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Preventing Antimicrobial-Resistant Bacterial Infections in Surgical Patients

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ABSTRACT

Background: **The Centers for Disease Control and Prevention (CDC) has identified the control of antimicrobial resistance as an important effort to reduce the morbidity and mortality associated with health care. Methods to prevent these infections in surgical patients have rarely been addressed specifically.**

Methods: **The peer-reviewed literature and published guidelines were examined to identify proven or suggested techniques for controlling antimicrobial resistance that would be particularly relevant to surgeons and the surgical patient population.**

Results: **A multi-step approach to the prevention of antimicrobial-resistant infections in surgical patients was developed. This program consists of four major strategies: Infection prevention, effective diagnosis and treatment of infection, optimal antibiotic utilization, and the prevention of transmission.**

Conclusion: **The control of antimicrobial resistance in bacteria is an important objective for all physicians, including surgeons. An approach to attain this goal in surgical populations is outlined. Further research will be needed to determine the value of these practices and to develop newer, even more effective interventions.**

ANTIMICROBIAL RESISTANCE is a serious problem that many physicians must contend with on a daily basis. Antimicrobial resistance has been associated with increased morbidity, mortality, and cost of care [1–5]. The Centers for Disease Control and Prevention (CDC) estimates that treatment of infections with antimicrobial-resistant organisms costs over $4 billion annually [6]. In surgical patients, infections caused by antimicrobial-resistant gram-positive cocci result in significantly higher mortality and length of hospital stay in patients as compared to infections with antimicrobial-susceptible strains [4]. Furthermore, infections caused by resistant pathogens may result in increased rates of treatment failure [7,8].

This document synthesizes a program to combat antimicrobial resistance in surgical patients by using a multi-step approach consisting of four major strategies: (1) Infection pre-

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vention through active surveillance, reporting, and intervention to improve device and vaccine use; (2) prompt diagnosis and effective treatment of infection; (3) judicious antimicrobial use, including appropriate selection, dosing, and duration of therapy; and (4) an effective infection control program to prevent primary infection (i.e., source control) as well as secondary transmission [5,9]. In addition to adherence to recommendations, participation of surgeons in policy formation is critical, so that issues pertaining specifically to the care of surgical patients are considered when antimicrobial resistance prevention programs are developed.

TABLE 1. GUIDELINES FOR CENTRAL VENOUS CATHETER (CVC) MANAGEMENT [97]

Use CVCs judiciously and remove them as soon as clinically permissible.
Use single-lumen catheters when possible.
Subclavian insertion sites are preferable to jugular or femoral sites.
Maintain sterile technique when inserting catheter including appropriate skin preparation, mask, and sterile gown, gloves and drape.
Inspect insertion site daily for evidence of infection and change dressing if soiled, damp, or loosened.
Routine catheter exchange is not indicated.
Guidewire exchange is contraindicated if CVC infection is documented.
Replace IV tubing and stopcocks no more frequently than 72 hour intervals.
Conduct active surveillance programs to identify trends in CVC infections.

PREVENT INFECTION

Key principles of preventing infection are as follows:

- Minimize use of invasive devices
- Vaccinate at-risk surgical patients and staff

Infection prevention includes the conservative use of medical devices that compromise the body's normal defense mechanisms. A recent survey of nosocomial (i.e., healthcare-associated) infections in the United States revealed that 87% of bloodstream infections (BSI) were associated with central venous catheters (CVCs), 86% of pneumonias were associated with mechanical ventilation, and 95% of urinary tract infections (UTIs) were associated with urinary catheters [10].

Central venous catheter use is an independent risk factor for the development of healthcare-associated infection [11]. Infection is the most common complication of CVCs. Central venous catheter–related bacteremia is associated with increased morbidity, mortality, hospital length of stay, and cost [12–14]. Prevention of these infections requires strict observance of sterile technique during CVC insertion (including proper cutaneous antisepsis and proper gowning and draping), fastidious catheter care, and prompt removal when the catheter is no longer essential. Guidelines for CVC management are listed in Table 1. Although antimicrobial/antiseptic-impregnated catheters may decrease the rate of catheter colonization and catheter related BSI [15–18], their proper clinical use and overall risks and benefits are yet to be determined. The promotion of antimicrobial resistance due to low-level antimicrobial exposure with antimicrobial-impregnated catheters, for instance, remains a concern.

