Which prophylactic regimen for which surgical procedure?

Which Prophylactic Regimen for Which Surgical Procedure?

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For optimal prevention of infection subsequent to a surgical intervention, it is necessary to follow a series of general principles, including the classification of the type of surgical intervention, the characteristics of the antibiotic used, and the route and the time of its administration. Moreover, with reference to the different types of surgery, other factors assume importance: the etiology of the infection and the ability of the antibiotic to achieve adequate levels in the tissues at the beginning of the infective process.

In general abdominal, biliary, and obstetric–gynecologic surgery, which covers many clean-contaminated and contaminated interventions for which antibiotic prophylaxis has been shown to be the most effective, the etiology is often mixed (aerobic and anaerobic flora) with a predominance of gram-negative microorganisms. Thus, an appropriate prophylactic regimen must consider a third-generation cephalosporin, such as cefotaxime, that is effective against most gram-negative bacteria, in particular against *Klebsiella pneumoniae*. Acylureido penicillins can also be used because of their activity against enterococci, gram-positive microorganisms that are also causes of infection in this area of surgical intervention. Combining an antimicrobial such as clindamycin or metronidazole, which are particularly active against anaerobes, may be recommended as well.

In urologic surgery, most infections are caused by Enterobacteriaceae; in addition to the antimicrobial spectrum, the ability of the antibiotic to concentrate adequately in the urine and renal tissue must also be considered. Beta-lactam antibiotics are the agents of choice, in particular, third-generation cephalosporins, aztreonam, and acylureido penicillins.

In cardiac, orthopedic, and partially in neurologic surgery, where most infections are due to gram-positive bacteria (primarily methicillin-resistant staphylococci), antibiotic prophylaxis should include a glycopeptide agent (teicoplanin, vancomycin).

In the field of surgical prophylaxis, more experience has been accumulated with cefotaxime, used as a short-course regimen or as a convenient single dose, than with any other newer cephalosporin. Cefotaxime's broad spectrum of action provides coverage against most potential pathogens and, when used as a single dose, is both convenient and cost-effective.

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In spite of modern aseptic techniques, postsurgical infections remain a serious problem. Although estimates vary considerably, it is generally accepted that 2–5% of clean interventions and >40% of dirty procedures are complicated by infection [*1,2*]. When one considers the number of surgical interventions that take place in modern medicine, the extent of the consequences of postoperative infections can be easily understood.

The value of antibiotic prophylaxis in the prevention of postsurgical infections has been known for >100 years, since Lister performed his first studies. However, later experiences with surgical prophylaxis suffered from methodologic flaws that led investigators to conclude that prophylaxis might not prevent postoperative infections [*3*].

In the early 1960s, several important findings altered our understanding of antimicrobial prophylaxis in surgery. Studies carried out by Burke [*4*] demonstrated that the timing of antibiotic administration was crucial to the outcome. He showed that, prior to bacterial contamination, adequate tissue concentrations of an antibiotic were necessary to achieve maximum benefit. In addition, Chodak and Plaut [5] demonstrated that only 24 of the 131 studies of antibiotic prophylaxis in surgery met their criteria for adequate design. Since then the number and quality of studies have increased significantly. On the basis of these newer studies, it is now generally accepted that antibiotics are unquestionably effective in preventing postoperative wound infections, particularly during clean-contaminated and contaminated procedures.

In this article, we review the general principles involved in the choice and use of antibiotics to prevent a range of postsurgical infections.

CRITERIA FOR SELECTION OF ANTIBIOTICS

Despite the consensus regarding the effectiveness of surgical prophylaxis, a number of issues should be considered. These include: (a) the classification of the type of surgical intervention; (b) the characteristics of the antibiotic; and (c) the route, dose, and time of antibiotic administration.

Classification of the type of surgical intervention: On the basis of the expected degree of bacterial contamination, surgeons and hospital epidemiologists have historically stratified surgical procedures. A widely accepted classification system was presented by the U.S.

National Research Council of Medical Sciences in 1964 [*1*], which is outlined in **Table I**.

Since the use of preoperative antibiotics has become a standard practice in all types of surgery, this classification now has limited practical use. However, it is interesting to note that, with the introduction of routinely administered prophylactic antibiotics, the incidence of postoperative infections has dropped dramatically in all surgical categories (**Table II**) [*1,6*].

