SUPPLEMENT ARTICLE

Anaerobic Infections in the Surgical Patient: Microbial Etiology and Therapy

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Anaerobic infections occur in surgical patients in part because of structural or functional defects in the host that (1) cause a breech in the normal mucosal barriers, (2) create localized vascular insufficiencies, or (3) produce an obstruction. Any or all of these events may compromise the oxidation-reduction potential within the tissues, encouraging rapid anaerobic growth. Although diverse anaerobic populations are spread throughout the gastrointestinal tract, a relatively limited number of organisms are responsible for clinical infection in the surgical patient. Many of these offending organisms express overt virulence factors that enhance microbial adherence, tissue destruction, and, in the case of *Bacteroides fragilis,* facilitate abscess formation. The selection of an appropriate perioperative or therapeutic agent requires a fundamental knowledge of the microbial ecology of this microbial population. The failure to consider the anaerobic flora as a component in the etiology of mixed surgical infections is associated with a high rate of perioperative and therapeutic failures.

Although anaerobic infections in the surgical patient are typically associated with procedures that involve the gastrointestinal tract, virtually any anatomic site can harbor anaerobic growth (figure 1). Unlike nosocomial infections, which involve gram-positive and -negative aerobic/facultative bacteria, anaerobic infections arise from the host's own endogenous flora, provided that appropriate host and environmental factors are present. A 20-year interval, beginning in 1960 and continuing through the 1970s, has been generally viewed as the "golden age" of anaerobic bacteriology, in which the combined efforts of Sutter and Finegold in Los Angeles (Wadsworth VA), Dowell in Atlanta (Centers for Disease Control [CDC]), Holdeman and Moore in Blacksburg, Virginia (Virginia Polytechnic Institute [VPI]), and others were instrumental in expanding our clinical and laboratory knowledge of anaerobic infections [1–3]. The development of selective media and precise laboratory protocols for the recovery and identification of anaerobic bacteria has greatly enhanced our knowledge of their clinical importance. Depending on one's level of training, the Wadsworth, CDC, or VPI methods (or some hybrid thereof) has served as the foundation for the development of specialized anaerobic laboratories within hospitals and academic centers throughout the nation. However, within the present health care environment, the anaerobic work-up has become an endangered species and is often viewed more as an expendable luxury than a clinical necessity in many hospital laboratories.

Although institutional commitments to anaerobic laboratories have waned, the organisms themselves have not diminished in clinical importance; they remain a significant cause of morbidity and mortality in the surgical patient. Even in the era of minimally invasive surgical procedures, entry into a hollow viscus containing luxurious microbial populations is common, and at times these organisms are the nidus for postoperative surgical site infections. The predicted risk of infection is modulated in part by the intrinsic level of microbial contamination that may be encountered during the surgical procedure. Therefore, all surgical pro-

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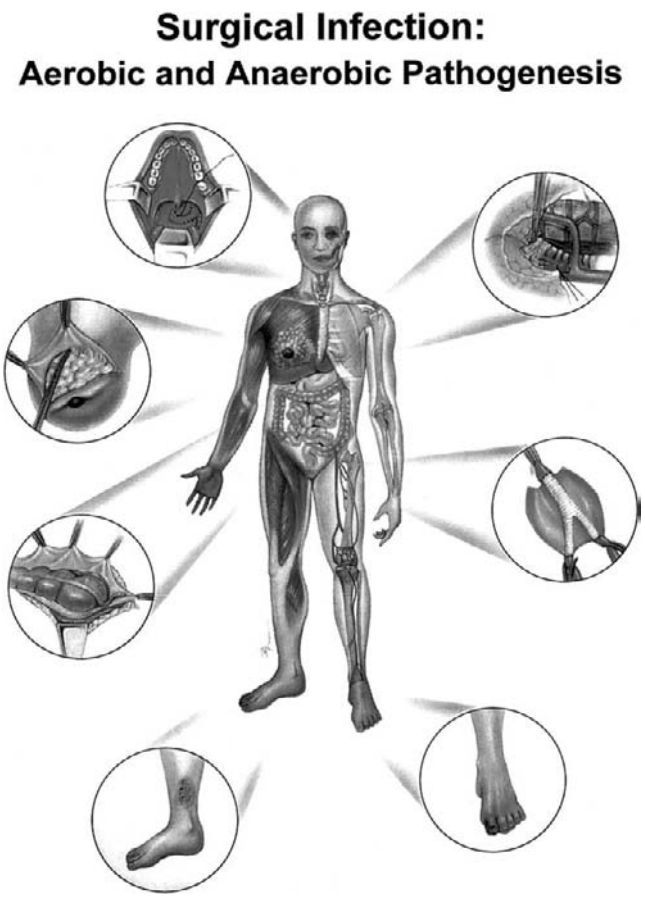