Thirty to forty percent of all healthcare-associated infections are attributable to the urinary tract [10,19]. Indwelling bladder catheter use is the single most important risk factor for the development of a UTI [19] and has also been identified as an independent predictor of UTI with antimicrobial-resistant organisms [20]. Prompt removal of all catheters is of paramount importance, since the risk of bacteriuria increases 5% for each day of catheter use [21]. Guidelines for the prevention of catheter-associated UTIs are listed in Table 2. As with CVCs, the clinical utility of antimicrobial/antiseptic-

TABLE 2. GUIDELINES FOR PREVENTION OF CATHETER-ASSOCIATED URINARY TRACT INFECTIONS [98]

Educate personnel in correct techniques of catheter insertion and care, including emphasis on hand hygiene.
Use catheters only when absolutely necessary.
Insert catheter and obtain samples using aseptic technique.
Secure catheter properly.
Maintain closed sterile drainage and unobstructed urine flow.

impregnated urinary catheters is yet to be established [22–26].

Pneumonia is the most common life-threatening infectious complication in surgical patients in the United States [27]. In intensive care unit (ICU) patients, mortality rates for healthcare-associated pneumonia range from 30–70%. It is estimated that as many as 15% of all in-hospital deaths are related to healthcare-associated pneumonia [28,29]. Prevention strategies target aerodigestive tract colonization, aspiration, and the interruption of normal pulmonary defense mechanisms by an endotracheal tube (Table 3).

An additional important means of preventing infections in the surgical patient involves vaccinating all at-risk individuals, including patients and hospital staff. For example, administration of vaccines for *Streptococcus pneumoniae, Hemophilus influenzae,* and *Neisseria meningitidis* is indicated for patients undergoing splenectomy (preoperatively if the procedure is elective, or postoperatively if emergent) in order to reduce the risk of overwhelming sepsis after splenectomy [30]. Application of this simple preventive step has not been uniform; in a recent single-center retrospective study, only 74% of patients undergoing splenectomy were vaccinated [31]. Additionally, staff should receive hepatitis B vaccine to prevent primary infection and transmission to patients, and influenza vaccine annually to prevent primary infection and transmission to patients and other personnel [32]. Finally, surgeons should identify patients who might benefit from recommended vaccinations not directly related to surgical illness, for example, administration of influenza and pneumococcal vaccine to patients over 65 or who are chronically ill [33]. Vaccination of these individuals before elective surgical admission or hospital discharge would most likely be beneficial.

TABLE 3. GUIDELINES FOR PREVENTION OF HEALTHCARE-ASSOCIATED PNEUMONIA [99]

Educate key personnel regarding healthcare-associated pneumonia.
Conduct healthcare-associated pneumonia surveillance to identify trends and potential problems.
Use sterile fluids for nebulization and dispense aseptically.
Wear gloves and wash hands before and after contact with mucous membranes, respiratory secretions, and respiratory devices.
Elevate head of bed to 30–45° for mechanically ventilated patients at risk for aspiration, if possible.
Periodically drain condensate collecting in ventilator tubing.
Potential beneficial techniques requiring further study:
Continuous subglottic suctioning
Oropharyngeal decontamination
Selective gut decontamination

DIAGNOSE AND TREAT INFECTION EFFECTIVELY

Key principles of diagnosing and treating infection effectively are as follows:

- Target likely pathogens and use microbiologic data to tailor antimicrobial therapy
- Access the experts. Identify a local infectious disease authority for guidance with difficult issues. Provide surgical representation on key committees.

The absolute necessity for adequate surgical intervention for source control of infection cannot be overemphasized. This includes removal of invasive devices or prosthetic material if infection is suspected, drainage of abscesses, and aggressive debridement of devitalized tissue [34]. In conjunction with these mechanical interventions, antimicrobial therapy should initially be limited to likely pathogens and subsequently adjusted based on culture results.