Characteristics of the antibiotic: Before prescribing an antibiotic, the surgeon should be familiar with its microbiologic characteristics (i.e., spectrum of activity, susceptibility to inactivating enzymes), pharmacokinetics (i.e., elimination half-life, protein binding, elimination route, tissue diffusion), and clinical behavior (i.e., side effects, interaction with other drugs). Optimal antibiotics should have: (a) a wide spectrum of activity, including both aerobic and anaerobic microorganisms; (b) bactericidal action; (c) high tissue diffusion; and (d) no serious side effects.

Route, dosage, and timing of antibiotic administration: In surgical prophylaxis, the preferred route of administration is the intravenous bolus: this allows high plasma and tissue levels to be obtained a short time after administration. It has been demonstrated that lower plasma peak levels are obtained by intramuscular, intravenous, and oral routes. To administer antibiotics orally, proper functioning of the gastrointestinal tract is essential, but this might be a problem in patients undergoing general abdominal surgery.

As we have seen, the timing of the administration is fundamental. Early studies of the use of antibiotics in surgical prophylaxis failed to show a reduction in infection rates because the antibiotics were administered inappropriately. As early as 1946, Howes [*7*] noted a correlation between the amelioration of infection and the interval from the contamination of the wounds to the administration of the antibiotics. In 1961 Burke demonstrated the crucial relationship between the timing of the administration of an antibiotic and its prophylactic efficacy in the guinea pig [*4*]. In early studies, antibiotics were not usually administered until the patient was in the recovery room, by which time bacterial contamination had already occurred. It is now accepted that in the administration of preoperative antibiotics, care should be taken to ensure that adequate serum and tissue levels are present *during* the surgical procedure.

Considering that wounds can be infected within 3–4 hours from the surgical intervention, single-dose prophylaxis may be considered sufficient when antibiotics with a prolonged half-life are used. For others, it is necessary to administer a second dose 6–8 hours after the first dose and, under certain conditions, even a third dose is necessary after 16 hours (short-term prophylaxis).

Recent data indicate that single-dose administration can be given with antibiotics that do not have a particularly long half-life, for example, cefotaxime (in general abdominal, biliary, and obstetric–gynecologic surgery) and aztreonam (in urologic surgery). Treatments of a long duration are not recommended because they do not improve the efficacy of prophylaxis, they are costly, and they increase bacterial resistance.

TABLE I
Classification of Operative Wounds by Level of Bacterial Contamination [*1*]

- **Clean Wound**
  - Elective, primarily closed and undrained
  - Nontraumatic, uninfected
  - No inflammation encountered
  - No break in technique
  - Respiratory, alimentary, or genitourinary tracts not entered (e.g., varicocelectomy)
- **Clean-contaminated Wound**
  - Nontraumatic
  - Respiratory, alimentary, or genitourinary tracts entered under controlled conditions and without significant spillage (oropharynx or vagina entered, genitourinary or biliary tracts entered in the presence of sterile urine or bile)
  - Minor breaks in technique
  - Mechanical drainage (e.g., appendectomy, adenotonsillectomy)
- **Contaminated Wound**
  - Traumatic, open and fresh
  - Gross spillage from gastrointestinal tract
  - Genitourinary or biliary tracts entered in the presence of infected urine or bile
  - Major breaks in technique
  - Presence of acute nonpurulent inflammation (e.g., cystectomy with preoperative infected urine)
- **Dirty Wound**
  - Traumatic, with retained devitalized tissue, foreign bodies, fecal contamination, delayed treatment, or from a dirty source
  - Perforated viscus encountered
  - Presence of acute purulent inflammation (e.g., bullet wound)

TABLE II
Incidence (%) of Postsurgical Infection With and Without Administration of Prophylactic Antibiotics [*1,6*]

Classification	No	Yes
Clean wound	5.1	0.8
Clean-contaminated wound	10.1	1.3
Contaminated wound	21.9	10.2

Role of cephalosporins in prophylaxis: The third-generation cephalosporins introduced in the 1980s have gained clinical acceptance based on their broad antibacterial spectrum, favorable pharmacokinetics, and low incidence of allergic and other side effects. These cephalosporins have emerged as the drugs of choice for the majority of surgical procedures.

