Infection is morbid and costly, but also preventable to some degree; therefore, it behooves every practitioner to do the utmost to prevent infection. An ensemble of prevention methods is necessary because any single method is universally effective. Infection control is paramount, but often underemphasized. Surgical incisions and traumatic wounds must be handled gently, inspected daily, and dressed if necessary using aseptic technique. Drains and catheters must be avoided if possible, and removed as soon as practicable. Prophylactic and therapeutic antibiotics should be used sparingly so as to minimize antibiotic selection pressure on the development of multidrug-resistant (MDR) pathogens. Surgical patients are at particular risk of infection for many reasons. Surgery is inherently invasive, which creates portals...
of entry in natural epithelial barriers for pathogens to invade the host. Surgical illness is immunosuppressive (e.g., trauma, burns, malignant tumors), as is therapeutic immunosuppression following solid organ transplantation. General anesthesia almost always means a period of mechanical ventilation and a period of reduced consciousness during emergence from anesthesia that poses a risk of pulmonary aspiration of gastric contents, all of which increase the risk of pneumonia. Nosocomial pneumonia occurs more frequently among surgical patients than comparably ill medical patients. Surgical patients are also uniquely afflicted by infections of incisions. Considering that the development of a postoperative infection has a negative impact on surgical outcomes, recognizing risk, minimizing it, and taking an aggressive approach to the diagnosis and treatment of such infections is crucial to improve surgical outcomes.

Surgical infections are traditionally considered to be infections that require surgical therapy (e.g., complicated intra-abdominal and soft tissue infections). However, the recognition that surgical patients are especially vulnerable to nosocomial infection has led to an expansive definition to include any infection that affects surgical patients. Intra-abdominal and soft tissue infections are considered in detail elsewhere in this textbook. The emphasis of this chapter is on the epidemiology, prevention, and management of postoperative and posttraumatic infections.

RISK FACTORS FOR POSTOPERATIVE INFECTION

The general principles of surgical care, critical care, and infection control cannot be overemphasized. Resuscitation must be rapid, yet precise. Pathology must be identified and treated as soon as possible. Infection control is sometimes sacrificed under the often chaotic conditions of resuscitation, but it must not be (see below). Central venous catheters inserted under suboptimal barrier precautions (i.e., lack of cap, mask, sterile gown, and sterile gloves for the operator and a full-bed drape for the patient) must be removed and replaced (if necessary) by a new puncture at a new site as soon as the patient’s condition permits. Detailed evidence-based guidelines for the general prevention of infection (1,2) and the prevention of ventilator-associated pneumonia have been published (3,4). All who provide critical care must be familiar with the guidelines and adhere to them insofar as possible.

CONTROL OF BLOOD SUGAR

Hyperglycemia is deleterious to host immune function, and may also reflect the catabolism and insulin resistance associated with the surgical stress response. Poor perioperative control of blood glucose increases the risk of infection and worsens outcomes. Intra-abdominal and soft tissue infections are associated with the surgical stress response. Post perioperative control of blood glucose increases the risk of infection and worsens outcomes from sepsis. Diabetic patients undergoing cardiopulmonary bypass surgery have a higher risk of infection of both the sternal incision and the vein harvest incisions on the lower extremities (5). Moderate hyperglycemia (>200 mg/dL) at any time on the first postoperative day increases the risk of surgical site infection (SSI) fourfold after cardiac (6) and noncardiac surgery (7). Insulin infusion to keep blood glucose concentrations <110 mg/dL was associated with a 40% decrease in mortality among critically ill postoperative patients, and also fewer nosocomial infections and less organ dysfunction (8). Meta-analysis of 15 trials of control of blood glucose indicates that the risk of mortality is decreased significantly (risk ratio [RR] 0.85, 95% confidence interval [CI] 0.73–0.97) by tight glucose control, especially so for critically ill surgical patients (RR 0.38, 95% CI 0.22–0.62), regardless of whether the patients had diabetes mellitus (RR 0.71, 95% CI 0.54–0.93) or stress-induced hyperglycemia (RR 0.73, 95% CI 0.58–0.90) (9).

Nutritional support is crucial, considering that surgical stress causes catabolism and that restoration of anabolism requires the provision of calories and protein while avoiding hyperglycemia. Parenteral nutrition appears to convey no advantage over not feeding the patient at all (10), perhaps because of the inherent morbidity of central intravenous feeding (i.e., the risk of catheter-related bloodstream infection [CR-BSI] and hyperglycemia). In contrast, early enteral feeding (within the first 48 hours, perhaps immediately if the gut is functional) is clearly beneficial, with the possible exception of pneumonia prevention (see below). The risk of infection was reduced by 55% (odds ratio [OR] 0.45, 95% CI 0.30–0.66) in a meta-analysis of 15 randomized trials of early enteral feeding following surgery, trauma, or burns (11).

Blood Transfusion

Blood transfusion can be life-saving after trauma or hemorrhage, but an increased risk of infection is the consequence. Transfusions exert immunosuppressive effects through presentation of leukocyte antigens and the induction of a shift to the Thelper 2 (immunosuppressive) phenotype, although the mechanism remains somewhat controversial because transfusion of leukocyte-depleted red blood cell concentrates does not reduce the risk of infection (12).Claridge et al. identified an exponential relationship between transfusion risk and infection risk among trauma patients, detectable with even 1 unit of transfusion and becoming a virtual certainty after more than 15 units of transfused blood (RR 1.084, 95% CI 1.028–1.142) (13). Hill et al. has estimated by meta-analysis the risk of infection related to blood transfusion to be increased for trauma patients by more than fivefold (OR 5.26, 95% CI 5.03–5.43), and for surgical patients by more than threefold (14). This increased risk for infection by transfusion has also been identified for critically ill patients in general (15), and for CR-BSI (16) and ventilator-associated pneumonia (VAP) (17) specifically.

Banked blood is affected by a “storage lesion” characterized by loss of membrane 2-3-diphosphoglycerate and adenosine triphosphate, leading to loss of membrane deformability (18). As a result, erythrocytes cannot deform as they must to transit the microcirculation, causing disruption of nutrient blood flow and impaired oxygen offloading. Consequently, blood transfusion does not increase oxygen consumption for critically ill patients with sepsis (19), and may actually increase the risk of organ dysfunction. The storage lesion becomes fully manifest after about 14 days of storage; transfusion of older blood is an independent risk factor for the development of infection (20). It is safe to be conservative in the administration of red blood cells.
cell concentrates to stable patients in the intensive care unit (ICU) (21).

### INFECTION CONTROL

Infection control is an individual and a collective responsibility of the critical care team and unit. Hand hygiene is the most effective means known to reduce the spread of infection, yet whenever studied it is invariably underutilized. Hand cleansing with soap and water requires a minimum of 30 to 45 seconds to be effective. Alcohol gel hand cleansers are equally effective (except against the spores of Clostridium difficile), compliance with use is higher, and when used, the prevalence of MDR bacteria is reduced (22). Universal precautions (i.e., cap, mask, gown, gloves, and protective eyewear) must be observed whenever there is a risk of splashing of body fluids. The source of most bacterial pathogens is the patient’s endogenous flora. Skin surfaces, artificial airways, gut lumen, wounds, catheters, and inanimate surfaces (e.g., bed rails, computer terminals) may become colonized. Any break in natural epithelial barriers (e.g., incisions, percutaneous catheters, airway or urinary catheters) creates a portal of entry for invasion of pathogens. The fecal–oral route is the most common manner by which pathogens reach the portal, but health care workers definitely facilitate the transmission of pathogens around a unit. Many organisms that cause infection following surgery are inherently avirulent (e.g., Candida, Enterococcus, Pseudomonas). Whether infection develops is determined by complex interactions among host defenses, pathogen, and therapy. Contact isolation is an important part of infection control, and should be used selectively to prevent the spread of pathogens such as methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE), or MDR Gram-negative bacilli. However, contact isolation may decrease the amount of direct patient contact. An appropriate balance must be struck, because reduced nurse staffing of ICUs has been independently associated with an increased risk of a number of nosocomial infections (23).

### CATHETER CARE

Optimal catheter care includes avoidance of use when unnecessary, appropriate skin cleansing and barrier protection during insertion, proper catheter selection, proper dressing of indwelling catheters, and removal as soon as possible when no longer needed, or after insertion under less than ideal circumstances (e.g., trauma bay, cardiac resuscitation).

The benefit of the information gained by catheterization must always be weighed against the risk of infection. Almost all indwelling catheters carry a risk of infection, but nonuntunneled central venous catheters (and pulmonary artery catheters) pose the highest risk, including local site infections and CR-BSIs (see below). Other catheters that pose increased infection risk include intercostal thoracostomy catheters (if inserted as an emergency), ventriculostomy catheters for intracranial pressure monitoring, and urinary bladder catheters. Each day of endotracheal intubation and mechanical ventilation increases the risk of pneumonia by 1% to 3%; it is controversial whether tracheostomy decreases that risk.

Chlorhexidine (which is bactericidal, viricidal, and fungicidal) should be used preferentially for skin preparation for vascular catheter insertion, having been shown to be superior to povidone-iodine solution (24). If povidone-iodine solution is used (of which use is discouraged), it must be allowed to dry, as it is not bactericidal when wet. Full barrier precautions are mandatory for all bedside catheterization procedures (2) except arterial and urinary bladder catheterization, for which sterile gloves and a sterile field suffice. Whenever a central venous catheter is inserted under suboptimal conditions it must be removed (and replaced at a different site if still needed) as soon as permitted by the patient’s hemodynamic status, but no more than 24 hours after insertion. A single dose of a first-generation cephalosporin (e.g., cefazolin), but no more, may prevent some infections following emergency tube thoracostomy or ventriculostomy, but is not indicated for vascular or bladder catheterizations. Topical antiseptics placed postprocedure at the insertion site are of no benefit for any type of indwelling catheter, and may actually increase the risk of infection.

Dressings must be maintained carefully (25). Maintaining the integrity of dressings is challenging if the patient is agitated or the body surface is irregular (e.g., the neck [internal jugular vein catheterization]), but its importance is crucial. Marking the dressing clearly with the date and time of each change is a simple and effective way to manage dressing changes. Dressing cars or similar apparatus should not be brought from patient to patient; rather, sufficient supplies should be kept in each patient’s room. The possibility for inanimate objects (e.g., scissors) to be transmission vectors if not cleaned thoroughly after contact with each patient must be borne in mind. Dedicated catheter care teams reduce the risk of CR-BSI substantially (26).

The choice of catheter may play a role in decreasing the risk of infection related to endotracheal tubes, central venous catheters, and urinary catheters. Continuous aspiration of subglottic secretions (CASS), via an endotracheal tube with an extra lumen that opens to the airway just above the balloon, facilitates the removal of secretions that accumulate below the vocal cords but above the endotracheal tube balloon, an area that cannot be reached by routine suctioning. The incidence of VAP is decreased by one half by CASS (26). Silver-impregnated endotracheal tubes are effective in reducing airway colonization, but whether the incidence of VAP is reduced is not yet known (27). Antibiotic- (e.g., minocycline/rifampin) or antiseptic-coated central venous catheters (e.g., chlorhexidine/silver sulfadiazine) can reduce the incidence of CR-BSI (28), especially in high-prevalence units; minocycline/rifampin-coated catheters may be more effective. Urinary bladder catheters coated with ionic silver reduce the incidence of catheter-related bacterial cystitis by a similar amount (29).

Ventilator weaning by protocol, combined with daily sedation holidays and spontaneous breathing trials, allows earlier endotracheal extubation and decreases the risk of VAP (see below) (30). An even better strategy may be avoidance of endotracheal intubation entirely. Respiratory failure can sometimes be managed with noninvasive positive pressure ventilation delivered by mask (e.g., continuous positive airway pressure [CPAP]) (31). Improved resuscitation techniques and noninvasive monitoring techniques have decreased the utilization of pulmonary artery catheters, which pose a particularly high risk of infection (32). Most drains do not decrease the risk
of infection; in fact, the risk is probably increased (33) because the catheters hold open a portal for invasion by bacteria.

**RISK FACTORS FOR SURGICAL SITE INFECTION**

The spectrum of bacterial contamination of the surgical site is well described (34). Clean surgical procedures affect only integumentary and musculoskeletal soft tissues. Clean-contaminated procedures open a hollow viscus (e.g., alimentary, biliary, genitourinary, respiratory tract) under controlled circumstances (e.g., elective colon surgery). Contaminated procedures involve extensive introduction of bacteria into a normally sterile body cavity, but too briefly to allow infection to become established during surgery (e.g., penetrating abdominal trauma, enterotomy during adhesiolysis for mechanical bowel obstruction). Dirty procedures are performed to control established infection (e.g., colon resection for perforated diverticulitis).

Numerous factors determine whether a patient will develop an SSI, including factors related to the patient, the environment, and the therapy (Table 106.1) (33). As incorporated in the National Nosocomial Infections Surveillance System (NNIS) (34,35), the most recognized factors are the wound classification, American Society of Anesthesiologists class ≥3 (class 3: Chronic active medical illness), and prolonged operative time, where time is longer than the 75th percentile for each such procedure. According to the NNIS, the risk of SSI increases with an increasing number of risk factors present, irrespective of the type of operation (35). Laparoscopic surgery decreases the incidence of SSI under most circumstances (36). The reasons that laparoscopic surgery decreases the risk of SSI are possibly several, including decreased wound size, limited use of cautery in the abdominal wall, or a diminished stress response to tissue injury.