Figure 1. Anaerobic infections may involve a myriad of anatomic locations, including skin and skin structures, superficial incisions, deep incisions, and organ/space surgical sites.

cedures are classified into 1 of 3 categories, clean, clean-contaminated, and contaminated-dirty [4]. Table 1 identifies examples of selected surgical procedures on the basis of this tiered wound classification. Although anaerobic bacteria may be associated with clean-contaminated surgical wounds, cultures from contaminated-dirty surgical cases most frequently yield a mixed polymicrobial flora. As one moves down the gastrointestinal tract, the risk of contamination undergoes a significant qualitative and quantitative change (figure 2). In the proximal bowel, few anaerobic bacteria are recovered in culture, whereas in the terminal reaches of the gastrointestinal tract, anaerobic microbial populations flourish.

Although the surgeon generally links anaerobic recovery with the alimentary tract, soft-tissue infections such as necrotizing fasciitis represent the classical presentation of a polymicrobial infection in which facultative bacteria such as *Streptococcus* or *Staphylococcus* in combination with anaerobes (*Bacteroides* and *Peptostreptococcus*) produce an aggressive and often fatal synergistic disease [5, 6]. A previously unrecognized example of another mixed or polymicrobial infection is the nonpuerperal breast infection. Using fine-needle aspiration, investigators have revealed that these infections harbor an anaerobic flora that outnumbers the facultative populations by a factor of 2:1 [7]. It is evident that, by the use of appropriate sample collection techniques and laboratory work-up, clinically significant anaerobic populations can be recovered from the active site of many infections. Because of the recognized importance of anaerobic bacteria in clinical medicine and surgery, the pharmaceutical industry has continued to develop therapeutic agents whose spectrum includes activity against both aerobic and anaerobic bacteria.

ANAEROBIC BACTERIA IN SELECTED SURGICAL POPULATIONS

Anaerobic infections, with few exceptions, are derived from the host's own endogenous flora. In a nondiseased state, these organisms represent a significant component of the normal flora that inhabits the mucosal surfaces of the gastrointestinal tract, playing a key role in preventing the colonization of exogenous (pathogenic) microbial populations. In addition, the intestinal anaerobes contribute to the relative homeostasis of the host through vitamin K production, deconjugation of bile acids, and other biotransformation processes [8]. In order for these normally commensal microbial populations to produce disease in the host, there must be some structural or functional alteration of their normal ecological habitat. This may occur through disruption of mucosal barriers, obstruction of regional vascular supply, organic or mechanical obstruction of gastrointestinal transit, or other disease processes that compromise the oxidation-reduction potential within the tissues (table 2).

Once the mechanisms that normally prevent anaerobic bacteria from producing disease within their native environment have been compromised, selected anaerobic populations are free to express several well-documented virulence factors. After a penetrating injury to the gastrointestinal tract, anaerobic populations quickly adhere to the serosal mesothelium lining the peritoneal cavity with such tenacity that multiple mechanical lavages will fail to dislodge them from the surface [10]. A second important virulence mechanism, which has a profound impact on the pathogenesis of intra-abdominal infection, is the ability of selected encapsulated strains of *Bacteroides fragilis* to resist clearance from the peritoneal cavity, stimulating a series of cellular events, which leads to an influx of polymorphonuclear leukocytes into the site of infection and eventually promotes abscess formation [11]. A third virulence mechanism that is often exhibited in an anaerobic infection is the elaboration of toxin or enzymes, which causes widespread tissue damage. Several anaerobic bacteria, including *Bacteroides, Clostridium, Fusobacterium,* and selected strains of *Peptostreptococcus,* have demonstrated the ability to produce toxins or enzymes, influencing the pathogenesis of the infection [7, 9].