Surgeons most often choose antimicrobials for empiric treatment based on the site of infection. Knowledge of the most common organisms associated with each clinical syndrome, the hospital- and ward-specific antibiograms, and location of acquisition of the infection (community or hospital) is vital to that decision-making process. Table 4 lists organisms that should be considered when prescribing empiric antimicrobials.

Culture and susceptibility data are vital to the appropriate diagnosis and treatment of infections commonly encountered by surgeons, including BSI, CVC or other intravascular device infections, healthcare-associated pneumonia, healthcare-associated UTI, and deep-space abscesses. Diagnosis through acquisition of appropriate clinical samples for pneumonia is

TABLE 4. COMMON ORGANISMS BY SITE OF INFECTION AND POTENTIAL EMPIRIC ANTIBACTERIAL THERAPIES

	Community acquired	*Empiric therapy**	*Hospital acquired*	*Empiric therapy**
Pneumonia	*Streptococcus pneumoniae* *Hemophilus influenzae* *Moraxella catarrhalis* *Mycoplasma pneumoniae* *Chlamydia pneumoniae* *Legionella* spp.	• Macrolide • FQ	Non-ventilated Gram-negative rods (50–70%) *Pseudomonas aeruginosa, Escherichia coli, Klebsiella* spp., *Enterobacter* spp., *Acinetobacter* spp. Gram-positive cocci (20–40%) *Staphylococcus aureus, Streptococcal* spp Anaerobes (aspiration only) Ventilated or in ICU >2 days Must consider ICU-acquired organisms. (e.g. *Stenotrophomonas maltophilia*, MRSA†, *Enterococcus* spp.)	• 3rdCeph AP or AP Pen + APAG • 4thCeph • FQ • Antianaerobe for aspiration • Piperacillin/tazobactam • Carbapenem • APAG or 4thCeph or FQ plus enterococcal coverage§ (Consider double coverage for critically ill patients.)
Urinary tract infection (UTI)	Enterobacteriaceae (*E. coli*) *Staphylococcus saprophyticus* *Enterococcus* spp.	• Trimethoprim/sulfamethoxazole • FQ	Short-term catheterization—monomicrobial *Escherichia coli, Klebsiella* spp., *Proteus* spp., *Enterococcus* spp., *Pseudomonas aeruginosa, Enterobacter* spp., coagulase-negative staphylococci, *Serratia* spp., fungi Long-term catheterization—polymicrobial Must consider antimicrobial resistant species (e.g., VRE‡, MRSA†, resistant GNR)	• FQ • Aminoglycoside (Add enterococcal coverage if critically ill.) • Piperacillin/tazobactam • Carbapenem • APAG or 4thCeph or FQ plus enterococcal coverage§
Peritonitis	Enterobacteriaceae (*E. coli*), *Bacteroides fragilis, Enterococcus* spp.	• Cephamycin ("2ndCeph") • Ampicillin/sulbactam • FQ or aminoglycoside plus antianaerobe	Tertiary or hospital-acquired secondary peritonitis Enterobacteriaceae (*E. coli*), *Bacteroides fragilis, Enterococcus* spp., *Pseudomonas* spp., *Enterobacter* spp., *Staphylococcus epidermidis* and fungi—consider antimicrobial resistant organism.	• Piperacillin/tazobactam • Carbapenem • APAG or 4thCeph or FQ plus enterococcal and antianaerobe coverage§

*Knowledge of hospital/unit antibiogram is vital for appropriate empiric therapy.
†Methicillin-resistant *S. aureus*.
‡Vancomycin-resistant enterococci.
§Consider vancomycin if high prevalence of MRSA.
2ndCeph, cephamycin or "second generation" cephalosporin (e.g., cefoxitin, cefotetan); 3rdCeph AP, antipseudomonal third generation cephalosporin (e.g., ceftazidime); 4thCeph, 4thgeneration cephalosporin (e.g., cefepime); FQ, fluoroquinolone (e.g., ciprofloxacin, levofloxacin); APAG, antipseudomonal aminoglycoside (e.g., gentamicin, tobramycin), macrolide (e.g., azithromycin, clarithromycin).