**TABLE 106.1**

**RATES OF HEALTH CARE-ASSOCIATED PNEUMONIA AND CATHETER-RELATED BLOODSTREAM INFECTION AMONG VARIOUS INTENSIVE CARE UNIT (ICU) TYPES**

<table>
<thead>
<tr>
<th>ICU type</th>
<th>CVC use</th>
<th>CR-BSI rate Mean/median</th>
<th>TT use</th>
<th>VAP rate Mean/median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>0.52</td>
<td>5/0/3.9</td>
<td>0.46</td>
<td>4/9/3.7</td>
</tr>
<tr>
<td>Pediatric</td>
<td>0.46</td>
<td>6/6/5.2</td>
<td>0.39</td>
<td>2/9/2.3</td>
</tr>
<tr>
<td>Surgical</td>
<td>0.63</td>
<td>4/6/5.4</td>
<td>0.44</td>
<td>9.3/9.3</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>0.79</td>
<td>2/7/1.8</td>
<td>0.43</td>
<td>7/2/6.3</td>
</tr>
<tr>
<td>Neurosurgical</td>
<td>0.48</td>
<td>6/6/5.1</td>
<td>0.39</td>
<td>11/2/6.2</td>
</tr>
<tr>
<td>Trauma</td>
<td>0.61</td>
<td>7/4/2.2</td>
<td>0.36</td>
<td>15/2/1/4</td>
</tr>
</tbody>
</table>

CVC use, number of days of catheter placement per 1,000 patient-days in ICU; CR-BSI, catheter-related bloodstream infections; TT use, number of days of indwelling endotracheal tube or tracheostomy per 1,000 patient-days in ICU; VAP, ventilator-associated pneumonia. Infection rates are indexed per 1,000 patient-days.

Host-derived factors contribute importantly to the risk of SSI, including increased age (36), obesity, malnutrition, diabetes mellitus (5,7), hypercholesterolemia (38), and numerous other factors that are not accounted for specifically by the NNIS system (Table 106.1). In one 6-year study of 5,031 patients undergoing noncardiac surgery, the overall incidence of SSI was 3.2%. Independent risk factors for the development of SSI included ascites, diabetes mellitus, postoperative anemia, and recent weight loss, but not chronic obstructive pulmonary disorder, tobacco use, or corticosteroid use (39). In another prospective study of 9,016 patients, 12.5% of patients developed an infection of some type within 28 days after surgery (40). Multivariable analysis revealed that decreased serum albumin concentration, increased age, tracheostomy, and amputations were associated with an increased probability of an early infection, whereas factors associated with readmission due to infection included a dialysis shunt, vascular repair, and an early infection. Factors associated with 28-day mortality included increased age, low serum albumin concentration, increased serum creatinine concentration, and an early infection (40).

Lapses in the modern operating room can result in increased rates of SSI. Proper sterilization, ventilation, and skin preparation techniques require continuous vigilance. The operating team must be attentive to personal hygiene (e.g., hand scrubbing, hair). Recent data indicate that a brief rinse with soap and water followed by use of an alcohol gel hand rub is equivalent to the prolonged (and ritualized) session at the scrub sink (41).

Hypothermia during surgery is common if patients are not warmed actively, owing to evaporative water losses, and hypothermia is associated with a higher incidence of SSI (42). Maintenance of normal core body temperature is unequivocally important for decreasing the incidence of SSI. Mild intraoperative hypothermia is associated with an increased rate of SSI following elective colon surgery (43) and diverse operations (44).

It is intuitive that oxygen administration in the postoperative period would be beneficial for wound healing (45,46). The isoelectric line of the fresh surgical incision is vulnerable to bacterial invasion. Moreover, oxygen has been postulated to have a direct antibacterial effect (46). However, clinical trials have had conflicting results (47,48). Supplemental oxygenation administration specifically to reduce the incidence of SSI remains plausible, and further studies are needed.

Closure of a contaminated or dirty incision is widely believed to decrease the risk of SSI, but few good studies exist to help sort out the multiplicity of wound closure techniques available to surgeons. “Open abdomen” techniques of temporary abdominal closure for management of trauma or severe perforations are utilized increasingly. Retrospective studies indicate that antibiotics are not indicated for prophylaxis of the open abdomen (49), but infection of the abdominal wall, should it occur, is highly morbid. Inability to achieve primary abdominal closure is associated with several infectious complications (pneumonia, bloodstream infection, and SSI). Infectious complications, in turn, significantly increased costs from prolonged length of stay, but not mortality (50).

Drains placed in incisions probably cause more infections than they prevent. Epithelialization of the wound is prevented and the drain becomes a conduit, holding open a portal for invasion by pathogens colonizing the skin. Several studies of
drains placed into clean or clean-contaminated incisions show that the rate of SSI is not reduced (51,52); in fact, the rate is increased (53–56). Considering that drains pose a risk and accomplish little of what is expected of them, they should be used as little as possible and removed as soon as possible (57). Under no circumstances should prolonged antibiotic prophylaxis be administered to “cover” indwelling drains.

Wound irrigation is a controversial means to reduce the risk of SSI. Routine low-pressure saline irrigation of an incision does not reduce the risk of SSI (58), but high pressure (i.e., pulse irrigation) may be beneficial (59). An increasing body of knowledge suggests that intraoperative topical antibiotics can minimize the risk of SSI (60–62), but the use of antiseptics rather than antibiotics might minimize the possibility of the development of resistance.

### Risk Factors for Pneumonia

Surgical patients are susceptible to pneumonia, particularly if they require mechanical ventilation. Ventilator-associated pneumonia, defined as pneumonia occurring 48 to 72 hours after endotracheal intubation, is the most common ICU infection among surgical and trauma patients. Unfortunately, VAPs are partially autogenic. Nonspecific diagnostic criteria, indiscriminate antibiotic use, and unclear therapeutic end points have all contributed to increased episodes of VAP caused by MDR pathogens. In turn, MDR pathogens increase the likelihood of inadequate initial antimicrobial therapy, which exerts further selection pressure for these pathogens, and results in higher mortality.

Distinction is sometimes made between early-onset VAP (occurring <5 days after intubation) and late-onset VAP (occurring ≥5 days after intubation). Early-onset VAP, to which trauma patients are particularly prone, is often a result of aspiration of gastric contents, and is usually caused by antibiotic-resistant bacteria such as methicillin-sensitive S. aureus, Strep-tococcus pneumoniae, and Haemophilus influenzae (4,63,64). Conversely, patients with late-onset VAP are at increased risk for infection with MDR pathogens (e.g., MRSA, Pseudomonas aeruginosa, or Acinetobacter spp.).

The incidence of VAP depends upon the diagnostic criteria utilized, and thus varies in published reports. Clinical criteria alone overestimate the incidence of VAP as compared with either microbiologic or histologic data (65,66). A systematic review of 89 studies of VAP among mechanically ventilated patients (67) reported a pooled incidence of VAP of 22.8% (95% CI 18.8–26.9). The NNIS system reported recently that VAP occurred at a rate of 4.9 cases per 1,000 ventilator-days in medical ICUs and 9.3 per 1,000 ventilator-days in surgical ICUs (16) (Table 106.2). The risk for trauma patients, especially those with traumatic brain injury, is especially high. The incidence of VAP increases with the duration of mechanical ventilation at a rate of 3% per day during the first 5 days, 2% per day during days 5 to 10, and 1% per day after that (68).

Risk factors for VAP are summarized in Table 106.3 (27). Perhaps most important is airway intubation itself. The risk of VAP increases six- to 20-fold in mechanically ventilated patients (69,70); VAP is also especially common in patients with acute respiratory distress syndrome (ARDS), owing to prolonged mechanical ventilation and devastated local airway host defenses (71–73).

### Table 106.2

<table>
<thead>
<tr>
<th>Risk Factors for Ventilator-Associated Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤60 y</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease or other</td>
</tr>
<tr>
<td>underlying pulmonary disease</td>
</tr>
<tr>
<td>Coma or impaired consciousness</td>
</tr>
<tr>
<td>Serum albumin &lt;2.2 g/dL</td>
</tr>
<tr>
<td>Burns, trauma</td>
</tr>
<tr>
<td>Blood transfusion</td>
</tr>
<tr>
<td>Organ failure</td>
</tr>
<tr>
<td>Seizure position</td>
</tr>
<tr>
<td>Large-volume gastric aspiration</td>
</tr>
<tr>
<td>Sinusitis</td>
</tr>
<tr>
<td>Immunosuppression</td>
</tr>
</tbody>
</table>
to a lower incidence of VAP (74). If endotracheal intubation is required, the orotracheal route is preferred to nasotracheal intubation to decrease the risk of VAP by as much as one half (75), by decreasing the risk of nosocomial sinusitis (76), which often precedes and is caused by the same pathogen as that which caused VAP subsequently. Evidence-based strategies to decrease the duration of mechanical ventilation include daily interruption of sedation (77), standardized weaning protocols, and adequate ICU staffing (78).

After intubation, most VAP preventive measures aim to decrease the risk of aspiration. Both maintenance of endotracheal cuff pressure >20 cm H2O (51) and CASS reduce the incidence of VAP significantly (26).

Semirecumbent positioning (30° to 45° head-up) is also protective as compared to supine positioning, especially during enteral feeding (79–81). Compared to postpyloric feeding, intragastric feeding increases both gastrointestinal reflux and aspiration (82). A meta-analysis of 11 randomized trials reported a RR of 0.77 (95% CI 0.60–1.00, p = 0.0004) (17). Earley et al. documented a 90% decreased incidence of VAP in a surgical ICU following implementation of an aminoglycoside management protocol that resulted in fewer blood transfusions (93).

<table>
<thead>
<tr>
<th>TABLE 106.4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STRATEGIES TO PREVENT VENTILATOR-ASSOCIATED PNEUMONIA</strong></td>
</tr>
<tr>
<td>Strategy</td>
</tr>
<tr>
<td>Universal infection control precautions</td>
</tr>
<tr>
<td>Oronasal intubation</td>
</tr>
<tr>
<td>Maintenance of endotracheal cuff pressure &gt;20 cm H2O</td>
</tr>
<tr>
<td>Continuous aspiration of subglottic secretions</td>
</tr>
<tr>
<td>Semirecumbent positioning</td>
</tr>
<tr>
<td>Postpyloric feeding</td>
</tr>
<tr>
<td>Postintubation intubation</td>
</tr>
<tr>
<td>Selective decontamination of the digestive tract</td>
</tr>
<tr>
<td>Topical chlorhexidine</td>
</tr>
<tr>
<td>Transfusion restriction</td>
</tr>
<tr>
<td>Antibiotic cycling</td>
</tr>
</tbody>
</table>

Critically ill patients often require reliable large-bore central venous access (e.g., femoral, internal jugular, or subclavian vein), but the catheters are highly prone to infection. Strict adherence to infection control and proper insertion technique is crucial for prevention (94), because surgical and especially trauma patients are at high risk (Table 106.1). When placed under elective (controlled) circumstances, optimal insertion technique includes chlorhexidine skin preparation (not povidone-iodine) (24), draping the entire bed into the sterile field, and donning a cap, a mask, and sterile gown and gloves (2). If technique is breached, the risk of infection increases exponentially, and the catheter should be removed and replaced (if still needed) at a different site using strict asepsis and antisepsis as soon as the patient's condition permits, but certainly within 24 hours. Infection risk for femoral vein catheters is highest, and is lowest for catheters placed via the subclavian route (49). Peripheral vein catheters, peripherally inserted central catheters (PICCs), and tunnelled central venous catheters (e.g., Hickman, Broviac) pose less risk of infection than percutaneous central venous catheters (25). Information campaigns, educational initiatives (95), and strict adherence to insertion protocols are all effective to decrease the risk of CR-BSI. Antibiotic- and antiseptic-coated catheters are controversial, but may help decrease the risk of infection in units that have a high rate of infection (96).

**Risk Factors for Catheter-related Bloodstream Infection**

In the ICU, nosocomial sinusitis is an uncommon closed-space infection that may be clinically occult but can have serious consequences (97). Whereas sinusitis is often part of the differential diagnosis of fever, the incidence is low in comparison to other nosocomial infections in the ICU, and the diagnosis can be difficult to document convincingly. The likely pathogenesis of sinusitis is anatomic obstruction of the ostra draining the facial sinuses, especially the maxillary sinuses. Transnasal endotracheal intubation is the leading risk factor, with an incidence of...

**Risk Factors for Sinusitis**

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Antibiotic Prophylaxis

Prophylactic antibiotics are used most often to prevent infection of a surgical incision. Antibiotic prophylaxis of surgery does not prevent postoperative nosocomial infections, which actually occur at an increased rate after prolonged prophylaxis (98), selecting for more resistant pathogens when infection does develop (99).

Preoperative antibiotic prophylaxis is proved to reduce the risk of postoperative SSI in many circumstances. However, only the incision itself is protected, and only while it is open and thus vulnerable to inoculation. Therefore, antibiotics are not a panacea. If not administered properly, antibiotic prophylaxis is ineffective and may be harmful.

Antibiotic prophylaxis is indicated for most clean-contaminated and contaminated (or potentially contaminated) operations. An example of a clean-contaminated operation where antibiotic prophylaxis is usually not indicated is elective laparoscopic cholecystectomy (100); meta-analysis of five trials including 899 patients revealed no benefit compared with placebo for prevention of SSI (OR 0.68, 95% CI 0.24–1.91), “major infection,” or “distant infection.” Antibiotic prophylaxis is indicated for high-risk biliary surgery; high-risk is conferred by age older than 70 years, diabetes mellitus, or a recently instrumented biliary tract (e.g., biliary stent).

Elective colon surgery is a clean-contaminated procedure where preparatory practices are in evolution (101,102), although the evidence of benefit of systemic antibiotic prophylaxis is unequivocal. Antibiotic bowel preparation, standardized in the 1970s by the oral administration of nonabsorbable neomycin and erythromycin base in addition to mechanical cleansing, reduced the risk of SSI to its present rate of approximately 4% to 8% (101). However, mechanical bowel preparation and preoperative oral antibiotics are omitted increasingly out of the belief that there is no additive benefit beyond parenteral antibiotic prophylaxis. Current Surgical Care Improvement Project (SCIP) guidelines for antibiotic prophylaxis of elective colon surgery give equal weighting to oral prophylaxis alone, parenteral prophylaxis alone, or the combination (102) (Table 106.5), despite the fact that two meta-analyses (that asked different questions) are in conflict as to the efficacy of oral prophylaxis for colorectal surgery; Song and Glenny (103) examined oral antibiotics alone compared with oral/systemic antibiotic prophylaxis (five trials), and found a higher SSI rate with oral prophylaxis alone (OR 3.34, 95% CI 1.66–6.72), Lewis performed a meta-analysis of 13 randomized trials of systemic versus combined oral and systemic prophylaxis, and showed significant benefit for the combined approach (RR 0.51, 95% CI 0.24–0.78) (101).

