000 surgeries) ($p = 0.0011$).[671]

Route. There is no consensus on the most effective route of antimicrobial administration for the prevention of endophthalmitis. The routes of antimicrobial administration used in ophthalmic procedures

include preoperative topical antimicrobial ophthalmic drops, addition of antimicrobials to the irrigation solution, instillation of antimicrobials intracamerally at the end of surgery, subconjunctival injection of antimicrobials, and postoperative topical application of antimicrobials.[6,684,702,717]

The ESCRS randomized controlled study mentioned above found that patients not receiving intracameral cefuroxime were approximately six times more likely to develop postoperative endophthalmitis.[679,680,694] Surveys of the impact of the ESCRS study findings found that there was an increase in the use of intracameral over subconjunctival cefuroxime based on preliminary study results.[703] For respondents who had not adopted this practice, the reported reasons for not using intracameral cefuroxime included the need for further study, concerns about risk and cost of therapy, the lack of a subconjunctival comparator group, the high rate of endophthalmitis in the control groups, concerns about statistical analysis, and questions regarding the selection of cefuroxime due to gaps in ophthalmic pathogen coverage.[695,697] There is no commercially available cefuroxime formulation for intracameral administration, which was reported as one of the main barriers to use of this route. Concerns regarding compounded intracameral antimicrobials expressed by survey respondents included inflammation, dilution errors, corneal endothelial injury, and the risk for bacterial contamination and infection.

A retrospective cohort study compared the efficacy of intracameral cefuroxime versus subconjunctival cefuroxime in reducing the rate of endophthalmitis after cataract procedures at one center in northeast England.[718] A total of 19,425 patients received antimicrobial prophylaxis with preoperative povidone–iodine 5% in the conjunctival sac and subconjunctival injection of cefuroxime 50 mg at the end of the procedure, and 17,318 patients received intracameral cefuroxime 1 mg at the end of the procedure. There were two groups of patients excluded from the analysis: protocol violators who received no prophylaxis and patients who were enrolled in the ESCRS study. The overall rate of endophthalmitis in analyzed patients was 35 cases in 36,743 procedures (0.95 per 1,000 cases). Of these, 27 occurred in the subconjunctival cefuroxime group (1.39 per 1,000 cases), and 8 occurred in the intracameral group (0.46 per 1,000 cases) (OR, 3.01; 95% CI, 1.37–6.63; p = 0.0068).

Several studies found a lower rate of endophthalmitis with the addition of intracameral cephalosporins (cefazolin and cefuroxime) at the end of the surgical procedure after routine perioperative and postoperative topical antimicrobial prophylaxis regimens.[670,674] A case–control study revealed a 5.7 times increased likelihood of developing postoperative endophthalmitis with topical antimicrobial prophylaxis only (including gentamicin 0.3% and chlorhexidine 0.05%) compared with the addition of intracameral cefuroxime 1 mg to the regimen in cataract procedure.[677] Both intracameral cephalosporins and moxifloxacin have been shown as safe, with no adverse events and no effects on visual acuity and endothelial cell counts.[670,674,699,715,716]

One study involving healthy adult volunteers found that orally administered levofloxacin and moxifloxacin achieved adequate aqueous humor concentrations to provide activity against gram-positive and most gram-negative ocular pathogens without adverse events.[707]

The addition of subconjunctival antimicrobials to existing topical antimicrobial prophylaxis regimens has also been shown to reduce the rate and risk of endophthalmitis in intraocular procedures compared with topical antimicrobials alone.[668,681,686] Topical antimicrobials have been shown to be safe and effective in lowering rates of endophthalmitis,[671,673] decreasing bacterial organisms and CFUs in conjunctiva,[667,675,691,692,698,700] and achieving adequate concentrations to be effective against most ocular pathogens,[705,706,708-710,719] with no notable adverse events.[711-714]

Duration and timing. There are a lack of clear evidence and no consensus on the appropriate duration and timing of antimicrobial prophylaxis in ophthalmic procedures.[6,684] Commonly reported times of antimicrobial prophylaxis include preoperatively, intraoperatively, at the end of the procedure, and postoperatively.[684] Few studies have investigated the differences between the timing and duration of antimicrobial prophylaxis regimens. Many of the regimens are used in combination, making it difficult to determine the optimal timing and duration. Preoperative antimicrobial timing reported in the literature has ranged from one to multiple drops within an hour preoperatively on the day of the procedure[671,673,679,680,692-694,698,703,709,710,716] or one to three days before the procedure.[667,698,700,703,708,710,712,714]

Two topical moxifloxacin regimens were compared for conjunctival bacterial flora and aqueous humor concentrations in a randomized controlled study of patients undergoing cataract procedures.[691,719] In one regimen, patients were administered moxifloxacin 0.5% four times a day beginning one day before the procedure plus one drop two hours before the procedure (total of five drops before the procedure); the other group received moxifloxacin 0.5% two hours before surgery and every 15 minutes for the first hour of the procedure (total of five drops). There were no cases of postoperative endophthalmitis up to six months after the procedure in any patient. Administration of moxifloxacin on the day of the procedure was found to result in a significant decrease in median CFU compared with baseline

and was found (based on change in log CFU) to be more effective than antimicrobial administration on the day before the procedure. Mean aqueous humor concentrations of moxifloxacin at the beginning of the procedure were significantly higher in the group who received the drug on the day of the procedure.

A small, randomized controlled study compared aqueous humor concentrations of levofloxacin and ciprofloxacin in patients undergoing a cataract procedure with routine phacoemulsification given as (1) one or two drops four times daily for two days before the procedure, with the last dose given immediately before bedtime on the night before the procedure, (2) five doses (one or two drops) delivered every 10 minutes in the hour before the procedure, or (3) a combination of both dosing strategies.[706] Aqueous humor concentrations of levofloxacin were significantly higher than those of ciprofloxacin. Significantly higher doses of drug were delivered to the aqueous humor in the group receiving same-day prophylaxis than in patients receiving levofloxacin or ciprofloxacin two days before surgery. No cases of endophthalmitis or ocular or systemic toxicities were reported.

A randomized controlled study compared the effectiveness of topical ofloxacin in the reduction or elimination of conjunctival bacterial flora when given as one drop every five minutes for three applications one hour before the procedure alone (control group) or combined with ofloxacin one drop four times daily for three days (study group) before cataract procedures.[688] No differences in positive conjunctival cultures were seen between groups five days before topical antimicrobials or before the administration of ofloxacin on the day of the procedure. Significantly higher positive culture rates were seen in the control group than in the study group one hour after the administration of the preoperative antimicrobial and before povidone–iodine, immediately before the procedure, and at the conclusion of the procedure. Mean CFU counts did not significantly differ five days preoperatively and immediately before the procedure but were significantly higher in the control group at all other time points. Neither outcomes of endophthalmitis nor patient compliance with antimicrobial use was reported. The study's authors concluded that three days of topical ofloxacin was more effective than administration just one hour before the procedure in reducing the number of positive bacterial cultures at several time points perioperatively.

Numerous studies have evaluated the efficacy of intracameral and subconjunctival injections of antimicrobials given at the end of surgery.[6,674,677,679-682,697,699,703,716,718] The most commonly reported dose of intracameral cefuroxime was 1 mg,[677,679,680,682,699,718] and the most commonly reported subconjunctival dose was 50 mg.[718] Doses of 2.5 or 1 mg of intracameral cefazolin were studied,[670,674] as were 250- and 500-µg doses of intracameral moxifloxacin.[715,716] Postoperative dosing strategies reported in the literature include four times daily for 3–7 days[667,670,671,673-675,679,680,692,711,712,715] and for up to 15 days[713,714] or until the bottle was empty.[716]

Despite the lack of well-controlled trials, the consequences of bacterial endophthalmitis support the use of prophylactic antimicrobials. No definitive studies have clearly delineated superiority of antimicrobial route, timing, or duration.

Recommendation. Due to the lack of robust data from trials, specific recommendations cannot be made regarding choice, route, or duration of prophylaxis. As a general principle, the antimicrobial prophylaxis regimens used in ophthalmic procedures should provide coverage against common ocular pathogens, including *Staphylococcus* species and gram-negative organisms, particularly *Pseudomonas* species.

Preoperative antisepsis with povidone–iodine is recommended, based on available evidence. Appropriate topical antimicrobials include commercially available neomycin–polymyxin B–gramicidin solution or fluoroquinolones (particularly fourth-generation agents) given as one drop every 5–15 minutes for five doses within the hour before the start of the procedure (Table 2). The addition of subconjunctival cefazolin 100 mg or intracameral cefazolin 1–2.5 mg or cefuroxime 1 mg at the end of the procedure is optional. While some data have shown that intracameral antimicrobials may be more effective than subconjunctival antimicrobials, there are no commercially available antimicrobials approved for these routes of administration. (Strength of evidence for prophylaxis = B.)

Orthopedic procedures

Background. Orthopedic procedures considered in these guidelines include clean orthopedic procedures (not involving replacement or implantations), spinal procedures with or without instrumentation, repair of hip fractures, implantation of internal fixation devices (screws, nails, plates, and pins), and total-joint-replacement procedures. Grade III open fractures (extensive soft tissue damage and crushing) are often associated with extensive surgical-site contamination and are routinely managed with empirical antimicrobial treatment and surgical debridement, for which guidelines have been published separately.[720] Available guidelines recommend that antimicrobial prophylaxis in grade I (clean wound with ≤1-cm laceration) and grade II (clean wound with >1-cm laceration without extensive soft tissue damage) open fractures be handled similarly to other clean orthopedic procedures.[721-724]

Between 2006 and 2008, SSIs were reported nationally, based on risk category, in approximately 0.7–4.15 per 100 procedures for patients undergoing spinal fusion, 0.72–2.3 per 100 procedures in patients undergoing laminectomy, 0.67–2.4 per 100 procedures in patients undergoing hip prosthesis, and 0.58–1.60 per 100 procedures in patients undergoing knee prosthesis.[165] Postoperative SSI is one of the most costly complications of orthopedic procedures due to hospital readmissions, extended hospital length of stay, the need for additional procedures (often removal and reimplantation of implanted hardware), convalescent or nursing home care between procedures, and significant increases in direct hospital costs (e.g., prolonged antimicrobial therapy).[725,726] Studies have found that the estimated economic impact of one deep SSI was $100,000 in hospital costs alone after hip arthroplasty and $60,000 after knee arthroplasty.[727-731]

In light of the serious consequences, antimicrobial prophylaxis is well accepted in procedures involving the implantation of foreign materials.[8,732] Prophylaxis is also indicated in spinal procedures without instrumentation, where an SSI would pose catastrophic risks.[726,733-738]

Organisms. Skin flora are the most frequent organisms involved in SSIs after orthopedic procedures. The most common pathogens in orthopedic procedures are *S. aureus*, gram-negative bacilli, coagulase-negative staphylococci (including *S. epidermidis*), and β-hemolytic streptococci.[739-743] Spinal procedures may be complicated by polymicrobial infection that includes gram-negative bacteria.[740]

A contributing factor to SSIs in arthroplasty is the formation of bacterial biofilm, particularly with *S. aureus* and *S. epidermidis,* on inert surfaces of orthopedic devices. Bacterial biofilm confers antimicrobial resistance and makes antimicrobial penetration difficult.[744-748]

There is increasing concern regarding the emergence of SSIs due to resistant microorganisms, specifically VRE and MRSA in surgical patients. Several studies have investigated MRSA colonization and SSIs and evaluated the effect of decolonization, including the use of topical mupirocin, in orthopedic procedures.[150,157,741,749-753] Mupirocin decolonization protocols as an adjunct to i.v. cephalosporin prophylaxis in orthopedic patients resulted in significant decreases in nasal MRSA carriage[150,751] and overall SSIs.[157,750-752] Preoperative decolonization with intranasal mupirocin may have utility in patients undergoing elective orthopedic procedures who are known to be colonized or infected with either MRSA or MSSA.[150,151,157,741,749-755] Readers are referred to additional discussion in the Common Principles section of these guidelines.

Clean orthopedic procedures not involving implantation of foreign materials

Background. In clean orthopedic procedures, such as knee, hand, and foot procedures, and those not involving the implantation of foreign materials, the need for antimicrobial prophylaxis is not well established.[738,749,756] Antimicrobial prophylaxis in patients undergoing diagnostic and operative arthroscopic procedures is controversial.[6,757-760] The risks of SSI and long-term sequelae are low for procedures not involving implantation.

Efficacy. The efficacy of antimicrobial prophylaxis in clean orthopedic procedures was first investigated in the middle part of the 20th century. A number of these studies and reviews have since been found to be flawed, as patients were not randomized to treatment groups and the timing and duration of antimicrobial prophylaxis were not studied.[761,762] Further, patients were administered prophylactic antimicrobials after the surgical procedure, which may have led to invalid results. The low rate of infection and absence of serious morbidity failed to justify the expense or potential for toxicity and resistance associated with routine use of antimicrobial prophylaxis in the setting of clean orthopedic procedures.

Recommendations. Antimicrobial prophylaxis is not recommended for patients undergoing clean orthopedic procedures, including knee, hand, and foot procedures, arthroscopy, and other procedures without instrumentation or implantation of foreign materials. (Strength of evidence against prophylaxis = C.) If the potential for implantation of foreign materials is unknown, the procedure should be treated as with implantation.