Table 1. Wound classification of selected surgical procedures.

Wound type	Procedure
Clean site: uninfected operative site in which no inflammation is observed, nor has any mucosal (respiratory, alimentary, genital, or urinary tract) surface been transected. Operations that occur after selected nonpenetrating blunt trauma may also meet these criteria.	Mastectomy, herniorrhaphy, craniotomy, laminectomy, knee prosthesis, spinal fusion, or cardiac surgery (valve replacement or coronary bypass)
Clean-contaminated site: procedures that involve controlled entry into the respiratory, alimentary, genital, or urinary tract, provided there is no evidence of infection.	Gastric bypass; liver, kidney, and pancreas transplantation; abdominal hysterectomy; cholecystectomy; cesarean section; appendectomy (without rupture); colectomy; or open reduction of traumatic fracture
Contaminated-dirty site: any procedure that involves a fresh, accidental wound or operation where there has been a major break in sterile technique or gross spillage of intestinal contents. Many of these procedures may involve the presence of contaminated or infected body fluids such as urine or bile. Operative procedures involving old traumatic wounds, devitalized tissues, a perforated inflammatory tissue, or frank pus may be present intraoperatively.	Appendectomy with rupture, repair of gunshot or knife wound to the abdomen, or any abdominal surgical procedure in the presence of fecal contamination

Although anaerobic bacteria encompass a broad if not diverse microbial population, surgical practitioners have tended to focus on a limited but high-profile group of organisms belonging to 5–8 distinct genera (table 3). Because anaerobic bacteria occupy such a predominant position in the gastrointestinal tract, the typical anaerobic specimen may yield a myriad of anaerobic isolates that include both overt pathogens and innocuous commensal microorganisms [12]. After penetrating trauma to the gastrointestinal tract, contamination of the peritoneal cavity may be widespread, with cultures of lavage fluid yielding a highly pleomorphic microbial population (figure 3) that, under optimal culture conditions, results in the recovery of multiple anaerobic isolates. The mean number of anaerobic species recovered in culture increases as the site of injury and locus of infection progresses down the gastrointestinal tract [13].

Although the gastrointestinal tract is often viewed as the "mother lode" of anaerobic bacteria, the metabolic and physiological derangement that occur in the diabetic patient population places these patients at risk for selected anaerobic infection. The patient with diabetes is often afflicted with vascular occlusive disease, peripheral neuropathy, and a hyperglycemic state that enhances an environment conducive for microbial proliferation. Anaerobic bacteria can be recovered from >87% of diabetes-related foot infections (table 4), with *Bacteroides* and *Peptostreptococcus* representing the predominant anaerobic isolates.

Studies conducted during the 1970s and 1980s revealed that the diabetic foot infection is a classical polymicrobial infection and that conditions within the chronic ischemic tissues favor the growth of obligate anaerobic bacteria, permitting synergistic interactions with facultative bacteria that augment the overall microbial virulence of the infectious process [14–16]. One such anaerobic isolate that often interacts synergistically with facultative bacteria such as *Escherichia coli* or *Enterococcus* is *Peptostreptococcus magnus*. Certain strains have the capability to produce proteolytic enzymes and are associated with rapid and progressive soft-tissue destruction [17, 18].

REDUCING THE ANAEROBIC BURDEN PREOPERATIVELY

During the 1930s, Dr. W. A. Altemeier was the first surgical investigator to emphasize the importance of anaerobic bacteria in mixed, polymicrobial infections involving the gastrointestinal tract [19]. In the years since this sentinel observation was made, numerous investigators have characterized the microbial flora of the gut, identifying those microorganisms that pose a serious risk to patients undergoing surgical procedures that involve the gastrointestinal tract. Preoperative regimens that involve (1) mechanical cleansing of the bowel, (2) administration of oral antibiotics, and (3) the use of parenteral prophylaxis have demonstrated efficacy in reducing the risk of infectious complications in patients undergoing elective colorectal surgical procedures.