Antibiotic prophylaxis of clean surgery is controversial. Where bone is incised (e.g., craniotomy, sternotomy) or a prosthesis is inserted, antibiotic prophylaxis is generally indicated. Some controversy persists with clean surgery of soft tissues (e.g., breast, hernia). Meta-analysis of randomized controlled trials shows some benefit of antibiotic prophylaxis of breast cancer surgery without immediate reconstruction (104,105), but no decrease of SSI rate for groin hernia surgery (106,107), even when a nonabsorbable mesh prosthesis is implanted. Arterial reconstruction with prosthetic graft material is an example of clean surgery where the susceptibility to infection is high, owing to the presence of ischemic tissue and the infrarenal location of many such operations. A recent meta-analysis (108) identified 23 randomized, controlled trials of prophylactic systemic antibiotics for peripheral arterial reconstruction (Table 106.6). Prophylactic systemic antibiotics

### Table 106.5

<table>
<thead>
<tr>
<th>Type of operation</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac (including CARG), vascular*</td>
<td>Cefazolin, cefuroxime, or vancomycin*</td>
</tr>
<tr>
<td>Hip/Knee arthroplasty#</td>
<td>Cefazolin, cefuroxime, or vancomycin*</td>
</tr>
<tr>
<td>Colon*</td>
<td>Oral: Neomycin sulfate plus either erythromycin base or metronidazole, administered for 18 h before surgery. Parenteral: Cefoxitin, cefotetan, or cefazolin plus metronidazole or ampicillin-sulbactam or ertapenem</td>
</tr>
<tr>
<td>Hysterectomy#</td>
<td>Cefazolin, cefoxitin, cefotetan, cefuroxime, or ampicillin-sulbactam</td>
</tr>
</tbody>
</table>

*Prophylaxis may be administered for up to 48 h for cardiac surgery; for all other cases, the limit is 24 h.

# For β-lactam allergy, clindamycin or vancomycin is an acceptable substitute for cardiosurgery; valsalva, and orthopedic surgery.

*For β-lactam allergy, clindamycin plus gentamicin, a fluoroquinolone, or aztreonam; or metronidazole plus gentamicin or a fluoroquinolone in an acceptable choice.

*For colon surgery, either oral or parenteral prophylaxis alone, or both combined, is acceptable.

*For β-lactam allergy, clindamycin plus gentamicin, a fluoroquinolone, or aztreonam; or metronidazole plus gentamicin or a fluoroquinolone in an acceptable choice.

*Vancomycin is acceptable with a physician-documented justification for use in the patient's medical record.
reduced the risk of SSI by approximately 75%, and early graft infection by about 69%. There was no benefit to prophylaxis for more than 24 hours, antibiotic bonding to the graft material itself, or preoperative bathing with an antiseptic agent for more than 24 hours, antibiotic bonding to the graft material itself, or preoperative bathing with an antiseptic agent.

Four principles guide the administration of antimicrobial agents for prophylaxis: safety, an appropriate narrow spectrum of coverage of relevant pathogens, little or no reliance upon the agent for therapy of infection (owing to the possible induction of resistance with heavy usage), and administration within 1 hour before surgery and for a defined, brief period of time thereafter (no more than 24 hours [48 hours for cardiac surgery], ideally, a single dose) (109). According to these principles, quinolones or carbapenems are undesirable agents for surgical prophylaxis, although etampenem and quinolone prophylaxes have been endorsed by the SCIP for prophylaxis of colon surgery (the latter with metronidazole for penicillin-allergic patients) (Table 106.5).

Most SSIs are caused by Gram-positive cocci; therefore, prophylaxis should be directed primarily against staphylococci for clean cases and high-risk clean-contaminated elective biliary and gastric surgery. A first-generation cephalosporin is preferred in almost all circumstances (Table 106.7), with clindamycin used for penicillin-allergic patients (109). If Gram-negative or anaerobic coverage is required, a second-generation cephalosporin or the combination of a first-generation agent plus metronidazole is most experts’ regimens of first choice. Vancomycin prophylaxis is generally appropriate only in institutions where the incidence of MRSA infection is high (>20% of all SSIs caused by MRSA).

The optimal time to give parenteral antibiotic prophylaxis is within 1 hour prior to incision (110). Antibiotics given sooner are ineffective, as are agents given after the incision is closed.

A 2001 audit of prescribing practices in the United States indicated that only 36% of patients who received prophylactic antibiotics did so within 1 hour prior to the skin incision (111); timeliness was documented in only 76% of cases in a 2005 audit in U.S. Department of Veterans Affairs hospitals (112). Most inappropriately timed first doses of prophylactic antibiotic occur too early (111,112); changing institutional processes to administer the drug in the operating room can improve compliance with best practices (112). Antibiotics with short half-lives (<2 hours, e.g., cefazolin or cefoxitin) should be redosed every 3 to 4 hours during surgery if the operation is prolonged or bloody (113). Even though the SCIP specifies a 24-hour limit for prophylaxis, single-dose prophylaxis (with intraoperative redosing, if indicated) is equivalent to multiple doses for the prevention of SSI (114). Unfortunately, excessively prolonged antibiotic prophylaxis is both pervasive and potentially harmful. Recent U.S. data show that only 40% of patients who receive antibiotic prophylaxis do so for less than 24 hours (111). As a result of ischemia caused by surgical hemostasis, antibiotic penetration into the incision immediately after surgery is questionable until neovascularization occurs (24–48 hours). Antibiotics should not be given to “cover” indwelling drains or catheters, in lavage or irrigation fluid, or as a substitute for poor surgical technique. That prophylaxis is prolonged excessively is demonstrated by antibiotic utilization data for U.S. surgical ICUs (Table 106.8); high usage of first-generation cephalosporins in ICUs cannot be explained by therapeutic use.

Prolongation of antibiotic prophylaxis beyond 24 hours is not only nonbeneficial, but also may be harmful. *Clostridium difficile*-associated disease (CDAD) follows disruption of the normal balance of gut flora, resulting in overgrowth of the enterotoxin-producing *C. difficile* (115). Although virtually any antibiotic may cause CDAD (even a single dose), prolonged antibiotic prophylaxis increases the risk. Prolonged prophylaxis also increases the risk of nosocomial infections unrelated to the surgical site, and the emergence of MDR pathogens. Both pneumonias and vascular catheter-related infections have been associated with prolonged prophylaxis (116,117), as has the emergence of SSI caused by MRSA (99).

### Table 106.6

<table>
<thead>
<tr>
<th>Intervention</th>
<th>No. of trials</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic antibiotic prophylaxis</td>
<td>10</td>
<td>0.25</td>
<td>0.17–0.38</td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>10</td>
<td>1.28</td>
<td>0.82–1.98</td>
</tr>
<tr>
<td>Early graft infection</td>
<td>3</td>
<td>0.31</td>
<td>0.11–0.85</td>
</tr>
<tr>
<td>Rifampicin bonding of polyester grafts</td>
<td>3</td>
<td>0.63</td>
<td>0.27–1.49</td>
</tr>
<tr>
<td>Graft infection—1 mo</td>
<td>2</td>
<td>1.05</td>
<td>0.46–2.40</td>
</tr>
<tr>
<td>Suction wound drainage—grom</td>
<td>2</td>
<td>0.96</td>
<td>0.50–1.86</td>
</tr>
<tr>
<td>Preoperative antiseptic bath</td>
<td>3</td>
<td>0.97</td>
<td>0.70–1.36</td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>2</td>
<td>0.48</td>
<td>0.31–0.74</td>
</tr>
</tbody>
</table>


### Evaluation of Possible Postoperative Infection

A new temperature elevation usually triggers an automatic evaluation of possible postoperative infection, which includes many costly tests of limited utility, based on suspicion of a nosocomial infection. During the evaluation, the patient may be exposed to unneeded radiation, require transport outside the controlled environment of the ICU, or experience considerable blood loss due to this testing, which is often repetitive. With utilization of resources under intensive scrutiny, it is appropriate to assess such fevers in a prudent and cost-effective manner.

However, some infected patients do not become febrile, and may even become hypothermic. A hypothermic or euglycemic patient may have a life-threatening infection (118,119). Such patients include elderly patients, those with open abdominal wounds or large burns, patients on extracorporeal support (e.g., continuous renal replacement therapy) (120), patients with end-stage liver disease or chronic renal failure, and patients taking anti-inflammatory or antipyretic drugs. Absent a
### TABLE 106.7

**APPROPRIATE CEPHALOSPORIN PROPHYLAXIS FOR SELECTED OPERATIONS**

<table>
<thead>
<tr>
<th>Operation</th>
<th>Alternative prophylaxis in serious penicillin allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-generation cephalosporin (i.e., cefazolin, cefuroxime)</td>
<td>Clindamycin (for all cases herein except amputation)³</td>
</tr>
<tr>
<td>Cardiovascular and thoracic</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Median sternotomy</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Pacemaker insertion</td>
<td>Clindamycin (for all cases herein except amputation)³</td>
</tr>
<tr>
<td>Vascular reconstruction involving the abdominal aorta, insertion of a prosthesis, or a groin incision (except carotid endarterectomy, which requires no prophylaxis)</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Implantable defibrillator</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Pulmonary resection</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Lower limb amputation</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>General</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Cholecystectomy (High risk only)</td>
<td>Gentamicin and metronidazole</td>
</tr>
<tr>
<td>Gastrectomy (High risk only: Not uncomplicated chronic duodenal ulcer)</td>
<td>Gentamicin and metronidazole</td>
</tr>
<tr>
<td>Major debridement of traumatic wound</td>
<td>Gentamicin and metronidazole</td>
</tr>
<tr>
<td>General</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Cesarean section (stat)</td>
<td>Gentamicin and metronidazole</td>
</tr>
<tr>
<td>Hysterectomy (cefoxitin is a reasonable alternative)</td>
<td>Gentamicin and metronidazole</td>
</tr>
<tr>
<td>Head and neck/oral cavity</td>
<td>Gentamicin and clindamycin or metronidazole</td>
</tr>
<tr>
<td>Major procedures entering oral cavity or pharynx</td>
<td>Gentamicin and clindamycin or metronidazole</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>Gentamicin and metronidazole</td>
</tr>
<tr>
<td>Craniotomy</td>
<td>Metronidazole (after cord clamping)</td>
</tr>
<tr>
<td>Orthopedics</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Open reduction of closed fracture</td>
<td>Metronidazole (with or without gentamicin for all cases herein) Second generation (i.e., cefoxitin)³</td>
</tr>
<tr>
<td>Appendectomy</td>
<td>Metronidazole (with or without gentamicin for all cases herein) Second generation (i.e., cefoxitin)³</td>
</tr>
<tr>
<td>Colon surgery</td>
<td>Metronidazole (with or without gentamicin for all cases herein) Second generation (i.e., cefoxitin)³</td>
</tr>
</tbody>
</table>

*Should be given as a single intravenous dose just before the operation. Consider an additional dose if the operation is prolonged longer than 3–4 h.

²Primary prophylaxis with vancomycin (i.e., for the non–penicillin-allergic patient) may be appropriate for cardiac valve replacement, placement of a nonautogenous peripheral vascular prosthesis, or total joint replacement in institutions where a high rate of infection with methicillin-resistant *Staphylococcus aureus* or *Staphylococcus epidermidis* has occurred. The precise definition of “high rate” is debated. A single dose administered immediately before surgery is sufficient unless operation lasts for more than 6 h, in which case the dose should be repeated. Prophylaxis should be discontinued after a maximum of two doses, but may be continued for up to 48 h.

³An intraoperative dose should be given if cefoxitin is used and the duration of surgery exceeds 3–4 h, because of the short half-life of the drug. A postoperative dose is not necessary, but is permissible for up to 24 h.

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fever, any of hypotension, tachycardia, tachypnea, confusion, rigors, skin lesions, respiratory manifestations, oliguria, lactic acidosis, leukocytosis, leukopenia, immature neutrophils (i.e., bands >10%), or thrombocytopenia may indicate a workup for infection and immediate empiric therapy. The definition of fever is arbitrary, and depends on how and when temperature was measured. In addition to host biology, a variety of environmental forces in an ICU can also alter body temperature, such as specialized mattresses, lighting, heating or air conditioning, peritoneal lavage, and renal
replacement therapy (121–123). Thermoregulatory mechanisms can be disrupted by drugs or by injury to the central nervous systems. Thus, it is often difficult to determine if an abnormal temperature is a reflection of a physiologic process, a drug, or an environmental influence. Moreover, in surgical patients, the substantial possibility (∼50%) that a fever is due to a noninfectious cause must be considered (Fig. 106.1) (124). Many ICUs consider any patient with a core temperature $\geq 38.3^\circ C (\geq 101^\circ F)$ to be febrile and to warrant evaluation to determine if infection is present. However, a lower threshold may be decided upon for immunocompromised patients. However, laboratory tests or imaging studies to search for infection should be performed only after a clinical assessment (history and physical examination) indicates that infection might be present.

### Blood Cultures

Blood cultures should be obtained from patients with a new fever when clinical evaluation does not strongly suggest a noninfectious cause. The site of venipuncture should be cleaned with either 2% chlorhexidine gluconate in 70% isopropyl alcohol or 1% to 2% tincture of iodine. Povidone-iodine (10%), while acceptable, is not bactericidal until dry; some false-positive blood cultures may be due to premature specimen collection (125, 126). One blood culture is defined as a 20- to 30-mL sample of blood drawn at a single time from a single site, regardless of how many bottles or tubes are filled for processing. The sensitivity of blood culturing for detection of true bacteremia or fungemia is related to many factors, most importantly the volume of blood drawn and obtaining the cultures before initiation of anti-infective therapy (127, 128).