Spinal procedures with and without instrumentation

Background. Data support the use of antimicrobial prophylaxis for orthopedic spinal procedures with and without instrumentation, including fusions, laminectomies, and minimally invasive disk procedures, to decrease the rate of postoperative spinal infection.[8,543,563,732,733,739,763-766] SSIs after orthopedic spinal procedures, including minimally invasive disk procedures, are associated with high morbidity. Invasion of the epidural space in organ/space SSIs is of particular concern after spinal procedures.[8,145,767]

SSI rates vary with the complexity of the procedure. One retrospective, multicenter study of 1274 adult patients found an overall SSI rate of 0.22% with antimicrobial prophylaxis after minimally invasive spinal procedures (i.e., any spinal procedures performed through a tubular retractor-type system).[768] Procedures included simple decompressive procedures (such as microscopic or endoscopic discectomy or foraminotomy or decompression of stenosis), minimally invasive arthrodeses

with percutaneous instrumentation, and minimally invasive intradural procedures. The SSI rate in patients receiving antimicrobial prophylaxis undergoing spinal procedures with instrumentation has ranged from 2.8% to 9.7%.[165,764,765,769,770] Monosegmental instrumentation has a reported SSI rate of <2%, compared with 6.7% for instrumentation at multiple levels.[771]

Several case–control studies of adults undergoing spinal procedures with and without instrumentation have found the following notable patient-related risk factors for SSI: prolonged preoperative hospitalization,[771] diabetes,[767,772-775] elevated serum glucose concentration (>125 mg/dL preoperatively [within 30 days] or >200 mg/dL postoperatively),[773] older age,[767,776] smoking and alcohol abuse,[776] previous procedure complicated by infection,[774-776] and obesity.[770-775,777] Procedure-related risk factors include extended duration of procedure (defined in studies as two to five hours or greater than five hours,[775] greater than three hours,[771] and greater than five hours[776]), excessive blood loss (>1 L),[771,775] staged procedure,[776] multilevel fusions,[777] foreign-body placement (e.g., screw, rod, plate),[767] combined anterior and posterior fusion,[776] and suboptimal antimicrobial timing (>60 minutes before or after incision).[773] A significant decrease in SSIs was seen with procedures at the cervical spine level[772,773] or with an anterior surgical approach.[775]

Efficacy. Despite the lack of comparative studies evaluating prophylaxis for spinal procedures with and without instrumentation (implantation of internal fixation devices), antimicrobial prophylaxis is recommended due to the associated morbidity and assumed costs of SSIs.[771] A meta-analysis of six studies with 843 patients undergoing spinal procedures (types of procedures were not differentiated in the analysis) demonstrated an overall effectiveness of antimicrobial prophylaxis.[732] Antimicrobials studied included single-dose or multidose regimens of <24 hours' duration of cephaloridine (a first-generation cephalosporin no longer available in the United States), vancomycin and gentamicin, cefazolin with and without gentamicin, piperacillin, and oxacillin. The pooled SSI rate with antimicrobial prophylaxis was 2.2%, compared with 5.9% in controls (OR, 0.37; 95% CI, 0.17–0.78; $p < 0.01$). One randomized controlled study of 1237 adult patients undergoing spinal procedures to repair a herniated disk (hemilaminectomy, laminectomy, flavectomy, spondylosyndesis) found no significant difference in the rate of SSIs between single-dose cefuroxime 1.5 g i.v. (1.3%) and placebo (2.9%) given within 60 minutes before surgical incision. No significant difference was seen between treatment groups for incisional SSIs (0.98% and 1.12%, respectively) or deep SSIs (0.33% and 0.32%, respectively), but the difference in organ/space infections was significant between groups (0% and 1.44%, respectively; $p < 0.01$).[778]

Choice of agent. There is no clearly superior antimicrobial agent or regimen for spinal procedures.[563,769] The antimicrobials most often studied for prophylaxis in orthopedic procedures are first-generation cephalosporins, particularly cefazolin. Cefazolin has been noted as a suitable agent for spinal procedures with its spectrum of activity (e.g., against *Staphylococcus* species and gram-negative bacilli such as *E. coli*) and adequate tissue[121] and disk concentrations.[779,780]

Second- and third-generation cephalosporins offer no major advantages over first-generation agents. Their routine use is not recommended due to their higher cost and potential to promote resistance, particularly among health-care-associated gram-negative bacilli.[8] Broader coverage may be considered for instrumented fusion due to the risk of polymicrobial infections, including those caused by gram-negative bacteria.[563,769]

Clindamycin and vancomycin have adequate activity against the most common pathogens involved in orthopedic procedures and would be acceptable alternatives under certain circumstances, such as prophylaxis for patients with a β-lactam allergy. Vancomycin should be included with cefazolin or used as an alternative agent for routine antimicrobial prophylaxis for patients who are known to be colonized with MRSA.[6,8,41,733,781]

Duration. The majority of available studies of antimicrobial prophylaxis in spinal procedures have used single doses or regimens of <24 hours' duration.[732] There is no high-quality evidence supporting a duration of >24 hours,[782] and some sources recommend only a single preoperative dose.[8,769,778]

Pediatric efficacy. While no studies have evaluated the efficacy of antimicrobial prophylaxis in pediatric patients undergoing spinal procedures with or without instrumentation, the incidence and risk factors for SSIs in this population have been reported. The frequencies of SSIs in pediatric patients undergoing spinal fusion were 3.5% (<18 years old),[783] 3.8% (<19 years old),[784] 4.4% (ages 1–22 years old), and 5.2% (<17 years old)[764] for varying conditions, including Scheuermann's kyphosis,[784] myelodysplasia,[764] idiopathic scoliosis,[783,785] neuromuscular scoliosis,[785] kyphosis,[783] and spondylolisthesis.[783] The majority of patients in studies reporting antimicrobial prophylaxis received cefazolin, vancomycin, or clindamycin.[764,783,785]

Risk factors for SSIs after spinal procedures with instrumentation in a pediatric population include myelodysplasia,[764] procedure at the sacral spine, obesity,[785] ASA classification of >2, a complex medical condition (including spinal bifida, cerebral palsy, Marfan syndrome, achondroplasia, osteogenesis imperfecta, other unspecified genetic disease, muscular

dystrophy, spinal muscular atrophy, or other debilitating myopathies),[783] and previous spinal procedures. One study found a decreased risk of infection with hypothermia (core body temperature of <35.5 °C for the duration of the procedure).[785]

Two studies found suboptimal antimicrobial prophylaxis as a risk factor for SSIs in spinal procedures.[764,783] Optimal antimicrobial prophylaxis was defined as cefazolin 20 mg/kg (up to 2 g) given within 30 minutes[764] or 60 minutes[783] before surgical incision, vancomycin 10 mg/kg (up to 1 g) given within 60 minutes[783] or 150 minutes[764] before surgical incision, or clindamycin 10 mg/kg (up to 600 mg) given within 60 minutes before surgical incision.[783] Intraoperative redosing was defined as appropriate for cefazolin if administered for procedures lasting more than four hours and for vancomycin or clindamycin for procedures lasting more than six hours in one study[783] and for cefazolin administered every eight hours in the other study.[764] A third study found that use of clindamycin as the perioperative antimicrobial increased the risk of SSI.[785]

Recommendations. Antimicrobial prophylaxis is recommended for orthopedic spinal procedures with and without instrumentation. The recommended regimen is cefazolin (Table 2). (Strength of evidence for prophylaxis in orthopedic spinal procedures = A.) Clindamycin and vancomycin should be reserved as alternative agents as described in the Common Principles section. If there are surveillance data showing that gram-negative organisms are a cause of SSIs for the procedure, practitioners may consider combining clindamycin or vancomycin with another agent (cefazolin if the patient is not β-lactam allergic; aztreonam, gentamicin, or single-dose fluoroquinolone if the patient is β-lactam allergic). Mupirocin should be given intranasally to all patients known to be colonized with *S. aureus*.

Hip fracture repair

Background. Data support the use of antimicrobial prophylaxis for hip fracture repair to reduce the rate of SSIs, particularly in procedures that involve internal fixation (e.g., nails, screws, plates, wires). SSIs after hip fracture repair can result in extensive morbidity, including prolonged and repeated hospitalization, sepsis, persistent pain, device replacement, and possible death.[726,739,786-790]

Efficacy. The efficacy of antimicrobial prophylaxis in hip fracture repair has been illustrated in two meta-analyses.[787,788] One meta-analysis of 15 hip fracture procedure trials (the majority of procedures involved closed, proximal femoral, or trochanteric fractures with internal fixation) demonstrated that any dose and duration of prophylaxis are superior to no prophylaxis with respect to preventing SSIs (deep and superficial SSIs were analyzed together).[787] The rate of SSIs was 10.4% in controls versus 5.39% in treatment groups. A second meta-analysis of 22 studies reiterated the efficacy of antimicrobial prophylaxis in fracture procedures.[788] The analysis included the same hip fracture studies examined in the first meta-analysis, with additional studies of long-bone fracture repair (i.e., closed ankle fracture and other closed fractures, some noted with internal fixation). This second meta-analysis reviewed 10 studies of 1896 patients receiving a preoperative and two or more postoperative doses of a parenteral antimicrobial compared with a placebo or with no treatment. The authors found a relative risk of deep SSIs of 0.36 (95% CI, 0.21–0.65) and a relative risk of superficial SSIs of 0.48 (95% CI, 0.28–0.81) associated with antimicrobial use.

Choice of agent. The antimicrobials most often studied for prophylaxis in orthopedic procedures are first-generation cephalosporins due to their ease of administration, low cost, and safety profile.[787,788,791] Second- and third-generation cephalosporins have not been shown to offer clear advantages over first-generation agents. These agents are not recommended for routine use due to their higher cost, potential to promote resistance, and association with adverse events (e.g., *C. difficile*-associated diarrhea).[8,790,792]

Alternative regimens may be needed for institutions with highly resistant organisms, such as MRSA or *C. difficile*. Success in decreasing rates of *C. difficile*-associated disease and mortality was seen in a single-center study with the antimicrobial prophylaxis regimen change from three doses of cefuroxime[790,792] to a single preoperative dose of cefuroxime plus gentamicin.[792] In another study, *C. difficile*-associated disease decreased after the prophylaxis regimen was changed from cefuroxime to amoxicillin–clavulanate.[790]

Clindamycin and vancomycin have adequate activity against the most common pathogens involved in orthopedic procedures and would be acceptable alternatives under certain circumstances, such as prophylaxis for patients with a β-lactam allergy. Vancomycin should be included with cefazolin or used as an alternative agent for routine antimicrobial prophylaxis for patients who are known to be colonized with MRSA.[6,8,41,733,781]

Duration. For effective prophylaxis, the MIC of the antimicrobial needs to be exceeded at the target site from the moment of incision until surgical-site closure.[788] Two meta-analyses demonstrating the efficacy of antimicrobial prophylaxis in long-bone and hip fracture procedures also showed that multiple perioperative doses did not offer an advantage over a single preoperative dose.[787,788] These studies support a duration of antimicrobial prophylaxis of ≤24 hours.

Recommendations. The recommended regimen in hip fracture repair or other orthopedic procedures involving internal fixation is cefazolin. Clindamycin and vancomycin

should be reserved as alternative agents, as described in the Common Principles section. If there are surveillance data showing that gram-negative organisms are a cause of SSIs for the procedure, practitioners may consider combining clindamycin or vancomycin with another agent (cefazolin if the patient is not β-lactam allergic; aztreonam, gentamicin, or single-dose fluoroquinolone if the patient is β-lactam allergic). Mupirocin should be given intranasally to all patients with documented colonization with *S. aureus*. (Strength of evidence for prophylaxis = A.)

Total joint replacement

Background. In 2005, more than 750,000 hip or knee replacements were performed in the United States.[793] The reported frequency of SSIs complicating hip, knee, elbow, ankle, or shoulder replacement ranges from 0.6% to 12%.[743,786,794-797] SSI rates as high as 11% after hip replacement and 12% after elbow replacement have been reported.[786,797] However, for hip and knee replacements, the most common joint arthroplasties, infection rates are typically less than 2%.[165]

The introduction of antimicrobial prophylaxis, stringent infection-control protocols, and the use of ultraclean operating rooms has led to a substantial reduction in SSI rates (to ≤1%).[734,786,796,798,799] Postoperative prosthetic joint infection is an organ/space SSI that occurs early (within 3 months postoperatively), is delayed (3–12 months postoperatively), or occurs late (>12 months after surgery).[748] These infections frequently require removal of the prosthesis, a prolonged course of antimicrobials, and one- or two-stage reimplantation of the prosthesis and may result in permanent disability.[796,800] Studies have shown an estimated economic impact of one deep SSI of $100,000 in hospital costs alone after hip arthroplasty and $60,000 after knee arthroplasty.[727-731]

Common risk factors for prosthetic joint infection[748] include advanced age; obesity; diabetes mellitus; corticosteroid use; malignancy; rheumatoid arthritis; previous arthroplasty on the same joint; arthroplasty undertaken to treat a fracture; type of joint replaced (e.g., risk is greater for the knee than the hip); perioperative surgical-site complications, including superficial SSI; hematoma; and persistent surgical-site drainage. Operative risk factors include ASA classification of ≥3, duration of procedure exceeding the 75th percentile for the procedure or exceeding three hours, surgical site classified as contaminated or dirty, and no systemic antimicrobial prophylaxis. Excluding the presence of a systemic antimicrobial, patients with these operative risk factors are at the greatest risk of developing an SSI.

A contributing factor to SSIs in arthroplasty is the formation of bacterial biofilm, particularly with *S. aureus* and *S. epidermidis,* on inert surfaces of orthopedic devices to confer antimicrobial resistance and difficulty in antimicrobial penetration.[744-748]

Efficacy. The majority of studies that have evaluated antimicrobial prophylaxis in joint replacements have been conducted in patients undergoing total hip or total knee arthroplasty.[801] There is a lack of efficacy data involving elbow, shoulder, and ankle arthroplasty; however, the same antimicrobial prophylaxis principles can be applied. In light of the serious potential consequences, antimicrobial prophylaxis is well accepted in procedures involving the implantation of foreign materials.[8,543,732,733]

A meta-analysis supports the use of antimicrobial prophylaxis for SSI reduction in patients undergoing total joint replacement.[801] Of the 26 randomized controlled studies examined, 24 included patients undergoing total hip or total knee arthroplasty. The meta-analysis noted that the studies did not clearly state if the arthroplasties were primary or revision. The SSIs were defined as visible purulent exudates at the surgical site (deep or superficial) in the included studies. Seven studies (n = 3065 patients) pooled to compare antimicrobial prophylaxis with placebo found a relative risk reduction of SSIs of 81%.