Cefotaxime, as the first third-generation cephalosporin, has a very attractive balance of activity against gram-positive cocci (in particular, *Staphylococcus aureus* and streptococci), gram-negative aerobes (most Enterobacteriaceae and Pseudomonadaceae, *Haemophilus* species, *Neisseria* species) and some anaerobic bacteria. Cefotaxime is among the first drugs to be studied in short-course or single-dose prophylaxis regimens.

The third-generation cephalosporin group of antibiotics has a broad spectrum, a very high intrinsic antibacterial activity, and a good resistance to β-lactamases, a characteristic which the semisynthetic penicillins do not have. Among the cephalosporins, cefotaxime has an active metabolite, desacetylcefotaxime, which is active also against anaerobes, a valuable aspect for single-dose antibiotic prophylaxis. Cefotaxime's one disadvantage is its lack of activity against *Enterococcus faecalis*.

Single-dose cefotaxime obtained the best or comparable results in a number of clinical studies in the field of surgical prophylaxis when compared with single-dose cefoperazone, cefoxitin in five successive doses, cefazolin in four doses, and ticarcillin/clavulanic acid in single dose [*8*].

Antibiotic prophylaxis by type of procedure: Presented in this section are the uses of antibiotics in the following major surgical categories: (a) abdominal surgery, including obstetric–gynecologic and biliary surgery; (b) urologic surgery; (c) neurosurgery and cardiac surgery; and (d) orthopedic surgery.

ABDOMINAL SURGERY, INCLUDING OBSTETRIC–GYNECOLOGIC AND BILIARY SURGERY: Antibiotic prophylaxis for abdominal procedures has been used since antibiotics became available in the 1940s [*9*]. Since these early studies, numerous investigations have attempted to define the optimal antibiotic, number of doses, risk factors, and cost-effectiveness of prophylaxis in this field of surgery.

In terms of microbiology, infections are predominantly the result of gram-negative aerobes, mainly *Escherichia coli*, but a significant role (except in biliary surgery) is also the result of anaerobic microorganisms, particularly the *Bacteroides* species.

Cefotaxime's broad spectrum and high bactericidal activity against gram-negative anaerobes plus the activity of its metabolite, desacetylcefotaxime (which is active against gram-negative anaerobes in general and *Bacteroides fragilis* in particular) make cefotaxime ideally suited for use in prophylaxis in this area of surgical intervention. In a study including patients undergoing general abdominal, biliary, and obstetric–gynecologic procedures, single-dose cefotaxime was as effective as single-dose cefoperazone and ticarcillin/clavulanic acid or multiple-dose cefoxitin and cefazolin [*8*]. Regarding biliary surgery, the lower concentration of cefotaxime in bile is compensated by its broad spectrum and high intrinsic antibacterial activity.

UROLOGIC SURGERY: One of the earliest attempts to use antibiotic prophylaxis during a urologic procedure was in 1938 [*10*]. Since then numerous trials have been carried out, most with conflicting results. Many trials have attempted to define the risk factors that predispose a patient to postoperative infection. These include: (a) duration, extent, and type of surgery; (b) duration of catheterization; (c) presence of neurogenic bladder or serious underlying diseases; and (d) treatment with immunosuppressive agents [*11*].

The most commonly isolated pathogens are Enterobacteriaceae (in particular *E. coli*, but also *Proteus*, and bacilli of the *Klebsiella–Enterobacter–Serratia* group) and Pseudomonadaceae. A much less frequent cause of infection are from gram-positive cocci, mainly staphylococci and enterococci.

Early studies suggested that multiple-dose regimens favored the development of resistant strains [*12*]. This phenomenon is less likely to occur with short-term or single-dose prophylaxis with a β-lactam antibiotic.

As previously discussed, single-dose antibiotic prophylaxis with a third-generation cephalosporin, such as cefotaxime, is effective. Two studies with aztreonam (active only against gram-negative bacilli) have shown that this antibiotic is also effective in preventing infection following urologic surgery; and like cefotaxime it is effective in a single-dose regimen, with both antibiotics having good tolerability profiles [*13,14*].