highly controversial [28,35–38]. Additional controversy surrounds the utility of intraoperative peritoneal cultures. The routine use of intra-abdominal cultures for the treatment of community-acquired, secondary peritonitis is probably not justified [39–43]. Patients who might benefit from intraperitoneal cultures are those at high risk for fungal infection or antimicrobial-resistant infection. This group includes patients with recent hospitalization or residence in a nursing home/chronic care facility, recurrent gastrointestinal (GI) perforation or anastomotic leak, chronic alkalinization of the upper GI tract, tertiary peritonitis, ICU stay >2 days prior to infection, significant exposure to antimicrobials in the previous 6–12 months, and known colonization with resistant organisms.

Since most surgeons cannot remain current on every single infectious disease issue, the identification of a medical or surgical colleague who is an expert in this area may be helpful. In addition, it is beneficial for a hospital surgical group to identify an interested member who can act as a representative and participate in committees that determine hospital formularies, guidelines, and other matters related to healthcare epidemiology and infection control. Using appropriate expertise, evidence-based standardization of clinical practice and surveillance of infection trends within an institution are advocated.

OPTIMIZE ANTIMICROBIAL USE

Key principles of optimizing antimicrobial use are as follows:

- Practice thoughtful antimicrobial control
- Use local data. Use knowledge of common pathogens and the hospital antibiogram to guide empiric therapy.
- Use broad-spectrum antibiotics, for example, vancomycin, only when necessary
- Limit treatment of contamination, including surgical prophylaxis. Use perioperative antimicrobial prophylaxis appropriately when indicated.
- Treat infection aggressively, but not colonization. If cultures are negative, consider non-infectious causes of an inflammatory response and stop empiric antimicrobial therapy.
- Stop antimicrobial treatment when the infection is cured.

Of paramount importance in the fight against the emergence of resistant organisms is judicious antimicrobial use. Antimicrobial control may involve the education of physicians regarding the appropriate selection, dosing, and duration of prophylaxis and therapy as well as restriction or rotation policies to reduce the misuse of antimicrobials [5,44–51]. Surgeons should participate actively in the formulation and enforcement of these policies since antimicrobial resistance varies among patient populations within an institution [52,53].

For the individual surgeon, knowledge of the hospital and unit-specific antibiograms, if available, is vital for appropriate empiric antimicrobial use. Hospital antibiograms and local surgical or medical infectious disease experts can help guide the clinician further in therapeutic decision-making. Following the receipt of patient-specific microbiologic data, susceptibility data should be used to narrow the spectrum of coverage to limit exposure to broad-spectrum agents prescribed empirically that may promote resistance with long-term exposure. Almost all broad-spectrum antimicrobials have been linked to the development of resistant pathogens, for example, association of vancomycin use with vancomycin-resistant *Enterococcus faecium* infections [54]. Equally important is the appropriate interpretation of microbiologic data through avoidance of treating contaminants or colonization as true pathogens. Examples of this include skin contaminants of blood, catheter tip, or open wound cultures, or nasopharyngeal contamination of sputum culture.

Perioperative antimicrobial prophylaxis reduces the probability of infection after contamination of the surgical site [55]. The ideal prophylactic agent is effective against microorganisms at the surgical site and is present at appropriate concentrations during the critical interval, most commonly defined as the first three hours after incision or other time of contamination [56,57]. Prophylactic antimicro-

TABLE 5. NATIONAL RESEARCH COUNCIL WOUND CLASSIFICATION CRITERIA [59]