Choice of agent. There are no data supporting superiority of one class of antimicrobials over another for antimicrobial prophylaxis in total joint replacement. A meta-analysis of studies, mainly in total hip or total knee replacement, found no difference in SSIs between cephalosporins with teicoplanin (not available in the United States) in five studies with 2625 patients, cephalosporins and penicillin derivatives in three studies of 386 patients, and first- and second-generation cephalosporins in eight studies of 2879 patients.[801] Selection should be based on cost, availability, and local resistance patterns. First-generation cephalosporins are the agents most commonly studied and used for antimicrobial prophylaxis in joint replacement procedures.

Clindamycin and vancomycin have adequate activity against the most common pathogens involved in orthopedic procedures and would be acceptable alternatives under certain circumstances, such as prophylaxis for patients with a β-lactam allergy. Vancomycin should be included with cefazolin or used as an alternative agent for routine antimicrobial prophylaxis in institutions that have a high prevalence of MRSA SSIs and for patients who are known to be colonized with MRSA.[6,8,41,733,781] Readers are referred to the section on implantation of internal fixation devices for further discussion of antimicrobial prophylaxis choice.

Antimicrobial-laden bone cement. The use of antimicrobial-laden bone cement in conjunction with i.v. antimicrobial prophylaxis is common worldwide, particularly for the prevention of infection in primary hip and knee arthroplasties.[802-806] FDA

has approved premixed aminoglycoside (i.e., gentamicin and tobramycin) in bone cement products for use in hip, knee, or other joints in second-stage revision of total joint arthroplasty.[807] The products are not approved for prophylaxis in primary joint replacement procedures. While antimicrobial bone cement has not been shown to be superior to i.v. antimicrobials,[808,809] there is evidence that supports the combination of using antimicrobial-laden bone cement together with systemic antimicrobial prophylaxis.

Although the evidence for the prophylactic use of antimicrobial-laden bone cement in primary joint arthroplasty looks favorable, a recent multicenter evaluation of risk factors for SSI in patients undergoing total hip arthroplasty did not find that use of antimicrobial-laden bone cement reduced the risk for infection.[95] In addition, questions remain regarding the risk for antimicrobial resistance and allergy, as well as the increased cost.[41,802-807,810-813] Readers are referred to reviews of this topic for additional information about tissue penetration, clinical application, and safety.[805,810-815]

Duration. The duration of prophylaxis in joint replacement procedures has been controversial. More recent data and clinical practice guidelines do not support prophylaxis beyond 24 hours.[6,41,133,723] Studies involving total hip replacement have used antimicrobials for 12 hours to 14 days postoperatively.[726,734-737,816] A duration of 24 hours was supported in a randomized trial of 358 patients undergoing total hip arthroplasty, total knee arthroplasty, or hip fracture repair that compared prophylaxis that lasted 24 hours versus 7 days of either nafcillin or cefazolin started 20 minutes before the procedure.[816] The difference in SSI rates between groups was not significant. There is no evidence of benefit of antimicrobial administration until all drains or catheters are removed.[32,41,133]

Recommendations. The recommended regimen for patients undergoing total hip, elbow, knee, ankle, or shoulder replacement is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents, as described in the Common Principles section. If there are any surveillance data showing that gram-negative organisms are a cause of SSIs for the procedure, practitioners may consider combining clindamycin or vancomycin with another agent (cefazolin if the patient is not β-lactam allergic; aztreonam, gentamicin, or a single-dose fluoroquinolone if the patient is β-lactam allergic). Mupirocin should be given intranasally to all patients with documented colonization with *S. aureus*. (Strength of evidence for prophylaxis = A.)

Urologic procedures

Background. The goals of antimicrobial prophylaxis in urologic procedures are the prevention of bacteremia and SSIs and the prevention of postoperative bacteriuria.[59] Postoperative urinary tract infections (UTIs) are the main concern for morbidity in patients after urologic procedures.[817,818] Bacteriuria, defined as $>10^3$ or $>10^4$ CFU/mL in symptomatic UTI and $>10^5$ CFU/mL in asymptomatic bacteriuria, within 30 days postoperatively is a frequent primary outcome in urologic procedure studies.[819-825] The benefits of preventing postoperative bacteriuria are not clearly known.[825]

In addition to general risk factors discussed in the Common Principles section of these guidelines, urologic-specific risk factors include anatomic anomalies of the urinary tract,[818] urinary obstruction,[826] urinary stone,[817,825,826] and indwelling or externalized catheters.[817,818,822,826] Preoperative UTI, particularly if recurrent, is recognized as a high-risk factor for postoperative infection, which is typically treated before procedures and is a common exclusion criterion from studies of efficacy of antimicrobial prophylaxis in urologic procedures.[817,826-828] Additional urologic operation-specific risk factors include length of postoperative catheterization,[829] mode of irrigation (closed versus open), and postoperative pyuria.[821]

Organisms. *E. coli* is the organism most commonly isolated in patients with postoperative bacteriuria; however, other gram-negative bacilli and enterococci may also cause infection.[818,821,827,830-839] Organisms such as *S. aureus*, coagulase-negative *Staphylococcus* species, and group A *Streptococcus* species are also a concern in procedures entering the skin with or without entering the urinary tract.[818,827,830-832,838,840,841] There is also some concern with biofilm-forming bacteria (*S. epidermidis* and *P. aeruginosa*) in patients with prosthesis implantation.[842]

Efficacy. The efficacy of antimicrobial prophylaxis in select urologic procedures has been investigated in several clinical trials. Of note, many of these placebo-controlled studies have excluded patients with risk factors for infection, those requiring antimicrobial prophylaxis for another indication (e.g., infective endocarditis), and those with preoperative UTI or bacteriuria.

The efficacy of antimicrobial prophylaxis in clean procedures among patients at low risk of complications has been variable. One randomized, placebo-controlled study of oral antimicrobials in 2083 patients undergoing flexible cystoscopy found a positive urine culture (bacteriuria with $>10^5$ CFU/mL) in 9.1% of patients receiving placebo, 4.6% of patients receiving trimethoprim, and 2.8% of patients receiving ciprofloxacin.[839] The rates of bacteriuria compared with baseline were significantly higher with placebo and significantly lower with use of antimicrobials compared with placebo. A randomized, placebo-controlled study of 517 patients undergoing prostate brachytherapy found no significant difference in

postimplantation epididymitis with or without antimicrobial prophylaxis (0.4% and 1.5%, respectively).[843] A meta-analysis of eight randomized, placebo-controlled or no-treatment-controlled studies with 995 patients undergoing urodynamic studies found a decrease in bacteriuria with antimicrobial prophylaxis (OR, 0.39; 95% CI, 0.24–0.61).[820] The number needed to treat was 13 to prevent one episode of asymptomatic bacteriuria using a pooled rate of 13.7% for bacteriuria. One study found that not using antimicrobial prophylaxis was a significant risk factor for bacteriuria caused by urinary dynamic studies.[821]

Antimicrobial prophylaxis has been studied in urologic procedures involving entry into the gastrointestinal tract, with the majority of the literature on transurethral resection of the prostate (TURP) and prostate biopsy. Two large meta-analyses have suggested prophylactic antimicrobials may be effective in all patients undergoing TURP, including low-risk patients and those with preoperatively sterile urine.[844,845] One meta-analysis of 32 trials with 4260 patients found that prophylactic antimicrobials decreased the combined bacteriuria (>10^5 CFU/mL) event rate from 26% to 9.1%, for a relative risk reduction of 65% (95% CI, –55 to –72), and the combined clinical septicemia episode rate from 4.4% to 0.7% in TURP patients, including low-risk patients.[846] Another meta-analysis of 28 trials that included a total of 4694 patients found prophylactic antimicrobials decreased the post-TURP rate of bacteriuria, fever, and bacteremia, as well as the need for additional postoperative antimicrobials.[847] An additional multicenter, open-label, randomized, active- and placebo-controlled trial in patients with sterile urine undergoing TURP found a decreased rate of bacteriuria (≥5 CFU/mL) with antimicrobial prophylaxis (21% with levofloxacin and 20% with sulfamethoxazole–trimethoprim) compared with placebo (30%) ($p = 0.009$).[822]

Three randomized, placebo-controlled studies of patients undergoing transrectal needle biopsy of the prostate found significant differences in infectious complications (including bacteriuria, positive urine cultures, and UTI) in patients treated with single doses of oral antimicrobial prophylaxis compared with placebo.[819,837,838] These three studies support the routine use of antimicrobial prophylaxis in all patients undergoing transrectal needle biopsy of the prostate. Of note, all patients undergoing transrectal needle biopsy of the prostate received a cleansing enema before the procedure.[819,837,838] Use of MBP has been reported in urologic procedures that involve entering the gastrointestinal tract (e.g., urinary diversion).[844,846]

The use of antimicrobial prophylaxis in patients undergoing extracorporeal shock wave lithotripsy (ESWL) and ureterorenoscopy is supported by the results of a meta-analysis[847] and a small randomized controlled trial.[848] The meta-analysis included eight randomized controlled trials with 885 patients and six clinical case series involving 597 patients undergoing ESWL.[845] The overall rate of UTI in the randomized controlled trials ranged from 0% to 7.7% with antimicrobial prophylaxis and from 0% to 28% in the control groups (relative risk, 0.45; 95% CI, 0.22–0.93). A randomized, placebo-controlled study of 113 patients undergoing ureterorenoscopy found a rate of postoperative bacteriuria of 1.8% with antimicrobial prophylaxis and 12.5% without ($p = 0.0026$).[848] No patients had symptomatic UTI or inflammation complications of the urogenital tract postoperatively.

There are no studies of antimicrobial prophylaxis in major open or laparoscopic procedures (cystectomy, radical prostatectomy, and nephrectomy); therefore, data have been extrapolated from other major intraabdominal procedures.

Choice of agent. No single antimicrobial regimen appears superior for urologic procedures. A wide range of antimicrobial regimens, including cephalosporins,[658,835,836,843,849-855] aminoglycosides,[856,857] piperacillin–tazobactam,[849,858,859] trimethoprim–sulfamethoxazole,[822,838,860] trimethoprim,[839] nitrofurantoin,[861] and fluoroquinolones,[819,821,822,824,831,835-837,839,840,843,848,851,853-855,862,863] have been evaluated in urologic procedures. The efficacy of fluoroquinolones for antimicrobial prophylaxis in urologic surgical procedures has been well established. One study found better reduction of bacteriuria with either ciprofloxacin or trimethoprim compared with placebo,[839] while other studies found no difference in efficacy between a fluoroquinolone and sulfamethoxazole–trimethoprim, both of which were better than placebo.[822,838] No differences were found in studies between oral or i.v. fluoroquinolones (ciprofloxacin or ofloxacin) compared with i.v. or intramuscular cephalosporins (ceftriaxone, cefotaxime, or cefazolin) and intramuscular penicillin (piperacillin–tazobactam) in various urologic procedures.[835,836,851,854,855,858] In several studies, fluoroquinolones were administered orally, which appears to be feasible in patients undergoing procedures not involving opening the urinary or gastrointestinal tract, when the i.v. route would be preferred.[822,836,838,851,855,858] Recently, resistance to fluoroquinolones has been emerging; the fact that most of the literature was published before resistance became prevalent should be considered, since resistance may decrease the relevance of these studies.[836,846,847,858,864] Local resistance patterns to fluoroquinolones, particularly with *E. coli,* should be evaluated to help guide antimicrobial selection.

Broad-spectrum antimicrobials, such as third-generation cephalosporins and carbapenems, are no

more effective than first- or second-generation cephalosporins, aminoglycosides, or oral agents (trimethoprim–sulfamethoxazole, nitrofurantoin, or fluoroquinolones) and should be reserved for patients with active infection or who require additional coverage for intestinal organisms.[6,826,827] Their routine use is not recommended due to their higher cost and potential to promote resistance, particularly among health-care-associated gram-negative bacilli.[8]

Duration. While longer durations of postoperative prophylaxis (up to three weeks) have been studied,[856,858,860,861] more-recent data support the use of shorter durations (i.e., a single dose or less than 24 hours' duration) in urologic procedures.[658,817,818,823,824,826,831,832,834,836,846,853,857,859,862,865,866] Based on bioavailability, oral antimicrobial prophylaxis should be administered 1–2 hours before surgical incision or start of the procedure.[817,819-822,824,826,836,838,840,848,851,855]

Pediatric efficacy. Limited data on antimicrobial prophylaxis are available for pediatric patients undergoing urologic procedures. One prospective, open-label, nonrandomized study of boys undergoing hypospadias repair with tabularized incision plate urethroplasty allocated patients to receive cefonicid (no longer available in the United States) with one i.v. dose before the procedure only or the addition of oral cephalexin three times daily starting on postoperative day 1 until 2 days after catheter removal (median, 8.3 days).[833] More patients in the single-dose group had bacteriuria and complications (urethrocutaneous fistula and meatal stenosis); however, the rate of infection and infection-related complications did not significantly differ between groups.