Recent data suggest that the cumulative yield of pathogens is optimized when three blood cultures with adequate volume (20- to 30-mL each) are drawn (127). Each culture should ideally be drawn by separate venipuncture or through a separate intravascular device, but not through multiple ports of the same intravascular catheter (129). There is no evidence that the yield of cultures drawn from an artery or vein is different. Drawing two to three blood cultures with appropriate volume from separate sites of access at the onset of fever is the most effective way to discern whether an organism found in blood culture represents a true pathogen (multiple cultures are often positive), a contaminant (only one of multiple blood cultures is positive for an organism commonly found on skin and clinical
Pneumonia is the second most common cause of ICU-acquired infection and a ubiquitous cause of fever, with the majority of cases occurring in mechanically ventilated patients (65,136). The diagnosis of VAP is especially challenging, as patients commonly also have other, noninfectious processes producing abnormal chest radiographs and gas exchange (e.g., congestive heart failure, atelectasis, ARDS). Intubated, sedated patients cannot cough, or otherwise mobilize abnormal secretions without assistance. In addition, immunocompromised patients such as solid organ transplant recipients may have pneumonia without fever, cough, sputum production, or leukocytosis (137–138).

The diagnosis of VAP requires determination if the patient has pneumonia, and the etiologic pathogen. Poor specificity is problematic because it not only exposes patients to unnecessary risk from overtreatment with antibiotics, but also increases selection pressure and thus the emergence of MDR bacteria (139,140). Conversely, inadequate initial therapy in patients with VAP (poor sensitivity) is associated with increased mortality that cannot be reduced by subsequent changes in antibiotics (141).

Historically, the diagnosis of VAP requires one or more of the following: fever, leukocytosis or leukopenia, purulent sputum, hypoxemia, or a new or evolving chest radiographic infiltrate. However, several noninfectious processes may mimic those nonspecific signs, such as congestive heart failure, atelectasis, pulmonary thromboembolism, pulmonary hemorrhage, and ARDS, making clinical criteria alone unreliable. A new chest radiographic infiltrate, along with two of the three aforementioned criteria, was only 69% sensitive and 75% specific for VAP as compared to postmortem histology (142). Several subsequent reports have confirmed the low specificity of clinical acumen in the diagnosis of VAP (143–144); clinically diagnosed VAP is confirmed microbiologically in ~30% of cases (66,143,146). Computerized tomography (CT) is particularly sensitive for demonstrating parenchymal or pleural disease in posterior-inferior lung segments (147,148), although there is a maximum score of 12 points (150). A CPIS of >6 points indicates a high probability of VAP. However, the specificity of CPIS is no better than clinical acumen alone when compared to lower respiratory tract cultures obtained via bronchoscopy (137,138).

The Clinical Pulmonary Infection Score (CPIS) incorporates clinical, radiographic, and microbiologic criteria (i.e., temperature, leukocyte count, chest radiographic infiltrates, appearance and volume of tracheal secretions, PaO₂/FiO₂, culture and Gram stain of tracheal aspirate [0–2 points each]) to yield a maximum score of 12 points (150). A CPIS of >6 points indicates a high probability of VAP. However, the specificity of CPIS is no better than clinical acumen alone when compared to lower respiratory tract cultures obtained via bronchoscopy (137,138). However, the negative predictive value of a Gram stain showing no organisms in a clinically stable patient approaches 100% (133).

Because of the low specificity of traditional diagnostic criteria, culture of lower respiratory tract samples is mandatory for nosocomial pneumonia prior to any manipulation of antibiotics in order to minimize false-negative results. The method of specimen collection (invasive vs. noninvasive) and the method of specimen analysis (semiquantitative vs. quantitative) are...

Intravascular Devices

All intravascular devices and insertion sites must be assessed daily as part of a comprehensive physical examination to determine if they are still needed and whether signs of infection are present locally (e.g., inflammation or purulence at the exit site or along the tunnel) or systemically. Contaminated catheter hubs are common portals of entry for organisms colonizing the endoluminal surface of the catheter (131). Additionally, infusate (parenteral fluid, blood products, or intravenous medications) can become contaminated and produce bacteria or fungemia, which is especially likely to result in septic shock. Abrupt onset of signs and symptoms of sepsis or shock in patients with an indwelling vascular catheter should prompt suspicion of infection of an intravascular device. Recovery of certain microorganisms in multiple blood cultures, such as staphylococci or Candida spp., strongly suggests infection of an intravascular device.

Removal and culture of the catheter has historically been the gold standard for the diagnosis of CR-BSI, particularly with short-term catheters. Studies have demonstrated the reliability of semiquantitative or quantitative catheter tip culture methods for the diagnosis of CR-BSI (132), which is confirmed when a colonized catheter is associated with concomitant bloodstream infection with the identical organism, with no other plausible source. Some ICU clinicians culture central venous catheters routinely on removal, regardless of whether infection is suspected. Because ~20% of central venous catheters are colonized at removal, most unassociated with local or systemic infection, this practice is expensive and can lead to unnecessary therapy. The predictive value of a positive catheter culture is very low when there is a low pretest probability of line sepsis (132), and catheters removed from ICU patients should only be cultured if there is strong clinical suspicion of CR-BSI (133).

For patients with fever alone who do not have systemic inflammatory response syndrome (SIRS) (134), there is usually no need to remove or change all indwelling catheters immediately, although such an approach would be prudent in a patient with a prosthetic heart valve or a fresh arterial graft (133). If patients have severe sepsis or septic shock, peripheral embolization, disseminated intravascular coagulation, or acute respiratory distress syndrome (ARDS), removal of all intravascular catheters is indicated, even if the catheters are cuffed or tunneled devices (135).

Infected phlebitis (suppurative phlebitis) of a central vein due to a centrally placed catheter is unusual. With supplicative phlebitis, bloodstream infectioncharacteristically persists and originates from a peripheral vein catheter site with infected intravascular thrombus, producing a picture of overwhelming sepsis with high-grade bacteremia or fungemia. This syndrome is most often encountered in burn patients or other ICU patients who develop catheter-related infection that goes unrecognized, permitting micro-organisms to proliferate. In patients with persistent S. aureus bacteremia or fungemia, echocardiography is appropriate to assess for endocarditis and guide further therapy (133).
debated. Noninvasive techniques include endotracheal suction aspiration (EA), blinded plugged telescoping catheter, and intra-arterial PSB. The criteria for gallium uptake are less specific due to an increased likelihood of contamination by oropharyngeal flora reflecting colonization rather than infection.

Invasive techniques (BAL or PSB) collect samples using fiberoptic bronchoscopy, and also allow direct inspection of the airways, but are more expensive and resource-intensive than noninvasive techniques. Furthermore, arterial desaturation may persist for up to 24 hours postbronchoscopy, possibly due to alveolar flooding caused by residual lavage fluid. However, this desaturation has not been correlated with poorer outcomes (154).

Respiratory tract cultures may be reported either semiquantitatively or quantitatively. The crucial issue is distinction of colonization from infection (155). Whereas semiquantitative microbiology reports growth in terms of ordinal categories (e.g., light, moderate, or heavy), quantitative microbiology reports growth in terms of colony forming units (CFU/mL) of aliquot; a threshold value is assigned to distinguish colonization from infection. Commonly used thresholds are 10^4 CFU/mL for PSB, 10^5 CFU/mL for BAL, and 10^6 CFU/mL for EA. Any threshold should be lowered by one order of magnitude if antibiotics have been changed recently or started prior to sample acquisition (156). Clinical interpretation of quantitative cultures is likely to be hampered by prior antibiotic administration, which may lower the observed quantitative inoculum after 24 hours of ongoing antibiotic therapy, and for up to 72 hours after cessation of antibiotics (157,158). The diagnostic threshold is usually lowered by one order of magnitude in the presence of antibiotic or recent discontinuation therapy.

Endotracheal aspirates have lower specificity compared to either blinded plugged telescoping catheter (159) or bronchoscopic BAL or PSB (160-163). Two systematic reviews, one of bronchoscopic BAL (154) and one of blinded invasive techniques (163), reported similar test characteristics for the two techniques, but methodologic variability is rampant. Bronchoscopic techniques are more specific than blinded techniques, and both techniques are superior to EAs.

Shorr et al. performed a meta-analysis of randomized trials that compare outcomes of patients with VAP managed with invasive versus noninvasive sampling when both samples were cultured quantitatively (164). Although the pooled OR suggested a survival advantage to the invasive approach (OR = 0.62), the result was not significant. However, patients in the invasive group were significantly more likely to undergo changes in antimicrobial regimen.

Pulmonary secretions for culture should be transported to the laboratory and processed within 2 hours so that fastidious organisms such as S. pneumoniae remain viable. For any expectorated specimen, it is important for the laboratory to perform direct microscopy on the specimen to determine if squamous epithelial cells are present, which invalidates the specimen.

Organisms that may be pathogens in VAP or contaminants when recovered from the airway include P. aeruginosa, Entrobacteriaceae, S. pneumoniae, S. aureus, and H. influenzae. Conversely, isolation of enterococci, viridans streptococci, coagulase-negative staphylococci, and Candida spp. (165,166) should rarely be considered the cause of respiratory dysfunction, if ever. Although febrile postoperative patients in an ICU often have small pleural effusions due to fluid overload, hypoplasticinoma, or postoperative processes, it is not necessary to sample such fluid from every febrile patient.Thoracentesis is appropriate if there is sufficient fluid to aspirate safely using ultrasound (US) guidance and there is either an adjacent pulmonary infiltrate or possible contamination of the pleural space by surgery, trauma, or a fistula.

### Evaluation for Clostridium difficile Infection

Many ICU patients have diarrhea, often due to enteral feedings or drugs. By far the most common enteric cause of fever in the ICU is C. difficile, which should be suspected in any patient with diarrhea and fever or leukocytosis who has received an antibacterial agent or antineoplastic chemotherapy within 60 days prior to the onset of diarrhea (167,168). C. difficile accounts for 10% to 25% of all cases of antibiotic-associated diarrhea and virtually all of the cases of antibiotic-associated colitis (169). However, some patients, especially those who are postoperative, may present with deus or toxic megacolon, or leukocytosis without diarrhea, as the manifestation of CDAD. In these patients, the diagnosis is difficult to establish because stool specimens are not accessible (170). C. difficile-associated diarrhea may occur with any antibacterial agent, but the most common causes are clindamycin, cephalosporins, and fluoroquinolones (171).

Although less accurate than expensive tissue culture assays, most laboratories now use immunoassays for C. difficile toxins, which provide results within hours and are easy to perform. Lower sensitivity may require repeat tests to document disease in seriously ill patients (172). Most strains of C. difficile produce toxin A, but 2% to 3% of strains produce only toxin B so an assay that detects both toxins A and B is preferred (173). Cultures for C. difficile are technically demanding, and are not specific in distinguishing toxin-positive strains, toxin-negative strains, and asymptomatic carriage (172,174). Cultures may be useful in the setting of nosocomial outbreaks to identify isolates for epidemiologic purposes (168). The North American pulse-field gel electrophoresis type 1 (NAP1) strain, now epidemic in many hospitals in the United States, Canada, and Europe, is associated with serious complications (toxic megacolon, leukemoid reactions, septic shock, and death) (175,176).

Direct visualization of pseudomembranes is nearly diagnostic of CDAD, but only about 70% of seriously ill patients and 25% of patients with mild disease have pseudomembranes by direct visualization (177), diminishing the role of endoscopy for routine diagnostic use. However, a role for direct visualization may exist if false-negative C. difficile toxin assays are suspected (168).

### Urinary Tract Infection

Catheter-associated bacteriuria or candiduria usually represents colonization, is rarely symptomatic, and is an unlikely cause of fever or secondary bloodstream infection (178), even in immunocompromised patients (179), unless there is urinary tract obstruction; there is a history of recent urologic manipulation, injury, or surgery; or the patient is neutropenic (180,181).

Traditional signs and symptoms (dysuria, urgency, pelvic or flank pain, fever or chills) that correlate well with bacteriuria in noncatheterized patients are rarely reported in ICU patients
with documented catheter-associated bacteriuria or candiduria (>10⁵ CFU/mL) (180,181). In the ICU, the majority of urinary tract infections are related to urinary catheters and are caused by multiresistant nosocomial Gram-negative bacilli other than *Escherichia coli*, *Enterococcus* spp., and *Yeasts* (178,182,183).

When clinical evaluation suggests the urinary tract as a possible source of fever, a urine specimen should be evaluated by direct microscopy, Gram stain, and quantitative culture. The specimen should be aspirated from the catheter sampling port, not collected from the drainage bag. Health care personnel should wear clean gloves whenever manipulating a urinary device and should scrupulously clean the port with 70% to 90% alcohol prior to specimen collection. For patients without a catheter, a conventional midstream clean-catch urine specimen should be obtained. Urine collected for culture should reach the laboratory promptly to prevent multiplication of bacteria within the receptacle, which might lead to the misdiagnosis of infection; any delay should prompt refrigeration of the specimen.

In contrast to community-acquired urinary tract infections, where pyuria is highly predictive of important bacteriuria, pyuria may be absent with catheter-associated urinary tract infections. Even if present, pyuria is not a reliable predictor of urinary tract infection in the presence of a catheter (178). The concentration of urinary bacteria or yeast needed to cause symptomatic urinary tract infection or fever is unclear. Whereas it is clear that counts >10⁵ CFU/mL represent true bacteriuria or candiduria in catheterized patients (184), there are no data to show that higher counts are more likely to represent symptomatic infection. Gram stain of a centrifuged urine specimen, however, will show microorganisms most of the time if infection is present (185).

Whereas it is appropriate to collect urine specimens in the investigation of fever, routine monitoring or “surveillance” cultures of urine contribute little to patient management. Rapid dipstick tests, which detect leukocyte esterase and nitrite, are unreliable in the setting of catheter-related UTI. The leukocyte esterase test correlates with the degree of pyuria, which may or may not be present in a catheter-related UTI. The nitrite test reflects *Enterobacteriaceae*, which convert nitrate to nitrite, and is therefore unreliable to screen for *Enterococcus* spp., *Candida* spp., and *Staphylococcus* spp. (186,187).