The microbial flora of the gastrointestinal tract is complex and includes heterogeneous populations present in both the fecal stream and within the mucin that adheres to the brush-border surface (figure 4) of the intestinal epithelial cell. Preoperative mechanical cleansing regimens include the restriction of dietary intake, enemas, or whole-gut lavage for the purpose of reducing the intraluminal microbial burden within the distal gastrointestinal tract. When mechanical methods are combined with preoperative oral antibiotics such as neomycin and erythromycin base or metronidazole, there is a significant reduction in both the intraluminal and mucosal-associated aerobic and

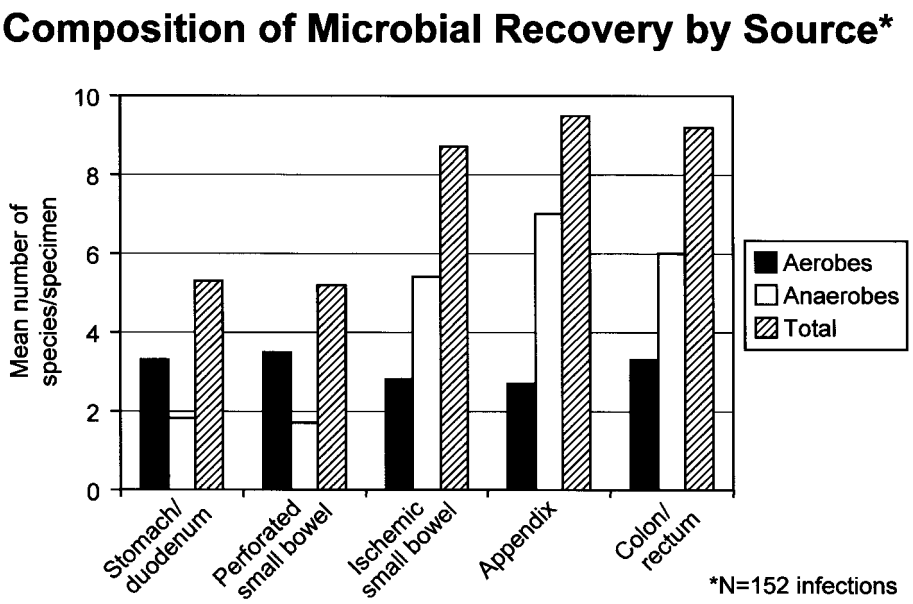

Figure 2. Mean number of anaerobic species recovered per clinical sample from intra-abdominal locus of infection. Adapted from Walker et al. [13]

anaerobic microbial populations [20]. Many surgeons will also include a broad-spectrum parenteral agent that is given 1 h prior to surgery, to provide systemic antimicrobial levels for the duration of surgery [21–23]. As a general rule, if the procedure goes beyond 3–4 h, a second prophylactic is administered. It is debatable whether the combination of oral antibiotic prophylaxis and a parenteral agent is more effective than the oral agent alone; however, the presence of a systemic (parenteral) drug may provide some additional benefit in selected surgical procedures in which the risk of postoperative contamination is high.

The risk of developing a surgical-site infection is dependent on a myriad of host (intrinsic) and operative (extrinsic) risk factors [24]. The delivery of timely and appropriate antibiotic prophylaxis is viewed as an important variable in patients undergoing surgical procedures classified as clean-contaminated, contaminated, or dirty. The use of both mechanical cleansing regimens and perioperative antimicrobial prophylaxis for surgical procedures involving the gastrointestinal tract has been designated by the CDC as a Category 1A recommendation in its *Guidelines for Prevention of Surgical Site Infection, 1999* [4]. This important designation is based on well-designed experimental, clinical, and epidemiological evidence-based studies.

The choice of a prophylactic agent hinges on 3 essential variables: (1) recognition of the potential the site of infection, (2) knowledge of the anticipated microbial flora contaminating the operative site, and (3) a clear understanding of the antimicrobial spectrum and pharmacokinetics of the selected prophylactic agent. The failure to select a prophylactic antibiotic for colorectal surgery that includes anaerobic activity results in surgical wound rates $\geq$20%, compared with rates $\leq$10% when anaerobe-active agents such as cefoxitin, cefotetan, or ampicillin/sulbactam are given for prophylaxis [25–27].