Recommendations. No antimicrobial prophylaxis is recommended for clean urologic procedures in patients without risk factors for postoperative infections. Patients with preoperative bacteriuria or UTI should be treated before the procedure, when possible, to reduce the risk of postoperative infection. For patients undergoing lower urinary tract instrumentation with risk factors for infection, the use of a fluoroquinolone or trimethoprim–sulfamethoxazole (oral or i.v.) or cefazolin (i.v. or intramuscular) is recommended (Table 2). For patients undergoing clean urologic procedures without entry into the urinary tract, cefazolin is recommended, with vancomycin or clindamycin as an alternative for those patients allergic to β-lactam antimicrobials. For patients undergoing clean urologic procedures with entry into the urinary tract, cefazolin is recommended, with alternative antimicrobials to include a fluoroquinolone, the combination of an aminoglycoside plus metronidazole, or an aminoglycoside plus clindamycin. For clean-contaminated procedures of the urinary tract (often entering the gastrointestinal tract), antimicrobials as recommended for elective colorectal surgery are recommended. This would generally include the combination of cefazolin with or without metronidazole, cefoxitin, or, for patients with β-lactam allergy, a combination of either a fluoroquinolone or aminoglycoside given with either metronidazole or clindamycin. The medical literature does not support continuing antimicrobial prophylaxis until urinary catheters have been removed. See the colorectal procedures section of these guidelines for recommendations pertaining to procedures entering the gastrointestinal tract. (Strength of evidence for prophylaxis = A.)

Vascular procedures

Background. Infection after vascular procedures occurs with low frequency but can be associated with extensive morbidity and mortality.[867,868] Postoperative infections involving vascular graft material can result in limb loss and life-threatening conditions.[868] As a result, antimicrobial prophylaxis is widely used in procedures that involve implantation of prosthetic material and procedures for which there is greater risk of infection, such as aneurysm repair, thromboendarterectomy, and vein bypass.[6,41,867,869] Patients undergoing brachiocephalic procedures (e.g., carotid endarterectomy, brachial artery repair) without implantation of prosthetic graft material do not appear to benefit from routine antimicrobial prophylaxis.[6,41,867,870]

Risk factors for postoperative SSI in patients undergoing vascular procedures include lower-extremity sites, delayed procedures after hospitalization, diabetes mellitus, and a history of vascular or aortocoronary bypass procedures.[871,872] Currently, prospective data from well-designed studies on prophylaxis for endovascular stenting do not exist. However, if prophylaxis is desired, the same antimicrobials and short duration of therapy used for open vascular procedures should be given. Risk factors that warrant consideration of prophylaxis in patients undergoing endovascular stenting include prolonged procedures (more than two hours), reintervention at the surgical site within seven days, vascular stent placement in the groin through a hematoma or sheath, procedures in immunosuppressed patients, and the presence of another intravascular prosthesis.[873-877]

Organisms. The predominant organisms involved include *S. aureus, S. epidermidis,* and enteric gram-negative bacilli. MRSA is an emerging organism of concern.

Several studies evaluated the rate of colonization, carriage, and infection with MRSA in patients undergoing various vascular procedures.[878-884] Independent risk factors for MRSA infection included MRSA colonization, open abdominal aortic aneurysm, tissue loss, and lower-limb bypass.[878] Patients who have or develop MRSA infections before

vascular procedures have increased risk of inhospital death, intensive care unit admission, repeat surgeries, increased length of stay, and delayed wound healing, compared with patients without infections.[880-883]

Efficacy. Prophylactic antimicrobials decrease the rate of infection after procedures involving the lower abdominal vasculature and procedures required to establish dialysis access. The follow-up time for patients with late surgical-site complications was at least once after hospital discharge (not further defined) for most studies,[829,865,871,885-887] at one month,[869,871,888,889] at six months,[872] and at three years.[138]

A meta-analysis of 10 randomized controlled trials in patients undergoing peripheral arterial reconstruction with biological or prosthetic graft procedures found an overall consistent reduction in SSIs with systemic antimicrobial prophylaxis compared with placebo (relative risk, 0.25; 95% CI, 0.17–0.38; $p < 0.00001$).[890] An overall reduction was found among 5 studies evaluating early graft infection (relative risk, 0.31; 95% CI, 0.11–0.85; $p = 0.02$), though no individual study found a significant reduction in SSIs.

The largest study included in the meta-analysis above was a randomized, prospective, double-blind, placebo-controlled study of patients undergoing peripheral vascular procedures ($n = 462$). The infection rate was significantly lower with cefazolin than with placebo (0.9% and 6.8%, respectively).[885] Four deep graft infections were observed in the placebo group; none occurred in the patients who received cefazolin. No infections were observed in patients who underwent brachiocephalic ($n = 103$), femoral artery ($n = 56$), or popliteal ($n = 14$) procedures.

Patients undergoing vascular access procedures for hemodialysis may benefit from the administration of antistaphylococcal antimicrobials. A placebo-controlled study of 408 patients undergoing permanent vascular access placement demonstrated an upper-extremity prosthetic polytetrafluoroethylene graft infection rate of 6% with placebo compared with 1% with vancomycin ($p = 0.006$).[869]

Choice of agent. Cefazolin remains the preferred and most cost-effective prophylactic agent for use in vascular procedures.[6,8,41,872,886,887] There was no significant difference in infection rates between cefazolin and cefuroxime in patients undergoing abdominal aortic and lower-extremity peripheral vascular procedures,[886] between cefazolin and cefamandole (no longer available in the United States) in patients undergoing aortic or infrainguinal arterial procedures,[887] or between cefazolin and ceftriaxone in patients undergoing arterial reconstruction involving infraclavicular sites.[872]

A multicenter, randomized, double-blind, prospective trial of 580 patients undergoing arterial procedures involving the groin who received either two doses of ciprofloxacin 750 mg orally or three doses of cefuroxime 1.5 g i.v. on the day of the procedure found an SSI rate of 9.2% (27 patients) and 9.1% (26 patients), respectively, within 30 days of the procedure[889] Although oral ciprofloxacin was shown to be as effective as i.v. cefuroxime, this study did not address concerns about resistance with routine use of fluoroquinolones.[891] Therefore, i.v. cefazolin remains the first-line agent for this indication. The efficacy of oral agents for prophylaxis needs to be further evaluated.

There are limited data regarding the choice of an antimicrobial for β-lactam-allergic patients undergoing vascular procedures. The main alternative agents are vancomycin and clindamycin, since prophylaxis is largely directed against gram-positive cocci. Vancomycin can also be used for prophylaxis in institutions with MRSA or methicillin-resistant *S. epidermidis* (MRSE) clusters or in patients with β-lactam allergy.[6,8,41] Clindamycin may be an acceptable alternative to vancomycin, though local antimicrobial resistance patterns should be taken into account.

An aminoglycoside may be added to vancomycin for the addition of aerobic gram-negative bacilli coverage if the procedure involves the abdominal aorta or a groin incision, due to the potential for gastrointestinal flora. See the Common Principles section of these guidelines for further discussion of the use of vancomycin. Alternative antimicrobials for β-lactam-allergic patients receiving vancomycin may include a fluoroquinolone or aztreonam.[6]

Duration. A meta-analysis of three randomized controlled studies involving vascular procedures, including lower-limb reconstruction and open arterial procedures, found no additional benefit of continuing prophylactic antimicrobials for over 24 hours postoperatively compared with no more than 24 hours (relative risk, 1.28; 95% CI, 0.82–1.98).[890]

A randomized, double-blind study compared infection rates of a one-day and a three-day course of cefuroxime with placebo in 187 patients undergoing peripheral vascular procedures.[888] The infection rates were 16.7%, 3.8%, and 4.3% in the placebo, one-day, and three-day groups, respectively. The difference in the infection rates between the one- and three-day groups was not significant.

A randomized controlled study compared one day and five days of amoxicillin–clavulanate 1.2 g in 100 patients undergoing 108 lower-limb reconstruction procedures.[892] No difference was seen in the postoperative SSI rate between groups (9 patients [16%] and 12 patients [23%], respectively). The study authors selected the agent based on extended spectrum of activity and good tissue penetration. However, they concluded that due to the high rate of infection

observed, the use of antimicrobial prophylaxis might not be as effective as once thought.

A randomized controlled study compared ticarcillin–clavulanate 3.1 g given as a single dose at induction of anesthesia with multiple doses given at induction and every 6 hours postoperatively until venous access lines were removed or a maximum of 20 doses (total of five days) in patients undergoing open arterial procedures.[893] Significantly more SSIs occurred in the single-dose group (28 [18%] of 153 patients) compared with the multidose group (15 [10%] of 149 patients) (relative risk, 2; 95% CI, –1.02 to 3.92; p = 0.041). Ticarcillin–clavulanate has a short duration of action and is not recommended as a routine agent for antimicrobial prophylaxis. Practice guidelines recommend single-dose prophylaxis in vascular procedures or a maximum duration of therapy of 24 hours postoperatively, regardless of the presence of invasive drains.[6,41]

Recommendations. The recommended regimen for patients undergoing vascular procedures associated with a higher risk of infection, including implantation of prosthetic material, is cefazolin (Table 2). (Strength of evidence for prophylaxis = A.) Clindamycin and vancomycin should be reserved as alternative agents as described in the Common Principles section of these guidelines. If there are surveillance data showing that gram-negative organisms are a cause of SSIs for the procedure, practitioners may consider combining clindamycin or vancomycin with another agent (cefazolin if the patient is not β-lactam allergic; aztreonam, gentamicin, or single-dose fluoroquinolone if the patient is β-lactam allergic), due to the potential for gastrointestinal flora exposure.

Heart, lung, and heart–lung transplantation

Background. Solid-organ transplant recipients are at high risk for infections due to the complexity of the surgical procedures, donor- or recipient-derived infections, reactivation of recipient-associated latent infections, preoperative recipient colonization, exposure to community pathogens, and opportunistic infections due to immunosuppression.[894-897] Infections occur more frequently in the first year after transplantation, due to aggressive immunosuppression. Transplant recipients with infections are commonly asymptomatic or have nonspecific symptoms or sequelae of infection, which makes detection and diagnosis of infections difficult.[855,857,894] Postoperative infections caused by bacterial, viral, and fungal pathogens, including SSIs, UTIs, bloodstream infections, and pneumonia, are of greater concern within the first month after transplantation.[895-897] Opportunistic infections that result from immunosuppression typically occur after the first month of transplantation. It is routine for transplant recipients to receive antimicrobial prophylaxis to prevent opportunistic infections.[894-897] A discussion of the prophylactic strategies for prevention of cytomegalovirus (CMV) infection, herpes simplex virus infection, pneumocystis, UTI in kidney transplant recipients, *Aspergillus* infection in lung transplant recipients, and other opportunistic infections outside of the immediate posttransplantation period is beyond the scope of these guidelines.

Few well-designed, prospective, comparative studies of antimicrobial prophylaxis have been conducted with patients undergoing solid-organ transplantation, and no formal recommendations are available from expert consensus panels or professional organizations; however, there are reviews that provide guidance.[8,41,894]

The recommendations given for each of the solid-organ transplant procedures are intended to provide guidelines for safe and effective surgical prophylaxis based on the best available literature. Antimicrobial surgical prophylaxis practice will vary considerably among transplantation centers throughout the United States, based on the organ involved, preexisting recipient and donor infections, and local antimicrobial susceptibilities.[894-897]

Heart transplantation. *Background.* Heart transplantation is an option for selected patients with end-stage cardiac disease. In 2007, the United Network for Organ Sharing (UNOS) reported that 2209 heart transplants were performed in the United States, including 327 in children (<18 years of age).[898] The mean graft survival rate 10 years after heart transplantation is approximately 49%. Infection continues to be an important cause of morbidity and mortality after heart transplantation and is a primary cause of death in approximately 14% of patients within the first year after transplantation.[899]

Despite the large number of heart transplantation procedures performed, few studies have specifically examined postoperative SSI rates in this population. General cardiothoracic procedures have been associated with SSI rates ranging from 9% to 55% in the absence of antimicrobial prophylaxis.[214,900,901] Studies of general cardiothoracic procedures, including heart transplantation, found SSIs, particularly mediastinitis, in 3–6% of patients who received antimicrobial prophylaxis.[170,902] The frequency was highest in heart transplant recipients. The SSI rates reported in patients undergoing heart transplantation who received antimicrobial prophylaxis ranged from 5.8% to 8.8%, including mediastinitis in 3–7% of patients.[903,904]

Several independent risk factors for SSIs after cardiac and thoracic procedures have been identified (see the cardiac and thoracic sections of this article). Heart transplantation has been identified as an independent risk factor for SSIs.[170] Other

independent risk factors for SSIs in heart transplantation include age,[905] receipt of ciprofloxacin alone for prophylaxis,[906] positive wire cultures,[907] a BMI of >30 kg/m^2, female sex,[908] previous cardiac procedures, previous left VAD placement, and hemodynamic instability requiring inotropic support.[903,904] Unfavorable functional outcomes were seen in patients who developed infections within the first year after heart transplantation associated with lung, bloodstream, and CMV infections.[909] Independent predictors of mortality in heart transplant recipients included serum creatinine levels, amyloid etiology, history of hypertension, pulmonary infection, and CNS infection. Additional predisposing factors for infection in heart transplantation include exposure to pathogens from the donor or transplant recipient, the time from organ recovery to reperfusion, and the immunosuppressive regimens used.[897,904,910] Similar risk factors for infection are noted in pediatric transplant recipients, with the addition of a naive immune system to several pathogens, most notably viruses, as well as incomplete primary immunization series.[897]

Patients with an indwelling VAD at the time of heart transplantation have additional prophylaxis concerns. Recipients who do not have a driveline infection and have no history of either colonization or infection should receive prophylaxis as described for recipients without a VAD in place. Patients with a history of colonization or previous infection should have the antimicrobial sensitivities of that organism considered when choosing the SSI prophylactic regimen administered, though the duration should still be less than 24 hours. Heart transplant recipients with an active VAD driveline infection at the time of heart transplantation should be given appropriate antimicrobials specifically for the treatment of that infection. This intervention will usually determine the actual perioperative prophylaxis regimen as well as the duration of therapy beyond the period of prophylaxis.