Classification	*Infection rate*	*Criteria*
Clean	<2%	Elective (not urgent or emergency), primarily closed; no acute inflammation or transection of gastrointestinal, oropharyngeal, genitourinary, biliary, or tracheobronchial tracts; no technique break.
Clean contaminated	<10%	Urgent or emergency case that is otherwise clean; elective, controlled opening of gastrointestinal, oropharyngeal, biliary or tracheobronchial tracts, minimal spillage and/or minor technique break; reoperation via clean incision within 7 days; blunt trauma, intact skin, negative exploration.
Contaminated	20%	Acute, nonpurulent inflammation; major technique break or major spill from hollow organ; penetrating trauma <4 h; chronic open wounds to be grafted or covered.
Dirty	40%	Purulence or abscess; preoperative perforation of gastrointestinal, oropharyngeal, biliary, or tracheobronchial tracts; penetrating trauma >4 h.

bials are indicated when there is high risk of either postoperative wound infection or consequences of infection [58]. Therefore, prophylaxis is indicated in clean-contaminated and contaminated cases according to the National Research Council classification [59] (Table 5) or, less commonly, in clean surgical cases in selected settings (Table 6). The antimicrobial chosen for prophylaxis should cover the most likely pathogens and have a favorable pharmacokinetic profile. Generally speaking, a first-generation cephalosporin, such as cefazolin, is adequate for any case that involves contamination primarily with endogenous skin flora, such as *S. aureus* and *S. epidermidis*, including cardiothoracic, orthopedic, neurosurgical, head and neck, biliary, and upper gastrointestinal procedures. Use of vancomycin in this setting should be discouraged unless the procedure involves implantation of prosthetic materials or devices at institutions with a high rate of infections due to MRSA. For cases involving enteric aerobes and anaerobes, such as colorectal surgery or abdominal trauma, a cephamycin (e.g., cefoxitin or cefotetan) or "second-generation" cephalosporin is indicated, although other antimicrobials with similar spectra may also be used. For elective colorectal procedures, oral antimicrobial and mechanical preparation of the bowel is also recommended and is given frequently in addition to systemic prophylaxis, although definitive evidence supporting this combination is lacking [58].

Effective antimicrobial prophylaxis is dependent on adequate concentrations of drug in the tissues throughout the entire procedure [60]. Administration of prophylaxis too early or too late has been linked to increased rates of postoperative wound infection [61–64]; therefore, a reasonable approach to ensure appropriate timing is administration upon induction of anesthesia. Intraoperative redosing of antimicrobials is necessary at an interval two times the plasma half-life of the antimicrobial [65] (e.g., every 4 h for cefazolin and every 2–3 h for cefoxitin) or when blood loss exceeds 1.5 L [66].

TABLE 6. INDICATIONS FOR PERIOPERATIVE ANTIMICROBIAL PROPHYLAXIS FOR CLEAN CASES

Insertion of prosthetic materials (e.g., vascular grafts, prosthetic joints)
Procedures involving cardiopulmonary bypass
Procedures involving the central nervous system
Two of three applicable SENIC* risk factors
  abdominal operation
  operation >2 h
  presence of at least three medical diagnoses (alternatively, ASA score >3)

*Study of the Efficacy of Healthcare-associated Infection Control [100].

The duration of antimicrobial prophylaxis is an important, yet poorly studied, issue. Many, if not most, surgeons continue to use a preoperative dose and one or two additional postoperative doses [57], despite studies of single vs. multiple dose prophylaxis revealing no difference in outcome [67–69]. Recommendations for duration of prophylaxis are summarized in Table 7. Of note, excessive prolongation of antimicrobial prophylaxis has been shown to promote antimicrobial resistance without conferring any beneficial effects on surgical site infection rates [70]. The practice of continuing antimicrobial prophylaxis while catheters or drains are in place is not justified [57,58,65, 71,72] and has been associated with isolation of resistant organisms [73].