THERAPEUTIC OPTIONS FOR THE TREATMENT OF ANAEROBIC INFECTIONS

The diabetes-related foot infection represents a surgical emergency because the cryptic infection progresses rapidly, extending into the tissue planes of the deep plantar space and proximally into the muscle fascial compartments of the lower leg. Typical surgical treatment involves the debridement of all infected and devitalized tissue, including involved bone, and drainage of the wound in combination with appropriate an-

Table 2. Factors that predispose the development of an anaerobic infection.

Metabolic or immunocompromised disease state
Diabetes mellitus
Neutropenia
Hypogammaglobulinaemia
Solid tumor malignancies
Hematologic malignancies
Cytotoxic or corticosteroid therapy
Alteration in tissue oxidation-reduction potential (redox)
Obstruction and stasis
Tissue anoxia
Trauma to tissues (wounds, bites, or surgery)
Vascular insufficiency
Foreign bodies

NOTE. Adapted from Johnson and Finegold [9].

Table 3. Important anaerobic bacteria encountered in surgery.

Gram-negative microorganisms (rods)
Bacteroides fragilis group
B. fragilis
Bacteroides thetaiotaomicron
Bacteroides distasonis
Bacteroides ovatus
Prevotella and *Prophyromonas*
Prevotella bivia
Prevotella melaninogenicus
Prevotella disiens
Prevotella intermedia
Prophyromonas asaccharolytica
Fusobacterium
Fusobacterium mortiferum
Fusobacterium necrophorum
Fusobacterium nucleatum
Miscellaneous
Bilophilia wadsworthia
Sutterella wadsworthensis
Gram-positive microorganisms
Peptostreptococcus (cocci)
Peptostreptococcus anaerobius
Peptostreptococcus magnus
Peptostreptococcus prevotii
Peptostreptococcus asaccharolyticus
Clostridium (rods)
Clostridium perfringens
Clostridium septicum
Clostridium ramosum
Clostridium histolyticum
Clostridium difficile
Clostridium tetani
Clostridium sordelli
Clostridium novyi
Clostridium innocuum
Clostridium clostridioforme
Actinomyces (branching rods)
Actinomyces israelii
Actinomyces naeslundii
Actinomyces odontolyticus

timicrobial therapy. Although these infections have a truly polymicrobial etiology, involving both aerobes and anaerobes, several selected antibiotic agents with anti-anaerobic activity have been used in the therapy of severe diabetic-related foot infection: these include [28, 29] ampicillin/sulbactam (2 g/1 g iv every 6 h), metronidazole (500 mg iv every 12 h), ticarcillin/clavulanate (3 g/100 mg iv every 8 h), clindamycin (600 mg iv every 8 h), piperacillin/tazobactam (3 g/375 mg iv every 6 h), imipenem/cilastatin (500 mg iv every 6 h), cefoxitin (2 g iv every 6 h), meropenem (0.5–1 g iv every 8 h), and cefotetan (2 g iv every 12 h).

The characterization of therapeutic failure may be confusing when the infection involves a mixed microbial flora with both aerobes and anaerobes. However, some clinical failures have been observed with selected *Bacteroides* species that under in vitro conditions were resistant to the therapeutic agent [30, 31]. However, these data are only available for patients in whom susceptibility studies have been performed, and in most hospital laboratories, anaerobic susceptibility testing is rarely, if ever, performed on a routine basis. The evidence of therapeutic failures in polymicrobial surgical infections related to overt cases of antimicrobial resistance among anaerobic bacteria is presently unknown. Twenty years ago, few, if any, cases of anaerobic antimicrobial resistance were reported in the clinical literature. Recent studies have documented plasmid- and transposon-mediated resistance to many of the traditional anti-anaerobic agents, such as clindamycin, metronidazole, the carbapenems, and anaerobe-active cephalosporins [32]. Although some anti-anaerobic agents have experienced a steady decline in their in vitro activity against *B. fragilis*–group and *Bacteroides* species, other compounds have experienced only a slight decline in activity over time. A report in 1995 reviewed 12 years of in vitro data from intra-abdominal infections based on MIC data and revealed that 96% and 92% of *B. fragilis* and non–*B. fragilis* strains were sensitive to ampicillin/sulbactam and clindamycin, respectively [33]. Two recently published in vitro studies have suggested that the β-lactam–β-lactamase inhibitor agent, ampicillin/sulbactam, continues to exhibit good-to-excellent ac-

Figure 3. Scanning electron micrograph of mixed microbial population recovered from the lavage fluid of a patient with peritonitis. Originial magnification, ×7800.