Patients requiring ECMO as a bridge to heart transplantation should be treated with a similar approach. If there is no history of colonization or previous infection, then the general recommendations for SSI antimicrobial prophylaxis for the specific procedure should be followed. In ECMO patients with a history of colonization or previous infection, changing the preoperative antimicrobial prophylaxis to cover these pathogens must be considered, weighing whether the pathogen is relevant to SSIs in the planned procedure.

Because heart transplantation is similar to other cardiac and thoracic procedures, similar considerations regarding the need for antimicrobial prophylaxis apply (see the cardiac and thoracic sections).[911] These guidelines do not address antimicrobial prophylaxis for infective endocarditis. Readers are referred to the current guidelines for prevention of infective endocarditis from AHA.[11,228]

Organisms. As with other types of cardiothoracic procedures, gram-positive organisms, mainly *Staphylococcus* species, are the primary pathogens that cause SSI after heart transplantation.[902,905-907,912,913] MRSA was reported in 12–21% of SSIs in several cohort studies.[903,905,906] Vancomycin-resistant *Enterococcus faecalis* was noted in 15% of infections in one cohort study.[903] Other gram-positive pathogens (e.g., coagulase-negative staphylococci, *Enterococcus* species)[903,905-907,913] and gram-negative organisms (e.g., Enterobacteriaceae, *P. aeruginosa, Stenotrophomonas maltophilia*) are also a concern for SSIs in heart transplant recipients, as are *Candida* species.[903,906]

Efficacy. Despite the paucity of literature on antimicrobial prophylaxis for the prevention of SSIs in heart transplantation, the efficacy noted in other cardiac surgical procedures has made it the standard of practice during transplantation.[896]

No randomized controlled trials have specifically addressed the use of antimicrobial prophylaxis in heart transplantation. In an open-label noncomparative study, the SSI rate was 4.5% among 96 patients administered cefotaxime plus floxacillin preoperatively and for 72 hours after cardiac procedures.[912] This rate of infection was similar to that seen in other cardiothoracic, nonheart transplantation procedures in which antimicrobial prophylaxis was used.

Choice of agent. Antimicrobial prophylaxis for heart transplantation should be similar to that used for other types of cardiothoracic procedures.[911] First- and second-generation cephalosporins are considered to be equally efficacious and are the preferred agents. There appear to be no significant differences in efficacy among prophylactic regimens using agents such as cefazolin and cefuroxime.[914] The use of antistaphylococcal penicillins, either alone or in combination with aminoglycosides or cephalosporins, failed to demonstrate superior efficacy to that of cephalosporin monotherapy (see the cardiac and thoracic sections) in other cardiothoracic procedures.

Several cohort studies examined antimicrobial prophylactic agents used for patients undergoing heart transplantation but did not evaluate efficacy.[902,903,905,906] Ciprofloxacin alone was found to be an independent risk factor for incisional SSIs.[906]

Duration. There is no consensus on the optimal duration of antimicrobial prophylaxis in cardiothoracic procedures, including heart transplantation. Cohort evaluations of patients undergoing heart transplantation reported durations of antimicrobial prophylaxis with cefazolin or vancomycin of 24 or 48 hours postoperatively.[902,903,905] Data from cardiothoracic procedures

also support a range of prophylaxis durations, from a single dose to 24 or 48 hours postoperatively.[41,131] The currently accepted duration for these procedures, which do not include transplantation, is 24–48 hours postoperatively.[41,59,131,201] The duration of antimicrobial prophylaxis for patients who do not have their chest primarily closed is unclear; most centers continue prophylaxis until the chest is closed, but there is no evidence to support this practice.

Pediatric efficacy. No randomized controlled studies have specifically addressed antimicrobial prophylaxis for heart transplantation in pediatric patients. Infants are at risk for mediastinitis caused by gram-negative as well as gram-positive organisms. Pediatric patients undergoing heart transplantation should be treated according to recommendations for other types of cardiothoracic procedures. The recommended regimen for pediatric patients undergoing cardiothoracic procedures is cefazolin 25–50 mg/kg i.v. within 60 minutes before surgical incision and every 8 hours for up to 48 hours. Cefuroxime 50 mg/kg i.v. within 60 minutes before surgical incision and every 8 hours for up to 48 hours is an acceptable alternative. Vancomycin 10–20 mg/kg i.v. over 60–120 minutes, with or without gentamicin 2 mg/kg i.v., should be reserved as an alternative on the basis of guidelines from HICPAC for routine antimicrobial prophylaxis in institutions that have a high prevalence of MRSA, for patients who are colonized with MRSA, or for patients with a true β-lactam allergy.[8] Additional doses may be needed intraoperatively for procedures >4 hours in duration, for patients with major blood loss, or for extended use of CPB depending on the half-life of the prophylactic antimicrobial. Fluoroquinolones are not routinely recommended in pediatric patients.

Recommendations. Based on data for other types of cardiothoracic procedures, antimicrobial prophylaxis is indicated for all patients undergoing heart transplantation (see cardiac and thoracic sections). The recommended regimen is a single dose of cefazolin (Table 2). There is no evidence to support continuing prophylaxis until chest and mediastinal drainage tubes are removed. Alternatives include vancomycin or clindamycin with or without gentamicin, aztreonam, or a single fluoroquinolone dose. (Strength of evidence for prophylaxis = A.) The optimal duration of antimicrobial prophylaxis for patients who do not have their chest primarily closed is unclear. No recommendation is made for these patients. Patients who have left VADs as a bridge and who are chronically infected might also benefit from coverage of the infecting microorganism.

Lung and heart–lung transplantation. *Background.* Lung transplantation is an accepted option for a variety of end-stage, irreversible lung diseases. The most common diseases for which lung transplantation is performed are idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, emphysema, cystic fibrosis, α-1-antitrypsin deficiency, and idiopathic pulmonary arterial hypertension.[915,916] UNOS reported that in the United States in 2007, 1468 lung transplantations and 31 heart–lung transplantations were conducted in adults, and 52 lung transplantations and 3 heart–lung transplantations were performed in children.[898,917] Ten-year survival rates were reported as 29.7% of double-lung, 17.5% of single-lung, and 25.8% of heart–lung transplant recipients.[899] The reported three-year survival rate for pediatric lung transplant recipients was 57%.[897]

Infections are the most common complications after lung and heart–lung transplantations.[899,915,918,919] In an analysis of UNOS data over an 18-year period, infection was the number one cause of death within the first year of transplantation, occurring in 24.8% of lung and 18.3% of heart–lung transplant recipients.[899] Among the top 10 primary causes of death within the first year after lung and heart–lung transplantations were sepsis, pneumonia, fungal infection (lung only), and CMV infection.[899] A study of two cohorts of patients undergoing heart, lung, and heart–lung transplantations who received antimicrobial prophylaxis evaluated the rate of SSIs and mediastinitis.[904,908] The rate of SSI among all transplant recipients was 12.98%, with the majority of infections (72%) being organ/space infections, followed by deep incisional infections (17%) and superficial incisional infections (10%).[908] The overall rate of mediastinitis in a similar cohort was 2.7%, with rates of 5.2% in heart–lung transplant recipients and 3.2% in bilateral lung transplant recipients.[904] Pneumonia was reported in 26.4% of transplantation patients overall, with rates of 20.7% in lung transplant recipients and 40% in heart–lung transplant recipients.[908] A cohort of lung transplant recipients reported a rate of 2.2 episodes of pneumonia per patient during a median follow-up period of 412 days (range, 1–1328 days).[920]

Bronchial anastomotic infections, especially fungal infections, can be serious and are potentially fatal in lung transplant recipients.[921,922] The lung allocation score (LAS) is a rating system adopted by the Organ Procurement and Transplant Network and UNOS in 2005 to improve organ allocation and transplantation outcomes. The LAS is based on the risk of death while on the waiting list for transplantation and the expected 1-year survival after transplantation. Patients with a low LAS are unlikely to undergo transplantation. A study of lung transplant recipients age 12 years or older revealed a higher rate of infection and other morbidities and a lower 1-year survival rate in patients with a high LAS at the time of transplantation than in patients

with a low LAS at the time of transplantation.[923] Thus, the potential for bronchial anastomotic infection and a poor posttransplantation outcome needs to be considered in patients undergoing lung transplantation. Among lung transplantation patients, risk factors for nosocomial infections included α-1-antitrypsin deficiency and repeat transplantation. Risk factors for pneumonia included colonized or infected donor bronchus and perfusate and preoperative colonization with gram-negative rods. Risk factors for mortality among the transplant recipients were cystic fibrosis, nosocomial infection, and ventilation before transplantation.[908] Risk factors for mediastinitis after heart, lung, and heart–lung transplantation were degree of immunosuppression, impaired renal function, previous sternotomy, and reexploration due to bleeding.[904] There was a positive association between pretransplantation colonizing microorganisms from suppurative lung disease patients and pneumonia after transplantation.[920] Transplantation alters the physiological function of lungs, including the impairment of mucociliary clearance and interruption of the cough reflex, leading to a higher risk of pulmonary infections.[896]

In patients requiring ECMO as a bridge to lung transplantation who have no history of colonization or previous infection, the general recommendations for SSI antimicrobial prophylaxis for the procedure should be followed. In ECMO patients with a history of colonization or previous infection, changing the preoperative antimicrobial prophylaxis to cover these pathogens must be considered, weighing whether the pathogen is relevant to SSIs in the planned procedure.

Organisms. While gram-positive and gram-negative organisms are of concern in heart transplantation, there is increased concern regarding gram-negative and fungal pathogens in mediastinitis and pneumonia in patients undergoing lung transplantation.[894,904,908] The most frequent organisms found in SSIs or mediastinitis in two cohort studies were *P. aeruginosa*,[904,908] *Candida* species, *S. aureus* (including MRSA),[908] enterococci, coagulase-negative staphylococci (e.g., *S. epidermidis)*, *Burkholderia cepacia*,[904] *E. coli*, and *Klebsiella* species.

Patients undergoing lung transplantation are also at risk for bacterial or fungal pneumonia due to colonization or infection of the lower and upper airways of the donor, recipient, or both.[915] Organisms reported to cause pneumonia in lung transplantation patients include *P. aeruginosa*,[894,896,904,908,920] *S. aureus* (including MRSA),[894,896,904,908] *B. cepacia*,[896,904,908] *Enterobacter* species,[908] *S. maltophilia, Klebsiella* species,[904,908] *S. epidermidis,*[904] *E. coli*, *Aspergillus* species,[920] and VRE.[894] Similarly, organisms frequently seen in pediatric lung infections are nonfermenting gram-negative bacteria, such as *Pseudomonas* species, *Stenotrophomonas* species, *Alcaligenes* species, and fungi, including *Aspergillus* species.[897]

The donor lung appears to be a major route of transmission of pathogens; 75–90% of bronchial washings from donor organs are positive for at least one bacterial organism.[920,924,925] Organ recipients may also be the source of infection of the transplanted organ. This is particularly true in patients with cystic fibrosis because of the frequent presence of *P. aeruginosa* in the upper airways and sinuses before transplantation.[896,919] These pathogens are often multidrug resistant, likely due, in large part, to frequent administration of broad-spectrum antimicrobials during the course of the disease. Multidrug-resistant strains of *B. cepacia* and *S. maltophilia* may be a problem in cystic fibrosis patients in some transplantation centers.[919,926]

Efficacy. Although much has been published about general infectious complications associated with lung transplantation, no randomized controlled trials regarding antimicrobial prophylaxis for lung or heart–lung transplantation have been published; however, antimicrobial prophylaxis is considered standard practice in these patients.[896] Antimicrobial prophylaxis is routinely administered to patients undergoing lung or heart–lung transplantation, with the aim of preventing pneumonia as well as SSIs. The rate of pneumonia within the first two weeks postoperatively has reportedly been decreased from 35% to approximately 10% by routine antimicrobial prophylaxis.[927-929] Improvements in surgical technique and postoperative patient care are also important factors in the apparently lower rates of pneumonia after lung transplantation.

Choice of agent. No formal studies have addressed optimal prophylaxis for patients undergoing lung transplantation. Antimicrobial prophylaxis for lung and heart–lung transplantation should generally be similar to that used for other cardiothoracic procedures (see the cardiac and thoracic sections). First- and second-generation cephalosporins are considered equally efficacious and are the preferred agents for these procedures. However, prophylactic regimens should be modified to include coverage for any potential bacterial pathogens, including gram-negative and fungal organisms, that have been isolated from the recipient's airways or the donor lung through preoperative cultures.[894,896,904,908,915,920] Patients with end-stage cystic fibrosis should receive antimicrobials on the basis of the known susceptibilities of pretransplant isolates, particularly *P. aeruginosa, B. cepacia* complex, and *Aspergillus* species.

Antimicrobial prophylaxis regimens reported in cohort evaluations of thoracic transplantation, including lungs, have varied.[904,908,920] One study used ceftazidime, floxacillin, tobramycin, and itraconazole

in these patients.[908] In addition, all patients received nebulized amphotericin B and oral itraconazole as antifungal prophylaxis. Another cohort study used cefepime for lung transplant recipients without known colonization; for those with known colonization, the selection of agents was based on organism susceptibility.[920] A third cohort reported use of metronidazole and aztreonam as prophylaxis for patients with a septic lung (positive sputum culture).[904]

Antifungal prophylaxis should be considered, especially when pretransplantation cultures reveal fungi in the donor lung[915] or the recipient's airway. There is no consensus on the appropriate antifungal agent for lung transplant recipients.[894,896,930] Selection is recommended based on patient risk factors for infection (e.g., cystic fibrosis) and colonization, pretransplantation and posttransplantation cultures, and local fungus epidemiology.[894,896,897,930] Because of the serious nature of fungal infections in the early posttransplantation period and the availability of antifungal agents, prophylaxis should be considered when *Candida* or *Aspergillus* species are isolated from the donor lung[915] or recipient's airway.