### SINUSITIS

The paranasal sinuses are normally sterile, but bacterial overgrowth occurs when drainage is impeded. The etiologic agents responsible for most cases of nosocomial sinusitis are those that colonize the naso- oropharynx (76,188), which occur at high frequency among critically ill patients. Gram-negative bacilli (particularly *P. aeruginosa*) constitute 60% of bacteria isolated from nosocomial sinusitis, whereas Gram-positive cocci (typically *S. aureus* and coagulase-negative staphylococci) comprise one third of isolates, and fungi the remaining 5% to 10% (76,189,190). Infections are often polymicrobial.

The diagnosis of sinusitis in critically ill, intubated patients is difficult to make. Complains of facial pain or headache may be impossible to elicit, and purulent nasal discharge is present in only 25% of proved cases of sinusitis. In the ICU, acute sinusitis is diagnosed most efficiently by CT of the facial bones (191), followed by sampling using an antiseptic technique if mucosal thickening or sinus fluid is documented. Microbial analysis of fluid obtained by minimally invasive sinus puncture and aspiration under anesthetic conditions is definitive for the diagnosis. Although less well studied, endoscopic-guided middle meatal tissue culture is a safe alternative for patients who are not candidates for antral puncture (e.g., coagulopathy) (192). Pathogen identification and susceptibility testing permit focused, narrow-spectrum antimicrobial therapy. However, specimen collection is susceptible to contamination by bacteria colonizing the overlying mucosa if rigorous antisepsis is not practiced when obtaining the specimen.

### INTRACRANIAL DEVICE-RELATED FEVER

When a patient with an intracranial device such as an extraventricular drain (EVD) (ventriculostomy catheter) or a ventriculo-peritoneal shunt becomes febrile, cerebrospinal fluid (CSF) should almost always be analyzed. Access to CSF in the patient with an EVD is straightforward. The patient with a shunt or Ommaya reservoir should have the reservoir aspirated. Patients with EVDs who develop stupor or signs of meningitis should have the catheter removed and the tip cultured.

Basic tests of CSF for suspected central nervous system (CNS) infection include cell counts and differential, glucose and protein concentrations, Gram stain, and bacterial cultures. Patients with bacterial meningitis typically have a CSF glucose concentration <35 mg/dL, a CSF-to-blood glucose ratio <0.25, a CSF protein concentration >200 mg/dL, <2,000 total white blood cells/μL, and >1,180 neutrophils/μL (193). Conversely, the presence of a normal opening pressure, <5 white blood cells/μL, and a normal CSF protein concentration essentially exclude meningitis (193). Measurement of CSF lactate concentration may be useful in neurosurgical patients to distinguish infection from postoperative septic meningitis (194,195).

### NONINFECTIOUS CAUSES OF FEVER IN THE INTENSIVE CARE UNIT

#### Postoperative Fever

Fever is common during the initial 72 hours following surgery, and is usually noninfectious in origin (196), presuming that unusual breaks in sterile technique or pulmonary aspiration did not occur. Considerable effort and money can be wasted in overzealous evaluation of early postoperative fever. However, once a patient is more than 96 hours postoperative, fever is more likely to represent infection. A chest radiograph is not mandatory for evaluation of postoperative fever unless respiratory rate, auscultation, abnormal blood gases, or pulmonary secretions suggest a high yield. Afebrile patients are more likely to have had a pneumococcal or influenza A.
Urinary tract infection is common postoperatively in non-trauma patients because of the use of urinary drainage catheters (397). The duration of catheterization increases the risk of bacteriuria by about 5% per day, which in turn increases the risk of nosocomial cystitis or pyelonephritis. A urinalysis or culture is not mandatory to evaluate fever during the initial 3 days postoperatively unless there is reason by history or examination to suspect an infection at this site. After trauma, urinary tract infection is common only after injury to the urinary tract.

Fever can be related to hematoma or infection of the surgical field. Surgical site infection is rare in the first few days after operation, except for group A streptococcal infections and clostridial infections, which can develop within hours to 1 to 3 days after surgery. These causes should be suspected on the basis of inspection of the incision.

Many emergency abdominal operations are performed for control of an infection (e.g., perforated diverticulitis). Even under optimal circumstances (definitive surgical source control and timely administration of appropriate broad-spectrum antibiotics), it may take ≥72 hours for such patients to defervesce. New or persistent fever more than 4 days after surgery should raise suspicion of persistent pathology or a new complication. Thus, it is mandatory to remove the surgical dressing to inspect the incision. Swabbing an open wound or collecting fluid from drains (if present) for culture is rarely helpful because the likelihood of colonization is high. Muscle compression injury (either direct trauma or as a result of compartment syndrome) and tetanus are two rare complications of traumatic wounds that may cause fever. Toxic shock may accompany infection with group A streptococci or S. aureus. Other exceptionally rare causes of postoperative fever include deep venous thrombosis, tissue ischemia or necrosis, pulmonary embolism, adrenal insufficiency, drug-induced fever, anesthesiareduced malignant hyperthermia, and acute allograft rejection.

Drug-related Fever

Any drug can cause fever due to hypersensitivity (198), but “drug fever” is decidedly unusual in surgical patients, and must be considered a diagnosis of exclusion. In addition, some drugs cause fever by producing local inflammation at the site of administration (phebitis, sterile abscesses, or soft tissue reaction), such as amphotericin B, erythromycin, and potassium chloride. Drugs or their delivery systems (diluent, intravenous fluid, or intravascular delivery device) may also contain pyrogens or, rarely, microbial contaminants (199). Some drugs may also stimulate heat production (e.g., thyroxine), limit heat dissipation (e.g., atropine or epinephrine), or alter thermoregulation (e.g., butyrophenone tranquilizers, phenothiazines, antihistamines, or antiparkinson drugs). Among drug categories, drug fever in surgical ICUs is most often attributed to antimicrobial agents (e.g., vancomycin, β-lactams) and anticonvulsants (especially phenytoin).

Two important syndromes, malignant hyperthermia and neuroleptic malignant syndrome, deserve consideration when fever is especially high because the results can be devastating if left untreated (200). Malignant hyperthermia is more often identified in the operating room than in the ICU, but onset can be delayed for as long as 24 hours, especially if the patient is on steroids. Malignant hyperthermia is believed to be a genetically determined response mediated by a dysregulation of cytoplasmic calcium flux in skeletal muscle, resulting in intense muscle contraction, fever, and increased creatinine phosphokinase concentration. However, unlike malignant hyperthermia, the initiator of muscle contraction is central, the syndrome is often less intense, and mortality is less.

Drug withdrawal syndromes may be associated with fever, tachycardia, diaphoresis, and hyperreflexia, including from alcohol, opioids, barbiturates, and benzodiazepines. It is important to recognize that a history of use of these drugs may not be available when the patient is admitted to the ICU. Withdrawal and related fever may therefore occur several hours or days after admission. Other noninfectious causes of fever are listed in Table 106.9.

### Table 106.9: Causes of Fever Related to Noninfectious States

<table>
<thead>
<tr>
<th>Cause</th>
<th>Description</th>
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<tbody>
<tr>
<td>Acute myocardial infarction</td>
<td></td>
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<tr>
<td>Acute respiratory distress syndrome (fibroproliferative phase)</td>
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<tr>
<td>Adrenal insufficiency</td>
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<tr>
<td>Cytokine release syndrome</td>
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<tr>
<td>Fat embolism</td>
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<tr>
<td>Gout</td>
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<tr>
<td>Hematoma</td>
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<tr>
<td>Heterotopic ossification</td>
<td></td>
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<tr>
<td>Immune reconstitution inflammatory syndrome (IRIS)</td>
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<tr>
<td>Intracranial hemorrhage</td>
<td></td>
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<tr>
<td>Pancreatitis</td>
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<tr>
<td>Pericarditis</td>
<td></td>
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<tr>
<td>Pulmonary infarction</td>
<td></td>
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<tr>
<td>Thyroid storm</td>
<td></td>
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<tr>
<td>Transfusion of blood or blood products</td>
<td></td>
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<tr>
<td>Transplant rejection</td>
<td></td>
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<tr>
<td>Tumor lysis syndrome</td>
<td></td>
</tr>
<tr>
<td>Venous thromboembolic disease</td>
<td></td>
</tr>
<tr>
<td>Withdrawal syndromes (drug, alcohol)</td>
<td></td>
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</tbody>
</table>

Infections of the biliary tree are similar to those found elsewhere in the body in that therapy consists of antibiotics directed at the causative pathogens and source control, typically in the form of drainage. Biliary tract infections remain an important cause of critical illness. They are difficult to diagnose in critically ill patients, owing to their relative rarity and the nonspecificity of symptoms that noncommunicative patients may manifest. Unless diagnosed and treated aggressively, organ dysfunction and death may ensue rapidly. Signs and symptoms...
of hepatobiliary infection commonly include abdominal pain, fever, nausea, and vomiting; the clinical presentation may range in severity from the appearance of a chronic disease state to overt septic shock. Leukocytosis is common to all but the patterns of liver enzyme abnormalities overlap to such a degree that it may be difficult to make a definitive diagnosis based on history, physical examination, and laboratory values alone. Furthermore, in the critically ill patient, it may be difficult to distinguish liver dysfunction caused by primary infection from that caused by multiple organ dysfunction syndrome. Imaging of the biliary tree is often of paramount importance in the diagnosis and treatment of biliary tract infections, but ultimately a thorough working knowledge of the differential diagnosis and treatment of biliary tract infections is the key to successful management.

**Acute Cholecystitis**

Among outpatients, acute cholecystitis usually occurs when gallstones migrate into the cystic duct, causing outflow obstruction. This obstruction causes sterile inflammation and edema of the gallbladder wall initially, followed by bacterial superinfection (202). Acute calculous cholecystitis presents with fever, right upper quadrant pain, nausea, and vomiting. Physical examination may range from arrest of inspiration due to tenderness on palpation in the right upper quadrant (Murphy sign) to signs of peritonitis in advanced cases. Concomitant jaundice suggests the presence of choledocholithiasis. Ultrasonography is a rapidly sensitive and specific test (95% and 97%, respectively) for acute cholecystitis and is the initial test of choice. Diagnostic findings include the presence of stones in the gallbladder, thickening of the gallbladder wall (>3.5 mm), pericholecystic fluid, and tenderness with application of the US probe (sonographic Murphy sign) (203). Most cases (~80%) of acute calculous cholecystitis resolve with bowel rest, fluid resuscitation, and intravenous antibiotics, and are treated ultimately by cholecystectomy. Patients who become ill enough to require ICU care generally have progressed to perforation, resulting in either subphrenic abscess or free perforation with bile peritonitis. Gangrene of the gallbladder is associated with a 30% mortality rate and tends to occur in older patients (204). Emphysematous cholecystitis, a severe manifestation of acute cholecystitis that occurs with a predilection for elderly patients and patients with diabetes mellitus, is defined by the presence of gas in the gallbladder wall visualized on US or CT and is characterized by polymicrobial infection including *Clostridium spp.*, E. coli, Klebsiella spp., and Streptococcus spp. Roughly one half of all cases of emphysematous cholecystitis are acalculous (see below); the reported mortality ranges from 15% to 25% (203,206). Acalculous cholecystitis has been reported in all age groups, but most often occurs in the setting of severe illness or injury. It may also occur in the postoperative setting, particularly in males after emergency surgery complicated by large-volume blood loss. One review of 31,710 cases of cardiac surgery found a 0.05% incidence of acalculous cholecystitis (207); after open abdominal aortic aneurysm repair, the incidence has been reported to be between 0.7% and 0.9% (208). Acute acalculous cholecystitis is a grave condition of insidious onset in patients who are often already critically ill, and the mortality approaches 30% (209). Therefore, the diagnosis of acalculous cholecystitis must always be entertained in a patient with sepsis for whom no clear source of infection can be determined.

The pathogenesis of acalculous cholecystitis is most likely splanchic ischemic-reperfusion injury. Critically ill patients probably have this pathophysiology even in the presence of gallstones. Alternatively, bile stasis associated with critical illness may lead to disintegration of the gallbladder, which in combination with hyperperfusion may cause ischemia and ultimately necrosis. Factors such as mechanical ventilation, total parenteral nutrition, cytokine activation, and endotoxemia may also be implicated (210).

The diagnosis of acalculous cholecystitis can be difficult to make in the ICU. Patients who are able to communicate may report abdominal pain localizing to the right upper quadrant or diffuse pain in the case of peritonitis. Fever is usually present. Physical examination may reveal signs ranging from localized tenderness in the right upper quadrant to frank peritonitis. A right upper quadrant abdominal phegmon may be palpable. All too often, the altered mental status that often accompanies critical illness may obscure any useful information that might be obtained from the history and physical examination. Laboratory values are nonspecific but usually include leukocytosis and elevated liver enzymes, particularly of bilirubin, transaminases, and alkaline phosphatase. Hyperbilirubinemia, perhaps representative of the cholestasis of sepsis, is typical and occurs more often in acalculous than calculous cholecystitis.

Ultrasound is perhaps the ideal radiologic study to investigate the diagnosis of acalculous cholecystitis in the ICU. Ultrasound may reveal hyperechoic of the gallbladder, pericholecystic fluid, or gallbladder wall thickening. At a gallbladder wall thickness ≥3.5 mm, US is 98.5% sensitive and 80% specific for the diagnosis of acalculous cholecystitis (211). Ultrasound conveniently can be diagnostically performed on ICU patients by false-positive scans due to fasting, liver disease, or technical sources of intra-abdominal infection. Interpretation of radiouclide biliary scans can be confounded in critically ill patients by false-positive scans due to fasting, liver disease, or parenteral nutrition, which are sufficiently common to diminish its utility in this population.

Upon making the diagnosis of acalculous cholecystitis, a decision about the method of source control must be made and empiric antibiotic therapy must be started. Even though up to one half of cases of acute acalculous cholecystitis are associated with culture-negative bile (at least initially, considering that ischemia-reperfusion is paramount and superinfection is a secondary phenomenon), empiric antibiotics are needed because distinguishing sterile from infected cases can be clinically impossible owing to the massive inflammatory response. The organisms most frequently cultured from the bile in acalculous cholecystitis are *E. coli*, Klebsiella, and Enterococcus faecalis (211).