Table 4. Percentage recovery of anaerobic microbial populations from diabetic foot-related infections: a 15-year experiment in the Department of Surgery, Medical College of Wisconsin.

Anaerobe	% recovered
Gram-positive	
Peptostreptococcus magnus	45–60
Peptostreptococcus anaerobius	15
Peptostreptococcus spp.	25–35
Actinomyces spp.	5
Propionibacterium spp.	<10
Gram-negative	
Bacteroides fragilis	40–50
B. fragilis group	55–65
Prevotella spp.	5–10
Fusobacterium spp.	10–20
Clostridium spp.	8–15
Veillonella spp.	<5

NOTE. Source: Surgical Microbiology Research Laboratory, Department of Surgery, Medical College of Wisconsin. Culture data reflect the period from 1983 to 1998.

tivity against most strains of anaerobic bacteria. In 1 multicenter study, ampicillin/sulbactam demonstrated an in vitro susceptibility of 92% and 87% against *B. fragilis* and non–*B. fragilis* clinical isolates, whereas the in vitro activity of clindamycin against the same strains was 77% and 67%, respectively [34]. In a separate report, 91% of all anaerobic isolates tested against ampicillin/sulbactam, including *Bacteroides distasonis*, *Bacteroides ovatus*, *Bacteroides thetaiotaomicron,* and *Bacteroides ureolyticus–Campylobacter gracilis,* had MIC_{90} values ≤ 4.0 μg/mL [35].

Figure 4. Scanning electron micrograph of aerobic and anaerobic microbial populations colonizing the mucus layer adjacent to the brush-border surface of intestinal (colon) mucosa. Original magnification, ×5700.

The older β-lactam–β-lactamase inhibitor agents appear to have retained much of their in vitro efficacy against anaerobic bacteria compared with the new compounds such as piperacillin-tazobactam [36]. Alternatively, the therapeutic activity of clindamycin appears to have diminished significantly against the genus *Bacteroides.* An intriguing hypothesis for this phenomenon suggests that the MIC values for clindamycin may have decreased within a subset of patients who have multiple or prolonged hospitalizations. The highest level of resistance has been observed among patients with hospital-acquired infections compared with community-acquired infections [37]. Metronidazole continues to maintain a high level of activity against clinically significant anaerobic bacteria, including virtually all gram-negative strains. However, a recent report has suggested that therapeutic failures have occurred because of metronidazole-resistant strains of *B. fragilis* that also exhibit high-level cross-resistance to imipenem, meropenem, piperacillin-tazobactam, clindamycin, and cefoxitin [38]. That report documented a single experience, and further studies are warranted to determine whether these findings are entirely drug-dependent or due to some other unexplained factors. Metronidazole activity against selected gram-positive bacteria is more problematic, with *Actinomyces* and *Proprionibacterium* species exhibiting resistance.

FINAL CONSIDERATION

Our current knowledge and understanding of the etiology, pathogenesis, and treatment of anaerobic infections has come in large part from the extraordinary efforts of Dr. Sidney M. Finegold and a select group of his colleagues, many of whom are cited in the present article. Future studies directed at the elucidation of both the molecular mechanisms of anaerobic pathogenesis and host-microbe interactions in diseases such as intra-abdominal and diabetic foot infection will likely lead to beneficial changes in patient care management and result in improved clinical outcomes in the surgical patient population.

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ERRATA

In the 1 May 2002 issue of the journal, an error appeared in table 1 of the Aging and Infectious Diseases invited article (Shay K. Infectious complications of dental and periodontal diseases in the elderly population. Clin Infect Dis 2002;34: 1215–23). One of the entries under "Possible regimens for patients allergic to penicillins" should have appeared as "Azithromycin or clarithromycin, 500 mg [*not* '2.0 g'] 1 h before the procedure." The corrected version of table 1 appears on the facing page. The author and the journal regret that this error was not corrected prior to publication and appreciate the astute observation of the reader who identified it.