Duration. No well-conducted studies have addressed the optimal duration of antimicrobial prophylaxis for lung or heart–lung transplantation. In the absence of positive cultures from the donor or the recipient, prophylactic regimens of 48–72 hours and no longer than 7 days have been reported.[896,904,905,931] In patients with positive pretransplantation cultures from donor or recipient organs or patients with positive cultures after transplantation, postoperative antimicrobial treatment for 7–14 days or longer has been reported, particularly for patients with cystic fibrosis and previous *P. aeruginosa* and multidrug-resistant infections.[896,915,919] Such antimicrobial administration is viewed as treatment and not as surgical prophylaxis. Treatment may include additional antibacterial agents or antifungal agents.

Recommendations. Based on data from other types of cardiothoracic procedures, all adult patients undergoing lung transplantation should receive antimicrobial prophylaxis, because of the high risk of infection. Patients with negative pretransplantation cultures should receive antimicrobial prophylaxis as appropriate for other types of cardiothoracic procedures.

The recommended regimen is a single dose of cefazolin (Table 2). There is no evidence to support continuing prophylaxis until chest and mediastinal drainage tubes are removed. Alternatives include vancomycin with or without gentamicin, aztreonam, and a single fluoroquinolone dose. (Strength of evidence for prophylaxis = A.) The optimal duration of antimicrobial prophylaxis for patients who do not have their chest primarily closed is unclear. No recommendation is made for these patients.

The prophylactic regimen should be modified to provide coverage against any potential pathogens, including gram-negative (e.g., *P. aeruginosa*) and fungal organisms, isolated from the donor lung or the recipient pretransplantation. The prophylactic regimen may also include antifungal agents for *Candida* and *Aspergillus* species based on patient risk factors for infection (e.g., cystic fibrosis) and colonization, pretransplantation and posttransplantation cultures, and local fungus epidemiology. Patients undergoing lung transplantation for cystic fibrosis should receive treatment for at least seven days with antimicrobials selected according to pretransplantation culture and susceptibility results. (Strength of evidence for prophylaxis = B.)

Liver transplantation

Background. Liver transplantation is a lifesaving procedure for many patients with end-stage hepatic disease for whom there are no other medical or surgical options.[932,933] In 2007, UNOS reported that 6494 liver transplantations were performed in the United States, 96% of which had a cadaveric donor and 4% had a living-related donor source.[934] These liver transplantations were performed in 5889 adults and 605 pediatric (<18 years old) patients. Reported 1-year patient survival rates for adults ranged from 76.9% to 95%[932,935-938] and from 80% to 91.7% for pediatric patients.[934,939-942] Survival at 3 and 5 years ranged from 68.5% to 80.9%[934] and from 61.6% to 76.5%[932,933] in adult patients, respectively. In pediatric patients, 3- and 5-year survival ranged from 73.2% to 86%[897,934,941] and from 69.2% to 80.1%,[934] respectively. One-year graft survival rates ranged from 74.2% to 94% in adults[934-936,938] and from 72.1% to 86.1% in pediatric patients.[934,941,942] Graft survival at 3 and 5 years ranged from 58.9% to 75.5% and from 51.6% to 70.5%, respectively, in adults and from 62.5% to 77.6% and from 68.4% to 71.4%, respectively, in pediatric patients.[934,941] No significant differences were noted in graft or patient survival between cadaveric and living-related donors in adult and pediatric liver transplant recipients.[934] Infection remains a major cause of morbidity and mortality in liver transplant recipients. Infections may occur in 31–83% of patients within three months of transplantation and are the cause of death in 4–53% of patients.[934,936,940,943-950] These rates are highly variable and do not seem to have changed despite advances in surgical technique and medical management. SSIs within 30 days after transplantation ranged from 4% to 48% with antimicrobial prophylaxis in several cohort and controlled studies.[935-938,941,942,948,949,951-964] Superficial SSIs are seen most often within the first two to three weeks postoperatively, whereas organ/space

infections and deep infections are seen after three to four weeks.

Liver transplantation is often considered to be the most technically difficult of the solid-organ transplantation procedures. Surgical procedures lasting longer than 8–12 hours have been consistently identified as one of the most important risk factors for early infectious complications, including SSIs, intraabdominal infections, and biliary tract infections.[896,938,939,945,947,957] Other important risk factors for infectious complications related to liver transplantation surgery include previous hepatobiliary surgery,[896,939,945,947,952,963] previous liver or kidney transplantation,[937,951,952,965] and surgical complications such as anastomotic leakage.[896,938,939,945,947,951,952] Patient-related risk factors for infection after liver transplantation include antimicrobial use within three to four months before transplantation,[935,954] low pretransplantation serum albumin concentration,[938,958,963] high pretransplantation serum bilirubin concentration,[939,945,947] ascites,[938] obesity,[963] diabetes, and hemochromatosis.[966] Procedure-related risk factors for infection include transfusion of >4 units of red blood cells,[896,951] bacterial contamination due to entry into the gastrointestinal tract,[963] surgical incision method,[963] and use of muromonab-CD3 within the first week after transplantation.[938]

Organisms. The pathogens most commonly associated with early SSIs and intraabdominal infections are those derived from the normal flora of the intestinal lumen and the skin. Aerobic gram-negative bacilli, including *E. coli*,[935,937,939,940,942,945,947-949,951,967,968] *Klebsiella* species,[933,936,937,939,940,945,947-949,967-969] *Enterobacter* species,[936,939,940,942,945,947,952,959,964,967,968] *Acinetobacter baumannii*,[935-937,942,951] and *Citrobacter* species,[939,940,945,947,952,959,967,968] are common causes of SSIs and intraabdominal infections and account for up to 65% of all bacterial pathogens. Infections due to *P. aeruginosa* may also occur but are much less common in the early postoperative period.[936,937,939,940,942,945,947,948,952,959,969] Enterococci are particularly common pathogens and may be responsible for 20–46% of SSIs and intraabdominal infections.[894,933,935,937,938,940,943,945-947,951,952,955,964,965,969] *S. aureus* (frequently MRSA) and coagulase-negative staphylococci are also common causes of postoperative SSIs.[936-938,940,942,943,945-949,955,957-961,964,965,970,971] *Candida* species commonly cause both early and late postoperative infections.[933,936,937,940,942,943,945-947,949,951,969]

Several studies have noted increasing concern about antimicrobial resistance based on detection of resistant organisms, including *E. coli*,[935,937] *Enterococcus* species,[933,937,964,965] *Enterobacter* species,[964] *Klebsiella* species,[933,937] coagulase-negative staphylococci,[937,964] and *S. aureus*.[937,948,957-961,970] General information on antimicrobial resistance is provided in the Common Principles section of these guidelines. Of specific concern to the transplantation community is the emergence of multidrug-resistant *A. baumannii*,[972] carbapenem-resistant Enterobacteriaceae,[973,974] *K. pneumoniae* carbapenemase-producing organisms,[975] and *C. difficile*.[976-978]

Efficacy. Although there remains a high rate of infection directly related to the liver transplantation procedure, there are few well-controlled studies concerning optimal antimicrobial prophylaxis. In evaluating the efficacy of prophylactic regimens, it is important to differentiate between early infections (occurring within 14–30 days after surgery) and late infections (occurring more than 30 days after surgery). Infections occurring in the early postoperative period are most commonly associated with biliary, vascular, and abdominal surgeries involved in the transplantation procedure itself and are thus most preventable with prophylactic antimicrobial regimens.[939,940,943,945] The frequency of these infections varies from 10% to 55% despite antimicrobial prophylaxis.[939,940,943,945,979] It is difficult to assess the efficacy of prophylactic regimens in reducing the rate of infection, because prophylaxis has been routinely used in light of the complexity of the surgical procedure; therefore, reliable rates of infection in the absence of prophylaxis are not available. No controlled studies have compared prophylaxis with no prophylaxis.

Choice of agent. Antimicrobial prophylaxis should be directed against the pathogens most commonly isolated from early infections (i.e., gram-negative aerobic bacilli, staphylococci, and enterococci). Traditional prophylactic regimens have therefore consisted of a third-generation cephalosporin (usually cefotaxime, because of its antistaphylococcal activity) plus ampicillin.[936,937,943,944,946-948,951,952,954,962,965,967,979] The use of cefoxitin and ampicillin–sulbactam, cefotaxime and ampicillin–sulbactam and gentamicin,[957-959] cefuroxime and metronidazole,[971] ceftriaxone and metronidazole,[980] cefotaxime and metronidazole,[953] ceftriaxone and ampicillin,[949] ceftizoxime alone,[955] cefotaxime and tobramycin,[956] cefoxitin alone,[960,961] cefazolin alone,[951] amoxicillin–clavulanate and gentamicin,[970] amoxicillin–clavulanate alone,[951] glycopeptides and antipseudomonal penicillin,[951] quinolone and amoxicillin–clavulanate or glycopeptide,[951] vancomycin and aztreonam,[951,981] and piperacillin–tazobactam[964,970] has also been reported. Alternative prophylaxis regimens for β-lactam-allergic patients have included cefuroxime and metronidazole,[970] clindamycin and gentamicin or aztreonam,[948,960-962] ciprofloxacin and metronidazole,[970] and vancomycin or ciprofloxacin.[936] Imipenem alone was used in one study for patients with renal failure.[956] The efficacy of these regimens compared

with cefotaxime plus ampicillin is difficult to assess due to different definitions of infection used in the available studies and variability of study design (many single-center cohort studies) in different countries. One prospective nonrandomized study found no difference in the frequency of SSIs in orthotopic liver transplant recipients with cefazolin alone and amoxicillin–clavulanate alone, both given one hour before surgical incision, with a second dose given in cases of significant bleeding or surgery lasting over six hours, as antimicrobial prophylaxis.[935] The study did find a significantly higher rate of *A. baumannii* in the cefazolin group than the amoxicillin–clavulanate group. The routine use of vancomycin as antimicrobial prophylaxis is not recommended because of the risk of developing vancomycin-resistant organisms,[8,950] but vancomycin may be reserved for centers with an MRSA or MRSE cluster.[8,950,957-959] No randomized controlled studies have been conducted to compare the efficacy of other antimicrobial prophylactic regimens in the prevention of early postoperative infections. For patients known to be colonized with MRSA, VRE, or resistant gram-negative pathogens, it is reasonable to consider prophylaxis specifically targeted at these organisms. See the Common Principles section for further discussion.

Postoperative infections with *Candida* species after liver transplantation are common, particularly in the abdomen, and are frequently considered organ/space SSIs. For this reason, the use of antifungal prophylaxis in the perioperative period has become common. Efficacy has been demonstrated for fluconazole,[964-984] lipid complex amphotericin B,[985-987] and caspofungin.[988] Finally, one meta-analysis found a decreased risk of fungal infection and death associated with fungal infection, though not overall mortality, among patients given antifungal prophylaxis.[989] Universal antifungal prophylaxis is probably not necessary, since the risk of invasive candidiasis is low in uncomplicated cases. Instead, prophylaxis is generally reserved for patients with two or more of the following risk factors: need for reoperation, retransplantation, renal failure, choledochojejunostomy, and known colonization with *Candida* species.[15] Risk is also increased with prolonged initial procedure or transfusion of >40 units of cellular blood products, but this cannot be predicted before the procedure.

Selective bowel decontamination to eliminate aerobic gram-negative bacilli and yeast from the bowel before the transplantation procedure has been evaluated in several studies and a meta-analysis.[936,943,949,955,956,967,968,980,990,991] These studies used combinations of nonabsorbable antibacterials (aminoglycosides, polymyxin B or E), antifungals (nystatin, amphotericin B), and other antimicrobials (cefuroxime in suspension) administered orally and applied to the oropharyngeal cavity in combination with systemically administered antimicrobials. Results are conflicting, with no differences in patient outcomes (e.g., infection rates, mortality) or cost and concerns of increasing gram-positive infections with potential resistance in several studies[939,955,956,980,991] and others with positive results.[936,949] Two randomized controlled studies found significantly fewer bacterial infections with early enteral nutrition plus lactobacillus and fibers.[971,980] Based on currently available data, the routine use of selective bowel decontamination or lactic acid bacteria and fibers in patients undergoing liver transplantation is not recommended.

Duration. No studies have assessed the optimal duration of antimicrobial prophylaxis in liver transplantation. Although antimicrobials have been administered in studies for five days[937,944,946,949,957-959] and seven days,[964] the majority of recent studies have limited the duration of prophylaxis to 72 hours,[981] 48 hours,[936,943,945,952,955,956,960,961,967,970,979,980,991] 36 hours,[981] 24 hours,[935,948,962,970] and a single dose,[963] with no apparent differences in early infection rates. A prospective, nonrandomized, controlled study found no difference in bacterial infections within the first three months after liver transplantation in patients receiving cefotaxime and ampicillin as short-term antimicrobial prophylaxis for two to three days, compared with long-term prophylaxis for five to seven days.[954] Of note, 5 of the 11 patients in the long-term prophylaxis group had detectable *C. difficile* toxin B in the feces and developed enteritis. No patients in the short-term group had detectable *C. difficile*. Two recent review articles noted that antimicrobial prophylaxis duration should be less than three days.[896,950]

Pediatric efficacy. There are few data specifically concerning antimicrobial prophylaxis in liver transplantation in pediatric patients. The combination of cefotaxime plus ampicillin has been reportedly used in children undergoing living-related donor liver transplantation; the efficacy of this regimen appeared to be favorable.[946] A small, retrospective, single-center cohort study reported outcomes of children undergoing liver, heart, small bowel, or lung transplantation receiving piperacillin–tazobactam 120–150 mg/kg/day beginning before surgical incision and continuing for 48 hours postoperatively and found favorable results, with a superficial SSI rate of 8% and no deep SSIs.[992]

Recommendations. The recommended agents for patients undergoing liver transplantation are (1) piperacillin–tazobactam and (2) cefotaxime plus ampicillin (Table 2). (Strength of evidence for prophylaxis = B.) For patients who are allergic to β-lactam antimicrobials, clindamycin or vancomycin given in combination with gentamicin,

aztreonam, or a fluoroquinolone is a reasonable alternative. The duration of prophylaxis should be restricted to 24 hours or less. For patients at high risk of *Candida* infection, fluconazole adjusted for renal function may be considered. (Strength of evidence for prophylaxis = B.)