Source control for cholecystitis, whether calculous or acalculous, has traditionally been by cholecystectomy. However, patients with acalculous cholecystitis are often critically ill and thus poor surgical candidates. Percutaneous cholecystostomy tube placement is a minimally invasive alternative to cholecystectomy that is favored increasingly. In this technique, the gallbladder is punctured through an anterior transhepatic approach under US guidance and a drainage catheter is inserted.
Cholangitis

Cholangitis is an acute infection of the main biliary ductal system. The pathogenesis of cholangitis requires both obstruction and bacterial superinfection. The most common cause of intrinsic obstruction in the Western world is choledocholithiasis (213). Both primary and metastatic malignant disease of the abdominal viscera may cause extrinsic obstruction, among other causes. Obstruction from calculi is more likely to cause cholangitis than malignant obstruction (214). Cholangitis may also occur in the postoperative setting, particularly after a biliary-enteric anastomosis.

Bile is sterile in the normal biliary tree. Bile is naturally bacteriostatic, and antegrade flow of bile from liver to duodenum serves as a flushing mechanism. The sphincter of Oddi is an anatomic barrier, preventing reflux of enteric flora. Bile salts serve to absorb intraluminal endotoxins and may also exhibit a trophic effect on small bowel mucosa, thus helping to prevent bacterial and endotoxin translocation. In the absence of bile flow, normal bacterial ecology is perturbed, leading to bacterial overgrowth and degradation of mucosal defenses. The hepatic reticuloendothelial system serves to filter translocated bacteria and endotoxin and is impaired when the biliary tree is obstructed, further increasing the risk of infection (215). Bacteria may gain access to the biliary tree either via the portal vein or by ascending directly from the duodenum (e.g., bile leak, bleeding) that may precipitate ICU admission. In the hemodynamically stable patient with cholangitis, ERCP should be considered strongly for unstable patients and other cases where intervention is likely to be necessary. Hemodynamic instability in the setting of suspected or confirmed bacterial cholangitis is a true emergency that requires immediate biliary decompression.

Treatment of cholangitis consists of immediate fluid resuscitation and broad-spectrum antibiotics, followed by urgent or emergent biliary decompression. Numerous antibiotic regimens have been successful historically, but many authorities prefer a single broad-spectrum agent such as piperacillin/tazobactam (219) or a carbapenem. The majority of patients respond to initial medical therapy followed by biliary decompression, but 10% to 15% will require emergent decompression (220). ERCP is the safest and most efficacious treatment for acute cholangitis with a success rate of 90% and a mortality rate of 10%, considerably lower than that of emergency surgical intervention. ERCP includes cholecystectomy, choledochotomy, and T-tube placement. Other complications of ERCP include pancreatitis, perforation, aspiration, systemic sepsis, and failure to decompress the biliary tree.

Endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) may be used preferentially for intrahepatic choledocholithiasis, for cholangitis from proximal bile duct stricture or neoplasm, or when ERCP is impossible secondary to surgically altered upper gastrointestinal tract anatomy (e.g., after Roux-en-Y reconstruction) or anatomic anomalies (e.g., ampulla of Vater located within a duodenal diverticulum).

Surgery is now infrequent in the primary management of acute cholangitis. In situations that require surgery (e.g., resectable malignant obstruction), patients may be temporized by ERCP or PTC, converting an emergency operation into an elective procedure that can be performed at lower risk. Surgery is also indicated in patients who fail less invasive treatment methods. Standard emergency surgical therapy includes cholecystectomy, choledochotomy, and T-tube placement.

Imaging of patients with cholangitis is possible using US, CT, or magnetic resonance imaging (MRI). Ultrasound detects cholelithiasis and bile duct dilation reliably, but is only 50% sensitive for detecting choledocholithiasis. Computed tomography detects ductal dilation with 98% accuracy and is superior to US in defining the level of obstruction, but may fail to visualize the 85% of biliary calculi that are radiolucent. Stones can be visualized on MRI; therefore, magnetic resonance cholangiopancreatography (MRCP) provides the most complete imaging as to the etiology of biliary obstruction. However, MRCP is expensive, time consuming, and cumbersome for ICU patients, and does not allow for therapeutic intervention. By contrast, ERCP and PTC are both 90% to 100% sensitive for defining the site and nature of biliary obstruction (218). Either can be used diagnostically or therapeutically to decompress the biliary tree. Both ERCP and PTC have rare potential complications (e.g., bile leak, bleeding) that may precipitate ICU admission. In the hemodynamically stable patient with cholangitis, US is the investigation of first choice, followed by further imaging as needed with CT or MRCP. Because of the potential for intervention, ERCP should be considered strongly for unstable patients and other cases where intervention is likely to be necessary.
Liver Abscess

The most common cause (50% to 65% of liver abscesses) is now ascending biliary tract infection (222) (e.g., cholangitis, direct extension of acute suppurative cholecystitis). Seeding from the portal vein accounts for 10% to 25% of abscesses and is typically a result of intra-abdominal sources of infection such as diverticulitis. Systemic seeding via the hepatic artery occurs in 1% to 5% of cases from processes such as bacterial endocarditis, dental abscesses, or interventions such as hepatic artery chemoembolization, intraoperative cryoablation, or radiofrequency ablation (221). Liver abscess complicates fewer than 1% of blunt liver injuries managed nonoperatively, and is more common in patients requiring damage-control laparotomy and perihepatic packing to control hemorrhage (222).

Patients with pyogenic hepatic abscess usually present with fever and chills, abdominal pain, and weight loss. Nonspecific abdominal complaints and constitutional symptoms are common, and presentation can range from the appearance of a chronic disease state to overt septic shock. The laboratory workup demonstrates leukocytosis in most patients, with liver enzymes being moderately abnormal as well. Due to the protean manifestations of liver abscess and the mimicry of a number of disease processes, radiographic imaging is crucial in confirming the diagnosis. Ultrasound and CT both have greater than 95% sensitivity for the diagnosis. One half of patients will present with more than one abscess, and approximately 75% of all liver abscesses will be found in the right lobe of the liver (223).

Pyogenic liver abscesses are equally likely to be polymicrobial as monomicrobial, and approximately 5% to 27% show no growth in culture. In many cases, failure to speciate bacte- ria in culture may reflect prior antibiotic treatment. The flora found in liver abscesses reflects the underlying source of the infection, but overall the most common Gram-negative aerobes found in pyogenic liver abscesses are E. coli and Klebsiella spp., whereas the most common Gram-positive aerobes are Enteroccocus spp., viridans streptococci, and S. aureus. Among cultured anaerobes, Bacteroides spp. predominate (224).

Historically, medical management of pyogenic liver abscess carried a mortality rate of 60% to 100% (225). Several recent case series demonstrate success rates for antibiotics alone of up to 80% when multiple (miliary) abscesses are too small or too numerous for percutaneous drainage. Although antibiotics are a necessary adjunct to the treatment of hepatic abscess, most authorities agree that this approach is not sufficient except in the case of very small abscesses or in patients in whom interven- tion poses a prohibitive risk. The preferred method of treatment is broad-spectrum antibiotics in conjunction with drainage of all abscesses. Most hepatic abscesses can be drained success- fully by image-guided percutaneous techniques, with a success rate of 70% to 93%. Surgical drainage is indicated in patients who fail percutaneous drainage, who require surgical manage- ment of the underlying problem (e.g., diverticulitis), or who have abscesses that are not amenable to minimally invasive techniques because of their location. Surgical options include simple drainage, debridement, and formal resection. Liver re- section should be considered in those patients with extensive tissue loss or with intrahepatic stones, which may serve as a nidus for recurrent infection.

Most contemporary series quote a mortality rate for hepatic abscess between 6% and 31% (221). Factors associated with a worse prognosis include an underlying diagnosis of malignant disease, multiple abscesses, and a high presenting APACHE II score (226).

Postoperative Infections after Biliary Tract Operations

Perihepatic infections may occur as a result of commonly performed hepatobiliary surgical procedures. Postoperative bile leaks may occur after any operation in which a bile duct is opened (such as hepatectomy, hepaticoenterostomy, hepatic transplant, or cholecystectomy). Leaking bile may induce chemical peritonitis, or cause infection with microbial flora present in or introduced into tissue at the time of operation, or by translocation from the gut, leading to an infected intrahepatic or perihepatic collection known as a biloma. After cholecystectomy, bile leaks occur in up to 1% of pa- tients regardless of the technique used. Bile leakage may occur from the transected cystic duct, the hepatic bed of the gallblad- der, or incidental injury to other portions of the biliary tree dur- ing dissection. Patients with postoperative bile collections may present with right upper quadrant pain, fever, nausea, vomit- ing, or jaundice. Discrimination between sterile bile peritonitis and infection may be difficult without culture of the collect- ion.

Postoperative fluid collections may be imaged with US, CT, or nuclear scintigraphy. The diagnosis of bile leak can also be made by image-guided aspiration of the collection. Nuclear scintigraphy is an excellent screening test for the diagnosis of bile leak, but it is not useful in determining the precise anatomy of the leak. For this reason ERCP is used to determine the anatomy once leakage is documented, with some leaks being amenable to concomitant endoscopic therapy by stent placement.

Treatment of postoperative bile leakage hinges first upon drainage and then definitive treatment of the underlying prob- lem. If the leak originates from the bed of the gallbladder, per- cutaneous drainage alone is indicated. Extravasation from the cystic duct is best managed endoscopically by stent placement with or without sphincterotomy to allow bile to drain preferen- tially through the ampulla of Vater (227). Major duct injuries discovered at ERCP generally require surgical management.

Perihepatic or intra-abdominal abscess complicates 8% to 30% of major liver resections, and is associated with preopera- tive biliary stenting, hepaticoenterostomy, increased operative time, greater extent of resection, and the need for blood trans- fusion (222). Preoperative hyperbilirubinemia as a result of bili- iary obstruction occurs frequently in patients with malignant biliary tract obstruction; such patients are at increased risk for complications of surgical resection (228). However, recent data demonstrate clearly that preoperative stent placement to allevi- ate biliary obstruction leads to increased rates of postoperative infectious complications (229).

Resection of hepatic parenchyma leaves dead space in the abdomen that collects bile and blood and is in proximity to iso- chemic tissue at the resection margin. Bacterial superinfection may occur, leading to the formation of an abscess. Infected bi- lomas are heralded by fever, right upper quadrant pain, leukocy- tosis, and elevated liver enzymes. Imaging modalities for post- hepatectomy abscesses include CT, US, and MRI as discussed in the prior section on pyogenic hepatic abscesses. Cultures re- veal that 50% to 75% of postoperative perihepatic abscesses are polymicrobial, with bacteria of enteric origin (e.g., E. coli,
Enterococcus) predominating (215). Image-guided percutaneous drainage is the treatment of choice where feasible, with reoperation reserved for those patients in whom percutaneous drainage is not possible or unsuccessful.

Despite recent advances in surgical technique and perioperative management, liver transplantation is plagued by complication rates ranging from 24% to 64%. The incidence of bile leak after orthotopic liver transplantation is between 10% and 40%, with the leaks arising most commonly from hepatic resection lines, T-tube sites, and biliary anastomoses (230). Patients may present up to 6 months after transplantation. Computed tomography is used to image the collection, which may be intrahepatic in up to two thirds of cases. Endoscopic retrograde cholangiopancreatography, PTC, or cholangiogram through a per-existing T tube may be used to delineate the origin of the leak. Most collections can be drained percutaneously, and in the event of direct communication with the biliary tree, ERCP can be used to re-establish preferential enteric drainage. Because the blood supply to the biliary tree is provided by the hepatic artery, anastomotic leaks after liver transplantation may occur as a result of ischemia from hepatic artery thrombosis. Therefore, assessment of the patency of the graft hepatic artery must be determined. Whereas some cases of biloma associated with hepatic artery thrombosis may respond to conservative measures, up to two thirds will require retransplantation (231).

**SURGICAL SITE INFECTION**

Surgical site infections are among the most frequently encountered complications in surgical patients regardless of specialty. Local surgical control of the infection remains the crucial aspect of therapy, oftentimes by simply opening and draining the incision in cases of superficial incisional SSI. Infections extending below the superficial fascia (deep incisional SSIs) invariably require formal surgical debridement and open wound care to resolve the infection. Vacuum-assisted closure (VAC) and antimicrobial therapy also improved outcomes, but MDR pathogens may complicate resolution of ostensibly simple infections in the postoperative period (232), especially among patients hospitalized for a period before surgery, particularly if they required antimicrobial therapy.

Surgical site infection remains a clinical diagnosis. Presenting signs and symptoms depend on the depth of infection, typically as early as postoperative day 4 or 5. Clinical signs range from local induration only to the hallmarks of infection (e.g., erythema, edema, tenderness, warm skin, and pain-related immobility), which may manifest before wound drainage. In cases of deep incisional SSIs, tenderness may extend beyond the margin of erythema, and crepitus, cutaneous vesicles, or bullae may be present (233). With ongoing infection, signs of SIRS herald the development of sepsis. If infection involves an intravascular space (organ/space), symptoms specific to that organ system will usually predominate, such as prolonged postoperative ileus, persistent respiratory distress, or altered neurologic status.

Cultures are not mandatory for management of superficial incisional SSIs, particularly if drainage and wound care alone will suffice without antibiotics. In cases of deeper infection or infection that has arisen in the hospital, exudates or infection that has arisen in the hospital, exudates or infection alone will suffice without antibiotics. In cases of deeper infection, tenderness may extend beyond the margins of the incision in cases of superficial incisional SSI. Infections extending below the superficial fascia (deep incisional SSIs) often make it necessary to explore the wound surgically opened wound (as opposed to the already opened wound, which becomes colonized) by the swab method has been shown experimentally to be reliable. Computed tomography and MRI are more sensitive in detecting small amounts of gas in soft tissues than plain radiographs, and CT-guided aspiration or drainage often facilitates treatment, and may serve as definitive source control for an organ/space SSI.