In an article in the supplement to the 1 September 2002 issue of the journal (Edmiston CE Jr, Krepel CJ, Seabrook GR, Jochimsen WG. Anaerobic infections in the surgical patient: microbial etiology and therapy. Clin Infect Dis 2002;35[Suppl 1]: S112–8), an error appeared in column 1 of table 4. The entry "*Clostridium* spp." should have been included under the subhead "Gram-positive" [*not* under the subhead "Gram-negative"]. The authors regret this error.

In an article in the 15 September 2002 issue of the journal (Canet J-J, Juan N, Xercavins M, Freixas N, Garau J. Hospital-acquired pneumococcal bacteremia. Clin Infect Dis 2002;35: 697–702), an error appeared in the Discussion section. The ninth sentence of paragraph 7 should read as follows: "The M phenotype [*not* 'The MLS_b phenotype'] is present in 40%–85% of all macrolide-resistant isolates in the United States.…" The journal regrets this error.

In a letter in the 15 September 2002 issue of the journal (Safdar A, Cross EW, Chaturvedi V, Perlin DS, Armstrong D. Prolonged candidemia in patients with cancer. Clin Infect Dis 2002;35:778–9), the first sentence should read as follows: "We observed 4 cases of prolonged [*not* 'recurrent'] candidemia in patients with neoplastic disease.…" The journal regrets this error.

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Table 1. Recommendations for antibiotic prophylaxis for bacterial endocarditis in patients scheduled to undergo dental procedures.

Cardiac conditions for which prophylaxis is recommended
High risk
Prosthetic heart valves
Previous diagnosis of endocarditis
Complex cyanotic congenital heart disease
Surgically constructed pulmonary shunts or conduits
Moderate risk
Patent ductus arteriosus
Ventricular septal defect
Primum atrial septal defect
Aortic coarctation
Bicuspid aortic valve
Acquired valvular dysfunction (e.g., rheumatic heart disease or collagen vascular disease, such as lupus erythematosus)
Hypertropic cardiomyopathy
Mitral valve prolapse with regurgitation evidenced by audible clicks and murmurs or Doppler-demonstrated mitral insufficiency (this includes myxomatous mitral valve degeneration and exercise-induced mitral insufficiency in men aged >45 years)
Dental procedures before which prophylaxis is recommended
Interligamentary injections
Placement of orthodontic bands, but not brackets
Subgingival periodontal procedures (e.g., scaling or root planing)
Periodontal probing
Tooth extraction
Periodontal surgery
Periapical surgery
Placement of medicated fibers into a periodontal pocket
Dental prophylaxis (unless no bleeding is anticipated)
Dental implant placement and reimplantation of avulsed teeth
Dental procedures before which prophylaxis is not recommended
Suture removal
Restorative dental procedures with or without use of a retraction cord
Intraoral injection of local anesthetic, if not intraligamentary
Endodontic procedures, if not extended beyond the root apex
Impressions
Dental radiography
Placement of a rubber dam
Fluoride treatment
Adjustment of an orthodontic appliance
Recommended regimens
Standard recommendation: amoxicillin, 2.0 g given 1 h before the procedure
Regimen for patients unable to take medications orally: ampicillin sodium, 2.0 g given im or iv before the procedure
Possible regimens for patients allergic to penicillins
Clindamycin, 600 mg given 1 h before the procedure
Cephalexin or cefadroxil, 1.0 g given 1 h before the procedure
Azithromycin or clarithromycin, 500 mg 1 h before the procedure
Other notes
Poor dental hygiene and periodontal or periapical infections produce bacteremia even in the absence of dental procedures, so people at risk should establish and maintain the best possible oral health
Antiseptic mouth rinse applied immediately before dental procedures may reduce magnitude and incidence of bacteremia; agents include 0.12% chlorhexidine gluconate and 10% povidone-iodine
For patients already taking antibiotics, an agent different from the one currently being used should be selected from among those listed above
Status after cardiovascular procedures
There is no evidence that coronary artery bypass graft introduces a risk for endocarditis
"Noncoronary vascular grafts may merit antibiotic prophylaxis for the first 6 months after implantation" [31]

NOTE. Data are from [31].