Pancreas and pancreas–kidney transplantation

Background. Pancreas transplantation is an accepted therapeutic intervention for type 1 diabetes mellitus; it is the only therapy that consistently achieves euglycemia without dependence on exogenous insulin.[993-997] Simultaneous pancreas–kidney (SPK) transplantation is an accepted procedure for patients with type 1 diabetes and severe diabetic nephropathy. In 2007, UNOS reported that 469 pancreas transplantations and 862 SPK transplantations were performed in the United States, of which 60 and 4 patients, respectively, were under age 18 years.[998] Pancreas graft 1-year survival rates ranged from 70.2% to 89%, and the 3-year rates ranged from 48% to 85.8%.[998-1002] Patient survival with pancreas transplantation has been reported between 75% and 97% at 1 year and between 54% and 92.5% at 3 years.[998] Allograft survival is higher in recipients of SPK transplantations, with allograft survival rates of 86.1–95.1% at 1 year and 54.2–92.5% at 3 years. Reported patient survival rates in SPK are 91.7–97.6% at 1 year and 84.4–94.1% at 3 years. During pancreas transplantation, surgical complications with portal-hepatic drainage significantly decreased the 1-year and 3-year survival rates to 48% and 44%, respectively, in one cohort study.[999]

Infectious complications are a major source of morbidity and mortality in patients undergoing pancreas or SPK transplantation; the frequency of SSI is 7–50% with antimicrobial prophylaxis.[993-997,1000-1009] The majority of SSIs occurred within the first 30 days to three months after transplantation.[1000-1002,1005,1008,1009] UTIs are also a significant concern during the same time frame, with rates ranging from 10.6% to 49% in pancreas transplant recipients who received antimicrobial prophylaxis, and are much more common in recipients with bladder drainage compared with enteric drainage.[1000-1008]

Pancreas and SPK transplantation patients may be at increased risk of SSIs and other infections because of the combined immunosuppressive effects of diabetes mellitus and the immunosuppressive drugs used to prevent graft rejection.[995,1000] Other factors associated with increased SSI rates include prolonged operating and ischemic times (>4 hours), organ donor age of >55 years, and enteric rather than bladder drainage of pancreatic duct secretions.[895,995,1000] Prolonged organ preservation time (>20 hours) was shown to increase the risk of complications, including duodenal leaks and decreased graft survival in cadaveric pancreas transplant recipients.[1003] Risk factors for UTI are reviewed in the kidney transplant section.

Organisms. A majority of superficial SSIs after pancreas or SPK transplantation are caused by *Staphylococcus* species (both coagulase-positive and coagulase-negative) and gram-negative bacilli (particularly *E. coli* and *Klebsiella* species).[993-997,1000-1002,1004-1006,1009-1011] Deep SSIs also are frequently associated with gram-positive (*Enterococcus* species, *Streptococcus* species, and *Peptostreptococcus* species) and gram-negative organisms (*Enterobacter* species, *Morganella* species, and *B. fragilis*), as well as *Candida* species.[993-997,1000-1002,1004-1006,1009-1011] Although anaerobes are occasionally isolated, the necessity for specific treatment of anaerobes in SSIs after pancreas transplantation remains unclear.

Efficacy. Although no placebo-controlled studies have been conducted, several open-label, noncomparative, single-center studies have suggested that antimicrobial prophylaxis substantially decreases the rate of superficial and deep SSIs after pancreas or SPK transplantation. SSI rates were 7–33% with various prophylactic regimens,[995,1000-1002,1004,1005] compared with 7–50% for historical controls in the absence of prophylaxis.[1009,1010] The reason for the wide disparity in infection rates observed with prophylaxis is not readily apparent but may include variations in SSI definitions, variations in antimicrobial prophylaxis, immunosuppression protocols, and variations in surgical techniques.[999-1002,1005,1007,1008]

Choice of agent. Because of the broad range of potential pathogens, several studies have used multidrug prophylactic regimens, including imipenem–cilastatin plus vancomycin[995]; tobramycin, vancomycin, and fluconazole[1010]; cefotaxime, metronidazole, and vancomycin[1012]; cefotaxime, vancomycin, and fluconazole[1008]; ampicillin and cefotaxime[1007]; and piperacillin–tazobactam and fluconazole.[1006]

HICPAC recommendations for SSI prevention include limiting the use of vancomycin unless there is an MRSA or MRSE cluster or as an alternative for β-lactam-allergic patients, though transplantation procedures were not specifically covered in the guidelines.[8] Limited data are available on the use of vancomycin as antimicrobial prophylaxis in kidney or pancreas transplantation, or both. A small, randomized, active-controlled, single-center study evaluated the impact of vancomycin-containing antimicrobial prophylaxis regimens in kidney and pancreas (alone or SPK) transplant recipients on the frequency of gram-positive infections.[1004] Renal transplantation patients received either vancomycin and ceftriaxone or cefazolin, and pancreas transplantation patients received either vancomycin and gentamicin or cefazolin and gentamicin.

There was no statistically significant difference in the risk of developing gram-positive infections between antimicrobial prophylaxis regimens with and without vancomycin. The study was not powered to detect a difference in efficacy between the antimicrobial regimens. For patients known to be colonized with MRSA, VRE, or resistant gram-negative pathogens, it is reasonable to consider prophylaxis targeted specifically for these organisms. See the Common Principles section for further discussion.

An evaluation of the surgical complications of pancreas transplant recipients with portal-enteric drainage found an intraabdominal infection rate of 12% in the 65 patients undergoing SPK transplantation and no cases in those undergoing pancreas transplantation alone.[999] All patients received either cefazolin 1 g i.v. every eight hours for one to three days, or vancomycin if the patient had a β-lactam allergy.

One study evaluated SSI rates in SPK transplantation after single-agent, single-dose prophylaxis with cefazolin 1 g i.v. to donors and recipients, as well as cefazolin 1-g/L bladder and intraabdominal irrigation in the recipient.[1009] Superficial SSIs developed in 2 patients (5%), and deep SSIs associated with bladder anastomotic leaks or transplant pancreatitis occurred in 4 additional patients (11%). This study reported similar SSI rates as with multidrug, multidose regimens.

Based on the regularity of isolation of *Candida* species from SSIs after pancreas transplantation and the frequent colonization of the duodenum with yeast, fluconazole is commonly added to prophylactic regimens. Although never studied in a randomized trial, a lower fungal infection rate was found in one large case series with the use of fluconazole (6%) compared with no prophylaxis (10%).[1013] Although enteric drainage of the pancreas has been identified as a risk factor for postoperative fungal infections, many institutions use fluconazole for prophylaxis with bladder-drained organs as well. In settings with a high prevalence of non-*albicans Candida* species, a lipid-based formulation of amphotericin B has been recommended in infectious diseases guidelines from the American Society of Transplantation and the American Society of Transplant Surgeons.[15]

Duration. Studies evaluating the use of antimicrobial prophylaxis regimens in pancreas and SPK transplantation, summarized above, ranged from a single preoperative dose of cefazolin to multidrug regimens of 2–5 days' duration.[995,1005,1009,1010,1012] More recent studies reported monotherapy regimens with cefazolin or vancomycin,[999] amoxicillin–clavulanate,[1001,1002] and piperacillin–tazobactam[1000-1002] 1–7 days in duration, with the majority using the regimen 48–72 hours after transplantation. The duration of fluconazole ranged from 7 to 28 days.[1002]

Recommendations. The recommended regimen for patients undergoing pancreas or SPK transplantation is cefazolin (Table 2). (Strength of evidence for prophylaxis = A.) For patients who are allergic to β-lactam antimicrobials, clindamycin or vancomycin given in combination with gentamicin, aztreonam, or a fluoroquinolone is a reasonable alternative. The duration of prophylaxis should be restricted to 24 hours or less. The use of aminoglycosides in combination with other nephrotoxic drugs may result in renal dysfunction and should be avoided unless alternatives are contraindicated. (Strength of evidence for prophylaxis = C.) For patients at high risk of *Candida* infection, fluconazole adjusted for renal function may be considered.

Kidney transplantation

Background. In 2007, UNOS reported that 16,628 kidney transplantations were performed in the United States; of these, 796 patients were younger than 18 years.[998] The rate of postoperative infection after this procedure has been reported to range from 10% to 56%, with the two most common infections being UTIs and SSIs.[1004,1014-1024] Graft loss due to infection occurs in up to 33% of cases.[1017,1023] One study of adult and pediatric kidney transplant recipients (both living-related and cadaveric donor sources) found patient survival rates at 7 years after transplantation of 88.9% and 75.5%, respectively, and graft survival of 75% and 55.5%, respectively.[1025] No patients developed an SSI. Mortality associated with postoperative infections is substantial and ranges from approximately 5% to 30%.[1015,1017,1019,1022,1026,1027]

The frequency of SSIs in kidney transplant recipients has ranged from 0% to 11% with antimicrobial prophylaxis[1023-1025,1028,1029] to 2% to 7.5% without systemic prophylaxis.[1030,1031] The majority of these infections were superficial in nature and were detected within 30 days after transplantation.[1023,1028-1030] Risk factors for SSI after kidney transplantation include contamination of organ perfusate[1027]; pretransplantation patient-specific factors, such as diabetes,[1029,1030] chronic glomerulonephritis,[1030] and obesity[1027,1030,1032]; procedure-related factors, such as ureteral leakage and hematoma formation[1027]; immunosuppressive therapy[1024,1027,1029]; and postoperative complications, such as acute graft rejection, reoperation, and delayed graft function.[1030] In one study, the frequency of SSI was 12% in patients receiving immunosuppression with azathioprine plus prednisone but only 1.7% in patients receiving cyclosporine plus prednisone.[1033] A significant difference in SSI rates was noted after kidney transplantation between immunosuppression regimens including mycophenolate mofetil (45 [3.9%] of 1150 patients) versus sirolimus (11 [7.4%] of 144

patients).[1029] Sirolimus-containing immunosuppression was found to be an independent risk factor for SSIs. These recommendations refer to kidney transplant recipients; recommendations for living kidney donors can be found in the discussion of nephrectomy in the urologic section.

Organisms. Postoperative SSIs in kidney transplant recipients are caused by gram-positive organisms, particularly *Staphylococcus* species (including *S. aureus* and *S. epidermidis*) and *Enterococcus* species, gram-negative organisms, *E. coli*, *Enterobacter* species, *Klebsiella* species, *P. aeruginosa*, and yeast with *Candida* species.[1004,1014-1021,1023,1024,1026,1028,1030,1034] One study site in Brazil reported a high level of antimicrobial resistance.[1030] Organisms recovered from infections included MRSA (77%), methicillin-resistant coagulase-negative *Staphylococcus* (53.5%), extended-spectrum β-lactamase-producing *K. pneumoniae* (80%), and carbapenem-resistant *P. aeruginosa* (33.3%). Another center in Brazil reported a significant difference in resistance to broad-spectrum antimicrobials in pathogens isolated in UTIs from cadaveric kidney transplant recipients (n = 21, 19.1%) compared with living-related donor kidney transplant recipients (n = 2, 3.7%) (p = 0.008).[1024] One center in the United States reported 94% susceptibility to vancomycin of *Enterococcus* species within the first month after transplantation, while *E. coli,* cultured most commonly more than six months after transplantation, was 63% resistant to sulfamethoxazole–trimethoprim.[1023] This resistance may be related to the routine use of sulfamethoxazole–trimethoprim in prophylaxis of *Pneumocystis carinii* pneumonia and UTI.

Efficacy. A number of studies have clearly demonstrated that antimicrobial prophylaxis significantly decreases postoperative infection rates in patients undergoing kidney transplantation. These have included at least one randomized controlled trial[1014] and many prospective and retrospective studies comparing infection rates with prophylaxis and historical infection rates at specific transplantation centers.[1015-1018,1021,1033-1035] Based on the available literature, the routine use of systemic antimicrobial prophylaxis is justified in patients undergoing kidney transplantation.