More severe SSIs, especially the dangerous forms of necrotizing soft tissue infection (NSTI), are true emergencies that need immediate surgical attention. Even modest delays can increase patient mortality substantially. Frenschlag et al. showed that mortality increased from 32% to 70% when therapy was delayed more than 24 hours (234). With an established diagnosis of NSTI, immediate and widespread operative debridement is indicated without waiting for precise determination of the causative pathogen or the identification of a specific clinical symptom. These patients often require planned, sequential, repetitive surgical debridement sessions to control the infection.

When faced with a potential SSI, the first steps in management are to remove the appropriate sutures, open and examine the suspicious portion of the incision, and decide about further surgical treatment (235). If the infection is not confined to the skin and superficial underlying subcutaneous tissue, urgent surgical exploration and debridement is essential to obtain local control of the infection, remove necrotic tissue, and restore aerobic conditions to prevent further spread of the infection. Surgical site infection must also be considered the cause of delayed or failed wound healing and prompt the same decisions as described above (235).

Superficial SSIs, which functionally are subcutaneous abscesses, rarely lead to systemic infection and usually do not make patients seriously ill. Antimicrobial therapy is not indicated for patients who do not have systemic signs of infection. Formal surgical intervention is limited to complications such as localized abscesses or necrosis of the skin or underlying tissue. In contrast, deep incisional SSIs typically present with extensive discomfort in more seriously ill patients. These infections extend to superficial fascia or beneath, and may cause extensive tissue necrosis and liquefaction beyond the obvious limits of the cutaneous signs, making it necessary to explore the wound formally in the operating room. The clinician must be alert to the possibility that necrotizing is present. Broad-spectrum antimicrobial therapy should be given empirically to cover likely pathogens, and reassessed following receipt of the microbiology report.

Organ/space SSIs occur within a body cavity, are directly related to a surgical procedure, and may manifest as intra-abdominal, intrapleural, or intracranial infections. They also may remain occult or present with few symptoms, mimicking incisional SSIs and leading to inadequate initial treatment, becoming apparent only when a major complication ensues. The diagnosis of organ/space SSI usually requires some form of imaging to confirm the site and extent of infection. Adequate source control requires a drainage procedure, whether open or percutaneous.

Experimentally, the value of vacuum-assisted wound closure was first appraised by Morykwas et al. in a swine model in 1997 (236). VAC optimizes blood flow, decreases tissue edema, and removes fluid from the wound bed, thereby facilitating the removal of bacteria from the wound. Mechanical deformation of
the wound promotes tissue expansion to cover the defect, and subatmospheric pressure in the milieu may trigger a cascade of intracellular signals that increases the rate of cell division and formation of granulation tissue (237). The clinical value of VAC systems has been described only in small case series and cohort studies, mostly for sternal infections following cardiac surgery, abdominal wall dehiscence, and the management of complex perineal wounds, or as a method to secure skin grafts (218,239). A lack of well-designed randomized, controlled trials precludes more specific recommendations.

PNEUMONIA

The decision to treat pneumonia with an antibiotic is based on clinical suspicion and microscopic examination of Gram-stained sputum, as culture data will not become available for 48 to 72 hours. Choice of agent is based on both individual patient risk factors for infection with MDR organisms and institution-specific susceptibility data. antimicrobial therapy may be withheld safely if the Gram stain reveals no organisms and the patient has no signs of sepsis (164). Clinical signs of infection with a negative sputum Gram stain suggest either an extrapulmonary source of infection or sterile inflammation.

Patients with micro-organisms on Gram stain or clinical instability should receive empiric therapy for VAP pending the results of cultures. The primary concern is the administration of “adequate therapy,” being collectively at least one antimicrobial agent to which the pathogen is sensitive, in the correct dose, via the correct route of administration, and in a timely manner. re-evaluated serially so that therapy is de-escalated to treat only the specific etiologic pathogen, an end point of therapy may be identified prospectively and adhered to, or therapy may be discontinued if cultures are negative and the patient remains stable.

Choice of initial antimicrobial therapy depends not only on patient risk factors, but also on local (ideally, unit-specific) microbiologic data, which increases the likelihood that appropriate empiric therapy will be prescribed (240). In general, a regimen for patients at risk for infection with an MDR organism should provide coverage against MRSA, P. aeruginosa, Acinetobacter spp., and extended-spectrum β-lactamase (ESBL)-producing Klebsiella spp. At least two drugs are usually required, one effective against MRSA (e.g., vancomycin, linezolid) and one effective against MDR Gram-negative bacilli, particularly P. aeruginosa (e.g., piperacillin-tazobactam, meropenem).

Increased mortality is associated with inadequate initial antimicrobial therapy of VAP (241), due to clinical failure and the emergence of MDR bacteria. Appropriate initial dosing is paramount to achieving adequate therapy, for example, of vancomycin (15 mg/kg q12h), aminoglycosides (gentamicin, tobramycin 7 mg/kg daily, amikacin 20 mg/kg daily), and fluoroquinolones (levofloxacin 750 mg daily, ciprofloxacin 400 mg q8h) (all doses assume normal renal function). Abundant data now document an association between fluoroquinolone use and the emergence of VAP caused by MDR pathogens, particularly Pseudomonas (242-244) and MRSA (245). Fluoroquinolone use should be judicious, based on current unit-specific susceptibility data.

Whereas multidrug empiric therapy is necessary to treat patients with suspected VAP until culture results become available, combination therapy of a specific pathogen (e.g., “double-coverage” of Pseudomonas) is unlikely to provide benefit and may worsen outcomes. Neither in vitro nor in vivo synergy of such combination therapy has been demonstrated consistently. A meta-analysis of β-lactam monotherapy versus β-lactam–aminoglycoside combination therapy for immunocompetent patients with sepsis (64 trials, 7,586 patients) found no difference in either mortality (RR 0.90, 95% CI 0.77–1.06) or the development of resistance (246). In fact, clinical failure was more common with combination therapy.

Following initiation of therapy for suspected VAP, lower respiratory tract cultures may reveal either (a) no growth or growth below the predetermined threshold value, (b) significant (above threshold) growth of a “sensitive” pathogen, or (c) significant growth of an MDR pathogen. Under the first scenario, antimicrobial therapy may be discontinued if the patient has not deteriorated (164,247). Under the second scenario, therapy is de-escalated to a narrow-spectrum agent active against the pathogen. In the last scenario, the initial broad-spectrum agent active against the pathogen is continued.

Once pathogen-specific therapy has been initiated, its duration must be determined with the goal of avoiding prolonged and unnecessary administration. Resolution of clinical and radiographic parameters typically lags the eradication of infection (248). Vialaur et al. found that improved oxygenation and normothermia occurred within 3 days in VAP patients without ARDS (156). Dennesen et al. observed a clinical response to therapy (e.g., normalization of temperature, white blood cell count, arterial oxygen saturation, and decreased bacterial count in sputum) within 6 days of therapy of VAP (249). In a randomized, multicenter trial of 401 patients (VAP proved by bronchoscopy and quantitative microbiology) (250) showed an 8-day course (vs. 15 days) of initially appropriate antimicrobial therapy to be effective, provided that the patient is stable and the pathogen is not a nonfermenting Gram-negative bacillus. In select patients i.e., those unlikely to have VAP based on a CPIS ≤6, a 3-day course of therapy may be effective for therapy of VAP (251).

Nonresponders to therapy for VAP pose a dilemma (247). Inadequate therapy, misdiagnosis, or a pneumonia-related complication (e.g., empyema, lung abscess) must be considered. The diagnostic evaluation should be repeated, including quantitative sputum cultures (using a lower diagnostic threshold when interpreting quantitative microbiology given recent antibiotic exposure). Broadened antibiotic coverage should be considered until new data become available.

CATHETER-RELATED BLOODSTREAM INFECTION

The pathogens of CR-BSI are predominantly Gram-positive cocci, most commonly methicillin-related Staphylococcus epidermidis (MRSE), MSSA, and enterococci. Unfortunately, MRSE is both the most common cause of CR-BSI and the most common cause of false-positive blood cultures because of contamination during the collection process. Most authorities consider the isolation of MRSE from a single blood culture to be a contaminant and do not treat, especially if the patient has no indwelling hardware that might become infected
secondarily (e.g., prosthetic joint or heart valve). Gram-negative bacillary pathogens are less common (but seldom are contaminants), and fungal CR-BSIs are less common in surgical patients than medical patients.

Treatment is by catheter removal (for peripheral or percutaneous central venous catheters) and parenteral antibiotics, at least initially. It is unclear whether a positive catheter culture requires therapy beyond catheter removal, absent local signs of infection or a true-positive blood culture. Catheter-related bloodstream infections caused by S. aureus probably require at least 2 weeks of therapy, although some authorities argue for a longer course (4–6 weeks) because of the risk of metastatic infection (e.g., pneumonia, endocarditis). Vancomycin or linezolid may be chosen for MRSA CR-BSI (or MRSE when treatment is indicated), with daptomycin as an alternative. Therapy for enterococcal or Gram-negative CR-BSI is dictated by bacterial susceptibility, with no clear consensus as to duration of therapy. Beyond removal of the catheter, treatment of fungal CR-BSI is controversial; some authorities recommend at least 2 weeks of systemic antifungal therapy.

FIGURE 106.2. Microbiology of community-acquired versus health care-acquired intra-abdominal infections. Results from a study in which peritoneal isolates from 67 patients with postsurgical peritonitis were compared to those of 68 patients with community-acquired peritonitis. A consequence of prior antimicrobial use, the flora of the peritoneum are altered. Whereas pathogens such as Escherichia coli and streptococci are more commonly isolated in cases of community-acquired intra-abdominal infection (CA-IAI), enterococci and Staphylococcus aureus are more prevalent in health care-acquired intra-abdominal infection (HA-IAI). CNS, central nervous system. (Adapted with permission from Nicolau DP, Freeman CD, Beliveau PP, et al. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother. 1995;39:630–635.)

PERITONITIS

Only about 15% of patients with secondary peritonitis are ill enough to require ICU care. Severe secondary peritonitis may follow penetrating intestinal injury that is not recognized or treated promptly (>12-hour delay). Other causes include dehiscence of a bowel anastomosis with leakage and development of an intra-abdominal abscess. Secondary peritonitis is polymicrobial, with anaerobic Gram-negative bacilli (e.g., Bacteroides fragilis) predominating, and E. coli and Klebsiella spp. isolated commonly from community-onset infections. Any of a number of antibiotic regimens of appropriate spectrum may be prescribed. Enterococci, Pseudomonas, and other bacteria may be isolated, but do not require specific therapy if the patient is otherwise healthy (e.g., not immunocompromised) and responding to therapy as prescribed.

When secondary peritonitis develops in a hospitalized patient as a complication of disease or therapy, the flora are more likely to reflect MDRI pathogens encountered in the hospital (252–254), and outcomes are worsened if empiric therapy is not appropriate. For example, enterococci, Enterobacter, and Pseudomonas are more prevalent, whereas E. coli and Klebsiella are less common (Fig. 106.2) (254,255). Antibiotic therapy must be adjusted accordingly, and surgical source control must be achieved. Failure of two source control procedures with persistent intra-abdominal collections is referred to as tertiary peritonitis. Tertiary peritonitis is also characterized by complete failure of intra-abdominal host defenses (256). There is controversy whether tertiary peritonitis is a true invasive infection, or rather peritoneal colonization with incompetent local host defenses, and thus, whether antibiotics should be prescribed and if so, for how long. Bacteria isolated in tertiary peritonitis are avirulent opportunists such as MRSE, enterococci, Pseudomonas, and Candida albicans, supporting the incompetent host defense hypothesis. Some authorities recommend management with an open-abdomen technique, so that
peritoneal toilet can be provided manually (at the bedside in some cases) under sedation or anesthesia, until local host de-
fenses recover. There may be no alternative to open-abdomen management if the infection extends to involve the abdominal wall and extensive debridement is required.

C. difficile-associated disease, formerly pseudomembranous colitis, develops because antibiotic therapy disrupts the balance of colonic flora, allowing the overgrowth of C. difficile, which is present in the fecal flora of about 3% of normal hosts. Any antibiotic can induce this selection pressure, even when given appropriately as surgical prophylaxis, although clindamycin, third-generation cephalosporins, and fluoroquinolones have a predilection (174). Paradoxically, even antibiotics used to treat CDAD (e.g., metronidazole) have been associated with CDAD. C. difficile-associated disease is unquestionably a nosoco-
mal infection. Spores can persist on inanimate surfaces for prolonged periods, and pathogens can be transmitted from pa-
tient to patient by contaminated equipment (e.g., bedpans, rec-
tal thermometers) or on the hands of health care workers. The alcohol gel that is used increasingly for hand disinfection is not active against spores of C. difficile, therefore, hand washing with soap and water is necessary when caring for an infected patient, or generally during outbreaks.

The clinical spectrum of CDAD is wide, ranging from asymptomatic (8% of affected patients do not have diarrhea) to life-threatening transmural pancolitis with perforation and severe sepsis or septic shock. The typical patient will have fever, abdominal distention, copious diarrhea, and leukocyto-
sis. Colon hemorrhage is rare, and if observed should prompt an alternative diagnosis.

Treatment of mild cases consists of withdrawal of the pu-
tative offending antibiotic; oral antibiotic therapy is often pre-
scribed but may or may not be necessary. More severe cases may require parenteral metronidazole or oral or enteral van-
comycin (by gavage or enema, if ileus precludes oral therapy); parenteral vancomycin is ineffective. Some patients with se-
vere disease may require a colostomy, usually a total abdominal colectomy (176). The prevalence of severe disease has increased markedly with the emergence of a new strain of C. difficile. The new strain has undergone a mutation of a gene that suppresses toxin production, such that far more toxin is elaborated, re-
sulting in clinically severe disease (175). More of these patients will require surgery, but it remains to be determined whether or how antibiotic therapy should be modified to combat this dangerous bacterium.

SINUSITIS

Nosocomial sinusitis is a dangerous, closed-space infection that is increasing in incidence, but is difficult to diagnose and there-
fore controversial as to its actual incidence and importance (257).