When an infection is diagnosed, treatment should begin promptly and aggressively. Eradication of infection depends on the adequate dosing and duration of antimicrobial therapy. Inappropriate dosing of antimicrobials may occur due to incorrect assumptions based on dosing in healthy volunteers [74–76], wide variations in pharmacokinetic parameters [77–81], or underdosing in critically ill patients [80–84]. Surgical patients may have an altered volume of distribution (V_d) or biologic half-life ($t_{1/2}$) possibly resulting in either undertreatment (e.g., as a result of the use of standard dosing when the patient has an expanded V_d) or toxicity (e.g., decreased renal function causing an increased $t_{1/2}$). Subtherapeutic antimicrobial concentrations may also foster antimicrobial resistance [76]. The surgeon should take these factors into account and obtain assistance from the hospital pharmacy or unit pharmacist when dosing questions arise. Furthermore, inadequate dosing should be considered when expected clinical responses are not achieved.

Following selection of an appropriate agent and determination of appropriate dosing, duration of therapy must be determined. Excessive length of therapy is often cited as the main reason for inappropriate antimicrobial therapy in surgical patients [71,85–88], yet the proper course of therapy for most surgical infections has not been well defined through rigorous study. Several position papers, however, have advocated shortening duration of treatment [87,89]. In practice, surgeons may either treat for a fixed interval or continue treatment until an appropriate clinical response is achieved [90]. If a patient has not achieved the expected clinical response following completion of a course of antimicrobials, aggressive repeat investigation is advisable, including imaging studies to identify occult sources of infection or inflammation, and repeat cultures to identify, the emergence of antimicrobial resistance, inadequate antimicrobial dosing, and insufficient antimicrobial coverage [89]. Re-evaluation is much more likely to yield important results than the undirected change or addition of antimicrobials for a patient who is failing therapy. Whichever course is chosen (fixed duration of therapy or monitoring of clinical response), a daily re-evaluation of the need for each antimicrobial in use is the most reliable method to avoid overtreatment and ensure cessation of therapy when infections are cured.

TABLE 7. SUGGESTED DURATION OF ANTIMICROBIAL PROPHYLAXIS [65,86,87,101]

Contamination—No postoperative antimicrobials
Gastroduodenal peptic perforations, <12 h
Traumatic enteric perforations, <12 h
Peritoneal contamination with bowel contents during elective/emergency procedures
Appendectomy for early or phlegmonous appendicitis
Cholecystectomy for early or phlegmonous cholecystitis
Resectable infection—24 h postoperative antimicrobials
Appendectomy for gangrenous appendicitis
Cholecystectomy for gangrenous cholecystitis
Bowel resection for ischemic bowel without frank perforation
High-risk procedures—48 h postoperative antimicrobials
Procedures involving cardiopulmonary bypass
Traumatic bowel lesions and gastroduodenal perforation without established infection, >12 h

PREVENT TRANSMISSION

Key principles of preventing transmission are as follows:

- Break the chain of contagion. Use proper hand hygiene with each patient contact.
- Isolate clinically-important pathogens. Adhere to hospital infection control programs.

The final strategy discussed to prevent antimicrobial resistance is the prevention of transmission. One of the simplest and most economical means to achieve this goal is hand hygiene. However, there is surprisingly poor compliance with this simple step [91–93]. Bischoff et al. [91] noted baseline hand hygiene rates of <10% in medical and cardiac surgery ICUs. Rates failed to improve after an educational program but did improve to roughly 50% following the introduction of alcohol-based hand antiseptics. In addition, isolation precautions also continue to be an integral, yet poorly studied, component of most hospital infection control programs. The hand hygiene guidelines were developed by the CDC's Healthcare Infection Control Practices Advisory Committee (HICPAC), in collaboration with the Society for Healthcare Epidemiology of America (SHEA), the Association of Professionals in Infection Control and Epidemiology (APIC), and the Infectious Disease Society of America (IDSA).[94-96] Surgeons should not only abide by these simple infection control policies but also participate in the formulation and promotion of these efforts.

CONCLUSION

Antimicrobial-resistant pathogens are an increasing threat in the surgical setting. This document has synthesized a program to limit the spread of antimicrobial resistance using the following strategies: preventing infection, diagnosing and treating infection effectively, optimizing antimicrobial use, and preventing transmission to other patients. Participation in institutional efforts to control antimicrobial resistance by practicing surgeons and others involved in the care of the surgical patient are critical for success.

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