Two studies that evaluated a triple-drug regimen consisting of an aminoglycoside, an antistaphylococcal penicillin, and ampicillin found infection rates of <2%, compared with 10–25% with no antimicrobial prophylaxis.[1018,1019] More specifically, infection rates in patients without antimicrobial prophylaxis (45 cadaveric and 44 living-related donors) were 10.1% in total (8.9% and 11.4%, respectively), compared with 1.5% in total (1.5% and 0%, respectively) with antimicrobial prophylaxis.[1018] Infection rates were as high as 33% in living-related patients with no antimicrobial prophylaxis and 0–1% in both cadaveric and living-related transplant recipients with antimicrobial prophylaxis.[1021] Piperacillin plus cefuroxime was also shown to be efficacious; infection rates were 3.7%, compared with 19% in cadaveric transplant recipients not receiving prophylaxis.[1018] Several studies have shown that single-agent prophylaxis with an antistaphylococcal penicillin,[1029,1034] a first-generation cephalosporin,[1016,1017,1023,1024,1029] a second-generation cephalosporin,[1028,1035,1036] or a third-generation cephalosporin (e.g., cefoperazone, cefotaxime, ceftriaxone)[1024,1029,1033,1037] can reduce postoperative infection rates to 0–8.4%. All studies included cadaveric transplant recipients, whereas living-related transplant recipients were also included in select studies.[1017,1024,1028,1036] Where compared directly, infection rates between cadaveric and living-related transplant recipients receiving antimicrobial prophylaxis were not statistically different.[1024]

Choice of agent. The available data do not indicate a significant difference between single-drug and multidrug antimicrobial regimens.[1014,1018,1021] In addition, there appears to be no significant differences between single-agent regimens employing antistaphylococcal penicillins and first-, second-, or third-generation cephalosporins.[1016,1017,1033-1035,1037] Studies have directly compared antimicrobial regimens in a prospective, controlled fashion. Single-agent prophylaxis with both cefazolin and ceftriaxone has been reported to result in SSI rates of 0%.[1016,1024,1037]

A survey of 101 kidney transplant centers in 39 countries reported that 65% of the centers used single antimicrobial prophylaxis regimens, 20.8% used two-drug regimens, and 3% used three drugs; no prophylaxis was used in 11% of centers.[1036] Cephalosporins were used in 68 centers (55 alone, 7 in combination with penicillin, and 6 with other antimicrobials). Penicillins were used by 28 centers (13 alone, 7 with cephalosporin, and 8 with other antimicrobials). Other antimicrobials (specifics were not reported) were used in 2 centers as the single agent.

As noted above, HICPAC recommendations for SSI prevention include limiting the use of vancomycin to situations in which there is an MRSA or MRSE cluster or as an alternative for β-lactam-allergic patients.[8] Transplantation procedures were not specifically covered in the guidelines.

Duration. Studies have used various prophylactic regimens, ranging from a single-drug cephalosporin regimen, administered as a single preoperative dose or for up to 24 hours postoperatively, to multidrug regimens of two to five days' duration.[981,1004,1014-1018,1021,1023,1024,1028,1029,1033,1036,1038] Cefazolin for 24 hours was equivalent to seven days of surgi-

cal prophylaxis in living-related kidney transplant donors.[1039] There appear to be no significant differences in SSI rates between single-dose, 24-hour, and multidose regimens; therefore, the duration of antimicrobial should be restricted to 24 hours.

Pediatric efficacy. Although pediatric patients were included in studies demonstrating the efficacy of antimicrobial prophylaxis, there are few data specific to pediatric patients.

One cohort of 96 pediatric patients who underwent 104 renal transplants (63% cadaveric and 37% living-related donors) ranged in age from six months to 18 years (mean age, 8.2 ± 5.5 years).[1040] Antimicrobial prophylaxis included one dose of cefotaxime 30-mg/kg i.v. bolus at the start of the procedure and cefotaxime 90 mg/kg/day in three divided doses during the intensive care unit stay, which averaged one to two days. No SSIs were reported.

Recommendations. The recommended agent for patients undergoing kidney transplantation is cefazolin (Table 2). (Strength of evidence for prophylaxis = A.) For patients who are allergic to β-lactam antimicrobials, clindamycin or vancomycin given in combination with gentamicin, aztreonam, or a fluoroquinolone is a reasonable alternative. The duration of prophylaxis should be restricted to 24 hours or less. The use of aminoglycosides in combination with other nephrotoxic drugs may result in renal dysfunction and should be avoided unless alternatives are contraindicated. (Strength of evidence for prophylaxis = C.) For patients at high risk of *Candida* infection, fluconazole adjusted for renal function may be considered.

Plastic surgery and breast procedures

Background. Plastic surgery encompasses a broad range of procedures focused on reconstructive, dermatological, and cosmetic procedures.[1041] The primary goal of these procedures is to restore function to the affected area, with a secondary goal of improving appearance. The scope of procedures ranges from simple primary surgical-site closure, skin grafts, and skin flaps to composite tissue transplantations. Composite tissue transplantation for tissue reconstruction of the knee joint, larynx, uterus, abdominal wall, hand, face, and penis has been performed in a small number of patients.[1042,1043]

Most dermatological, breast (reduction and reconstructive), clean head and neck, and facial procedures have an associated SSI rate of <5%.[1044-1053] Oral procedures, such as wedge excision of lip or ear, flaps on the nose,[1046,1054] and head and neck flaps, have SSI rates of approximately 5–10%.[1053,1055-1060] In addition to general risk factors as described in the Common Principles section, factors that increase the risk of postoperative infectious complications for plastic surgery procedures include implants,[1061] skin irradiation before the procedure, and procedures below the waist.[1062,1063]

Organisms. The most common organisms in SSIs after plastic surgery procedures are *S. aureus*,[1045,1049,1050,1053,1054,1056,1063-1068] other staphylococci, and streptococci.[1045,1054,1064,1066,1067] Procedures involving macerated, moist environments (e.g., under a panus or axilla of an obese individual), below the waist, or in patients with diabetes are associated with a higher rate of infection with gram-negative organisms such as *P. aeruginosa*,[1068] *Serratia marcescens*, or Enterobacteriaceae, including *E. coli*,[1065,1068] *Klebsiella* species,[1068] and *P. mirabilis*.[1065]

Efficacy. The efficacy of antimicrobial prophylaxis in select plastic surgery procedures has been investigated in several clinical trials and cohort studies.

Most placebo-controlled and retrospective studies for many clean plastic surgery procedures have found that antimicrobial prophylaxis does not significantly decrease the risk of infection. These studies have evaluated head and neck procedures (facial bone fracture, tumor excision and reconstruction, radical neck dissection, rhinoplasty),[1049] flexor tendon injury repairs,[1051] augmentation mammoplasty using periareolar submuscular technique,[1052] carpal tunnel,[1069] and breast procedures (reduction mammoplasty, lumpectomy, mastectomy, axillary node dissection).[1056,1058,1070,1071]

However, a Cochrane review of seven randomized, placebo-controlled trials of 1984 patients undergoing breast cancer procedures (axillary lymph node dissection and primary nonreconstructive surgery) evaluated the effectiveness of preoperative or perioperative antimicrobial prophylaxis (n = 995) compared with placebo or no treatment (n = 989) in reducing the rate of postoperative infections.[1072] Pooled study results revealed a significant difference in SSI rates with antimicrobial prophylaxis (80 [8%] of 995), compared with 10.5% (104 of 989) for no antimicrobial prophylaxis (relative risk, 0.72; 95% CI, 0.53–0.97). Review authors concluded that antimicrobial prophylaxis is warranted to decrease the risk of SSIs in nonreconstructive breast cancer procedures.

Guidelines also support no antimicrobial prophylaxis in patients undergoing clean facial or nasal procedures without an implant.[7] For patients undergoing facial or nasal procedures with an implant, antimicrobial prophylaxis should be considered.[7]

A randomized, double-blind, controlled trial of 207 patients evaluated the use of three antimicrobial prophylaxis regimens in patients undergoing abdominoplasty procedures.[1066] The reported SSI rates were 13% for patients receiving no antimicrobial prophylaxis, 4.3% for those receiving preoperative antimicrobials only, and 8.7% for those receiving

one preoperative dose and three days of postoperative antimicrobials. There was a significantly lower infection rate in the group receiving preoperative antimicrobials only compared with the placebo group ($p < 0.05$). The infection rate was slightly but not significantly higher in patients who received postoperative antimicrobials.

Choice of agent. There is no consensus on the appropriate antimicrobial agent to use for prophylaxis in plastic surgery procedures.[1055,1073] Agents with good gram-positive coverage and, depending on the site of surgery, activity against common gram-negative organisms are recommended for patients undergoing clean plastic surgery procedures with risk factors (listed in the Common Principles section and the background discussion of this section) or clean-contaminated procedures. Cefazolin or ampicillin–sulbactam is sufficient in most cases, with clindamycin and vancomycin as alternatives for patients with β-lactam allergy. There are no studies assessing the impact of MRSA on patients undergoing plastic surgery procedures or regarding the need to alter prophylaxis regimens in patients without known colonization with MRSA. When vancomycin or clindamycin is used and if a gram-negative organism is highly suspected, practitioners should consider adding cefazolin if the patient is not β-lactam allergic; if the patient is β-lactam allergic, the addition of aztreonam, gentamicin, or single-dose fluoroquinolone should be considered. If the surgical site involves the ear, an antipseudomonal fluoroquinolone may be considered to cover *Pseudomonas* species.[1045]

Although oral agents such as cephalexin, amoxicillin, clindamycin, and azithromycin have been recommended in reviews of antimicrobial prophylaxis in clean dermatological surgery, there is no evidence that supports their use.[13,1045,1046,1054]

Duration. Antimicrobial prophylaxis should be limited to the shortest duration possible to prevent SSIs (even if a drain or a catheter is left in place or an implant is inserted), limit adverse events, and prevent antimicrobial resistance.[8,512,1047,1048,1054,1056]

Multiple studies have found no significant differences in SSI rates after breast surgery with single-dose preoperative cephalosporin compared with extended-duration regimens that last from one to five days postoperatively.[1048,1054,1056]

A randomized, single-blind, controlled trial of 74 patients undergoing surgical ablation of head and neck malignancies with immediate free-flap reconstruction found no significant differences in SSI rate between clindamycin 900 mg i.v. every eight hours for 3 doses compared with 15 doses.[1057] Both groups were given clindamycin 900 mg i.v. immediately preoperatively, in addition to the postoperative regimens.

In a controlled study, 200 patients undergoing septorhinoplasty were randomized to a single preoperative dose of amoxicillin–clavulanate 2.2 g i.v. administered 30 minutes before surgical incision only ($n = 100$) or in combination with postoperative oral amoxicillin–clavulanate 1000 mg twice daily for seven days.[533] There was no significant difference in infection rates between the group receiving only a preoperative dose (0%) and the combination group (3%). There was a higher rate of adverse events (nausea, diarrhea, skin rash, and pruritus) among the combination group compared with the group receiving only a preoperative dose ($p = 0.03$). The study authors recommended the use of a single preoperative i.v. dose of amoxicillin–clavulanate for endonasal septorhinoplasty.

Pediatric efficacy. Limited data on antimicrobial prophylaxis are available for pediatric patients undergoing plastic surgery procedures. There is no consensus among surgeons regarding the use of antimicrobial prophylaxis in the repair of cleft lip and palate.[1074] The occurrence of postoperative infections after these procedures is 1.3%.[1075] No controlled trials have evaluated the use of antimicrobial prophylaxis in these procedures.

Recommendations. Antimicrobial prophylaxis is not recommended for most clean procedures in patients without additional postoperative infection risk factors as listed in the Common Principles section of these guidelines and the background discussion of this section. Although no studies have demonstrated antimicrobial efficacy in these procedures, expert opinion recommends that patients with risk factors undergoing clean plastic procedures receive antimicrobial prophylaxis. The recommendation for clean-contaminated procedures, breast cancer procedures, and clean procedures with other risk factors is a single dose of cefazolin or ampicillin–sulbactam (Table 2). (Strength of evidence for prophylaxis = C.) Alternative agents for patients with β-lactam allergy include clindamycin and vancomycin. If there are surveillance data showing that gram-negative organisms cause SSIs for the procedure, the practitioner may consider combining clindamycin or vancomycin with another agent (cefazolin if the patient is not β-lactam allergic; aztreonam, gentamicin, or single-dose fluoroquinolone if the patient is β-lactam allergic). Postoperative duration of antimicrobial prophylaxis should be limited to less than 24 hours, regardless of the presence of indwelling catheters or drains.

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Appendix A—National Healthcare Safety Network criteria for classifying wounds[35]

Clean: An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tracts are not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow nonpenetrating (blunt) trauma should be included in this category if they meet the criteria.

Clean-contaminated: Operative wounds in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered.

Contaminated: Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract and incisions in which acute, nonpurulent inflammation is encountered are included in this category.

Dirty or infected: Includes old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.

Appendix B—National Healthcare Safety Network criteria for defining a surgical-site infection (SSI)[8,36]

Superficial incisional SSI: Occurs within 30 days postoperatively and involves skin or subcutaneous tissue of the incision and at least one of the following: (1) purulent drainage from the superficial incision, (2) organisms isolated from

an aseptically obtained culture of fluid or tissue from the superficial incision, (3) at least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon and is culture-positive or not cultured (a culture-negative finding does not meet this criterion), and (4) diagnosis of superficial incisional SSI by the surgeon or attending physician.

Deep incisional SSI: Occurs within 30 days after the operative procedure if no implant is left in place or within one year if implant is in place and the infection appears to be related to the operative procedure, involves deep soft tissues (e.g., fascial and muscle layers) of the incision, and the patient has at least one of the following: (1) purulent drainage from the deep incision but not from the organ/space component of the surgical site, (2) a deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture-positive or not cultured and the patient has at least one of the following signs or symptoms: fever (>38 °C) or localized pain or tenderness (a culture-negative finding does not meet this criterion), (3) an abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination, and (4) diagnosis of a deep incisional SSI by a surgeon or attending physician.

Organ/space SSI: Involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure. Specific sites are assigned to organ/space SSI to further identify the location of the infection (e.g., endocarditis, endometritis, mediastinitis, vaginal cuff, and osteomyelitis). Organ/space SSI must meet the following criteria: (1) infection occurs within 30 days after the operative procedure if no implant is in place or within 1 year if implant is in place and the infection appears to be related to the operative procedure, (2) infection involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure, and (3) the patient has at least one of the following: (a) purulent drainage from a drain that is placed through a stab wound into the organ/space, (b) organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space, (c) an abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination, and (d) diagnosis of an organ/space SSI by a surgeon or attending physician.