Sinusitis should be suspected in any patient with sepsis, particularly if initial cultures (e.g., blood, sputum, urine, in-
dwelling vascular catheters) are unrevealing. If sinusitis is sus-
ppected, the diagnosis is confirmed by maxillary antral tap,

lavage, and culture using aseptic technique. Gram-positive cocci, Gram-negative bacilli (including P. aeruginosa), and fungi (incidence, 8%) are possible pathogens, so initial therapy should be based on local susceptibility patterns. Most antibi-
otics achieve adequate tissue penetration. The optimal duration of therapy is unknown, so it is based on the patient’s clinical response. Refractory cases may require repetitive lavage of the sinus, or a formal drainage procedure.

Sinusitis is a predisposing factor for VAP, and may be a source of lower respiratory tract pathogens. There is an 85% con-
cordance between pathogens of sinusitis and pneumonia in pa-
tients who develop VAP subsequently, lending credence to the hypothesis that purulent sinus drainage inoculates the lower airway.

PRINCIPLES OF ANTIBIOTIC THERAPY

Antimicrobial therapy is a mainstay of the treatment of infec-
tions, but widespread overuse and misuse of antibiotics have led to an alarming increase in MDR pathogens. New agents may allow shorter courses of therapy and prophylaxis, which are desirable for cost savings and control of microbial flora. To provide effective therapy with no toxicity requires an under-
standing of the principles of pharmacokinetics (PK).

Pharmacokinetic Principles

Pharmacokinetics is the principles of drug absorption, distri-
bution, and metabolism (258). Dose-response relationships are influenced by dose, dosing interval, and route of administra-
tion. Plasma and tissue drug concentrations are influenced by absorption, distribution, and elimination, which in turn depend on drug metabolism and excretion. The concentrations may or may not correlate, depending on tissue penetration. Relation-
ships between local drug concentration and effect are defined by pharmacodynamic (PD) principles (see below) (258).

Basic concepts of PK include bioavailability, the percentage of drug dose that reaches the systemic circulation. Bioavailabil-
ity is 100% after intravenous administration, but is affected by absorption, intestinal transit time, and the degree of hepatic metabolism after oral administration. Half-life (T½), the time required for the drug concentration to reduce by one half, re-
sults both clearance and volume of distribution (Vd) (258), and is useful to estimate for interpretation of drug concentration data. The proportionality constant Vd is a derived parameter of no particular physiologic significance that is independent of a drug's clearance or T½ is useful for estimating the plasma drug concentration achievable from a given dose. Volume of distri-
bution varies substantially due to physiologic load; reduced Vd causes a higher plasma drug concentration for a given dose, whereas fluid overload and hypoalbuminemia (which decrease drug binding) increase Vd, making dosing more complex.

Clearance refers to the volume of liquid from which drug is elimi-
nated completely per unit of time, whether by tissue distribution, metabolism, or elimination; knowledge of drug clearance is important for determining the dose of drug neces-
sary to maintain a steady-state concentration. Drug elimina-
tion may be by metabolism, excretion, or dialysis. Most drugs are metabolized by the liver to polar compounds for eventual
renal excretion, which may occur by filtration or either active or passive transport. The degree of filtration is determined by molecular size and charge and by the number of functional nephrons. In general, if ≥40% of administered drug or its active metabolites is eliminated unchanged in the urine, decreased renal function will require a dosage adjustment.

**Pharmacodynamic Principles**

Pharmacodynamics (PD) is unique for antibiotic therapy, because drug–patient, drug–microbe, and microbe–patient interactions must be accounted for (258). In contrast to most drug treatments, the key drug interaction is not with the host, but with the microbe. Microbial physiology, inoculum size, microbial growth phase, mechanisms of resistance, the microenvironment (e.g., local pH), and the host’s response are important factors. Because of microbial resistance, mere administration of drug may not be microbicidal. Antibiotic PD parameters determined by laboratory analysis include the minimal inhibitory concentration (MIC), the lowest serum drug concentration that inhibits bacterial growth (MIC₀ refers to 90% inhibition). However, some antibiotics may suppress bacterial growth at subinhibitory concentrations (postantibiotic effect [PAE]). Appreciable PAE can be observed with aminoglycosides and fluoroquinolones for Gram-negative bacteria, and with some β-lactam drugs (notably carbapenems) against S. aureus. However, MIC testing may not detect resistant bacterial subpopulations within the inoculum (e.g., “heteroresistance” of S. aureus) (259, 260). Moreover, in vitro results may be irrelevant if bacteria are inhibited only by drug concentrations that cannot be achieved clinically.

Sophisticated analytic strategies utilize both PK and PD, for example, by determination of the peak serum concentration/MIC ratio, the duration of time that plasma concentration remains above the MIC, and the area of the plasma concentration-time curve above the MIC (the area under the curve [AUC]) (261). Accordingly, aminoglycosides exhibit concentration-dependent killing (262,263), whereas β-lactam agents exhibit efficacy determined by time above the MIC (264). For β-lactam antibiotics with short T₁/₂, it may be efficacious to administer by continuous infusion (265,266). Some agents (e.g., fluoroquinolones) exhibit both properties; bacterial killing increases as drug concentration increases up to a saturation point, after which the effect becomes concentration independent.

**Empiric Antibiotic Therapy**

Empiric antibiotic therapy must be administered carefully. Injudicious therapy could result in undertreatment of established infection, or unnecessary therapy when the patient has only inflammation or bacterial colonization; either may be deleterious. Inappropriate therapy (e.g., delay, therapy misdirected against usual pathogens, failure to treat MDR pathogens) leads unequivocally to increased mortality (141,241,267,268).

Strategies have been promulgated to optimize antibiotic administration, including reliance upon physician prescribing patterns, computerized decision support (269), administration by protocol (140,270–275), and formulary restriction programs. Owing to the increasing prevalence of MDR pathogens, it is crucial for initial empiric antibiotic therapy to be targeted appropriately, administered in sufficient dosage to ensure bacterial killing, narrowed in spectrum (de-escalation) (276) as soon as possible based on microbiology data and clinical response, and continued only as long as necessary. Appropriately antibiotic prescribing not only optimizes patient care, but also supports infection control practice and preserves microbial ecology (277).

**Choice of Antibiotic**

Antibiotic choice is based on several interrelated factors (Table 106.10). Paramount is activity against identified or likely (for empiric therapy) pathogens, presuming infecting and colonizing organisms can be distinguished, and that narrow-spectrum coverage is always desired. Estimation of likely pathogens depends on the disease process believed responsible; whether the infection is community, health care, or hospital acquired; and whether MDR organisms are present. Local knowledge of antimicrobial resistance patterns is essential, even at the unit-specific level. Patient-specific factors of importance include age, debility, immunosuppression, intrinsic organ function, prior allergy or other adverse reaction, and recent antibiotic therapy; institutional factors of importance include guidelines that may specify a particular therapy, formulary availability of specific agents, outbreaks of infections caused by MDR pathogens, and antibiotic control programs.

Numerous agents are available for therapy (Table 106.11) (277–279). Agents may be chosen based on spectrum, whether broad or targeted (e.g., antipseudomonal, antianaerobic), in addition to the above factors. If a nosocomial Gram-positive pathogen is suspected (e.g., wound or surgical site infection, CR-BSI, pneumonia) or MRSA is endemic, empiric vancomycin (or linezolid) is appropriate. Some authorities recommend dual-agent therapy for serious Pseudomonas infections (i.e., an antipseudomonal β-lactam drug plus an aminoglycoside), but evidence of efficacy is lacking (247). It is important to use at least two antibiotics for empiric therapy of any infection that may be caused by either a Gram-positive or Gram-negative infection (e.g., nosocomial pneumonia) (248).

**Antifungal Prophylaxis and Therapy**

The incidence of invasive fungal infections is increasing among critically ill surgical patients. Several conditions are...
TABLE 106.11

ANTIBACTERIAL AGENTS FOR EMPRIC USE

<table>
<thead>
<tr>
<th>CLASS</th>
<th>EXAMPLES</th>
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<tr>
<td>ANTIPSEUDOMONAL</td>
<td>Piperacillin-tazobactam, Ceftolozane-tazobactam, Imipenem, meropenem,</td>
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<tr>
<td></td>
<td>Ciprofloxacin, levofloxacin (depending on local resistance patterns)</td>
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<td></td>
<td>Aminoglycoside</td>
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<tr>
<td>TARGETED SPECTRUM</td>
<td>Gram positive</td>
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<tr>
<td>BROAD SPECTRUM</td>
<td>Piperacillin-tazobactam</td>
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<tr>
<td></td>
<td>Fluoroquinolones</td>
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<tr>
<td></td>
<td>Metronidazole</td>
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<tr>
<td></td>
<td>β-Lactam/β-lactamase combination agents</td>
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</table>

Duration of Therapy

The end point of therapy is largely undefined, in part because quality data are few (140,249–240). If cultures are negative, empiric antibiotic therapy should be stopped in most cases. Unnecessary antibiotic therapy in the absence of infection clearly does increase the risk of MDR infection; therefore, therapy beyond 48 to 72 hours with negative cultures usually is unjustifiable. The morbidity of antibiotic therapy includes allergic reactions, development of nosocomial superinfections (e.g., fungal, enterococcal, and C. difficile infection), total parenteral nutrition, broad-spectrum antibiotic administration, bladder catheterization, azotemia, diarrhea, and coagulopathy or accentuation of warfarin effect.

The morbidity of antibiotic therapy includes allergic reactions, development of nosocomial superinfections (e.g., fungal, enterococcal, and C. difficile infection), total parenteral nutrition, broad-spectrum antibiotic administration, bladder catheterization, azotemia, diarrhea, and coagulopathy or accentuation of warfarin effect.

If bona fide evidence of infection is evident, then treatment is continued as indicated clinically. Some infections can be treated without therapy lasting 5 days or less. Every decision to start antibiotic therapy must be accompanied by a decision regarding the duration of therapy (66). A reason to continue therapy beyond the predetermined end point must be compelling. Bacterial killing is rapid in response to effective agents, but the host response may not subside immediately. Therefore, the clinical response of the patient should not be the sole determinant for continuation of therapy. If a patient still has SIRS at the predetermined end of therapy, it is more useful to stop therapy and watch for new cultures to look for persistent or new infection, resistant pathogens, and noninfectious causes of SIRS. Seldom should antibiotic therapy continue for more than 7 to 10 days. Examples of bacterial infections that require more than 14 days of therapy include tuberculosis of any site, endocarditis, osteomyelitis, and selected cases of brain abscess, liver abscess, lung abscess, postoperative meningitis, and endophthalmitis.

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as prophylaxis for stress ulcer: a randomized controlled trial. Am J Infect

antibiotic prophylaxis for major surgery: a systematic review. Ann N Y Ac-

mechanically ventilated patients receiving antacid, cold/hot food or sucralase
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170.

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119. Chlebicki MP, Safdar N. Topical chlorhexidine for prevention of ventilator-


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APPENDIX A. ABBREVIATIONS

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ARDS</td>
<td>Acute respiratory distress syndrome</td>
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<tr>
<td>AUC</td>
<td>Area under curve</td>
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<tr>
<td>BAL</td>
<td>Bronchoalveolar lavage</td>
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<tr>
<td>CASS</td>
<td>Continuous aspiration of subglottic secretions</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CDAD</td>
<td>Clostridium difficile-associated disease</td>
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<td>CFU</td>
<td>Colony forming units</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure</td>
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<td>CPIS</td>
<td>Clinical pulmonary infection score</td>
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<tr>
<td>CR-BSI</td>
<td>Catheter-related bloodstream infection</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>CSER</td>
<td>Chest radiograph</td>
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<td>DA</td>
<td>Drug allergy</td>
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<td>DEC</td>
<td>Digital endocystoscopy</td>
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<td>EVD</td>
<td>Extraventricular drain</td>
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<tr>
<td>ICU</td>
<td>Intensive care unit</td>
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<td>MDR</td>
<td>Multidrug resistant</td>
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<td>MBC</td>
<td>Minimal inhibitory concentration</td>
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<td>MRCP</td>
<td>Magnetic resonance cholangiopancreatography</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>MRSA</td>
<td>Methicillin-resistant Staphylococcus aureus</td>
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<td>MRSE</td>
<td>Methicillin-resistant S. epidermidis</td>
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<td>NAP1</td>
<td>North American pulse-field gel electrophoresis type 1</td>
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<td>NDDV</td>
<td>Noninvasive positive pressure ventilation</td>
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<td>NNISS</td>
<td>National Nosocomial Infections Surveillance System</td>
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<td>NSTI</td>
<td>Necrotizing soft tissue infection</td>
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<td>OR</td>
<td>Odds ratio</td>
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<td>PAE</td>
<td>Postantibiotic effect</td>
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<tr>
<td>PD</td>
<td>Pharmacodynamic</td>
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<tr>
<td>PICC</td>
<td>Peripherally inserted central catheters</td>
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<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
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<tr>
<td>PNB</td>
<td>Protected specimen brush</td>
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<tr>
<td>PTC</td>
<td>Plugged telescoping catheter</td>
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<tr>
<td>PTC</td>
<td>Percutaneous transhepatic cholangiopancreatography</td>
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<tr>
<td>RR</td>
<td>Relative risk</td>
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<tr>
<td>SCIP</td>
<td>Surgical care improvement project</td>
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<tr>
<td>SDD</td>
<td>Self-decontamination of the digestive tract</td>
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<td>SIRS</td>
<td>Systemic inflammatory response syndrome</td>
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<td>SM</td>
<td>Surgical site infections</td>
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<td>T1</td>
<td>Half-life</td>
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<td>US</td>
<td>Ultrasound</td>
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<td>UTI</td>
<td>Urinary tract infection</td>
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<tr>
<td>VAP</td>
<td>Ventilator-associated pneumonia</td>
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<tr>
<td>VD</td>
<td>Volume of distribution</td>
</tr>
<tr>
<td>VRE</td>
<td>Vancomycin-resistant enterococci</td>
</tr>
<tr>
<td>VAC</td>
<td>Vacuum-assisted closure</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood count</td>
</tr>
</tbody>
</table>