NEUROLOGIC SURGERY AND CARDIAC SURGERY: The search for optimal antibiotic prophylactic regimens for neurologic surgery has been intense because wound infection after surgery may be associated with severe processes (meningitis, cerebritis, or brain abscess). On the other hand, antibiotic prophylaxis in cardiac surgery has become a controversial issue only since open-heart procedures increased infection (mainly endocarditis) rates from 3.5% to 22% [*15*].

Postoperative infections in both fields of surgery are caused predominantly by gram-positive microorganisms. In a review of many well-conducted studies in neurologic surgery, *S. aureus* accounted for 49%, *Staphylococcus epidermidis* for 28% of the isolates, and the remainder were gram-negative bacilli (8%) and mixed infections, including anaerobes [*16*]. An important cause of infection in cardiac surgery is methicillin-resistant *S. epidermidis* [*17*].

Given the almost exclusively monomorphic etiology of infection in these procedures, glycopeptide agents appear to be suitable for prophylaxis. The most recent of these, teicoplanin, is of particular interest because it is less toxic and can be administered in a single-dose regimen.

In neurologic procedures, where the etiology is slightly more varied than in cardiac surgery, a third-generation cephalosporin, such as cefotaxime, which crosses the blood–brain barrier and reaches effective concentrations in the cerebrospinal fluid, would be appropriate as well.

Orthopedic surgery: The use of antibiotic prophylaxis in orthopedic surgery also has been the cause of much controversy and debate since Jensen *et al* [*18*] in 1939 demonstrated that the use of topical sulfonamides reduced the incidence of postoperative wound infection from 27% to 5% after reduction of open fractures.

The most important microorganisms in the etiology of orthopedic infections are staphylococci (mainly, *S. aureus*), which are responsible for approximately 90% of cases; the remainder can be attributed to gram-negative rods.

There is evidence from controlled studies that antibi-

otic prophylaxis is valuable during orthopedic surgery involving reduction of open fractures and the insertion of hardware. In addition, both short- and long-term regimens have been shown to be equally effective. In particular, a recent study with the administration of single-dose teicoplanin in prosthetic joint implantation surgery showed encouraging results in preventing post-surgical infections [*19*]. Single-dose prophylaxis with glycopeptides appears to be the best choice.

For short orthopedic surgical procedures in selected cases, an alternative would also favor the use of cefotaxime. Jones *et al* [*8*] reported that single-dose cefotaxime was at least as effective as single-dose cefoperazone and ticarcillin/clavulanic acid or multiple-dose cefoxitin and cefazolin. Single-dose prophylaxis with cefotaxime appears to be effective for short orthopedic surgical procedures, which has obvious benefits in reducing costs.

CONCLUSION

From the data presented, it can be concluded that antibiotic prophylaxis is effective in minimizing perioperative infectious morbidity and associated costs. In our opinion, with regard to procedures where gram-positive microorganisms (primarily staphylococci) are prevalent, antimicrobial prophylaxis should include a glycopeptide agent.

For the majority of surgical procedures, particularly in general abdominal, biliary, obstetric–gynecologic and urologic surgery, and only partly in orthopedic surgery, third-generation cephalosporins have emerged as the drugs of choice. This is based on their broad antibacterial spectrum, favorable pharmacokinetics, and low incidence of allergic and other side effects. As the first third-generation cephalosporin, single-dose cefotaxime has been shown to be effective, has a good tolerability profile, has a low emergence of bacterial resistance, and is cost-effective.

REFERENCES

1. U.S. National Research Council of Medical Sciences, Ad Hoc Committee of the Committee of Trauma. Postoperative wound infections: the influence of ultraviolet irradiation of the operating room and various other factors. Ann Surg 1964; 160 (Suppl 2): 1–132.
2. Cruse PJE, Foord R. The epidemiology of wound infection: a 10-year prospective study of 62,939 wounds. Surg Clin North Am 1980; 60: 27–40.
3. Kaiser AB. Antimicrobial prophylaxis in surgery. N Engl J Med 1986; 315: 1129–38.
4. Burke JF. The effective period of preventing antibiotic action in experimental incisions and dermal lesions. Surgery 1961; 50: 161–8.
5. Chodak GW, Plaut ME. Use of systemic antibiotics for prophylaxis in surgery: a critical review. Arch Surg 1977; 112: 326–34.
6. Olson M, O'Connor M, Schwartz ML. Surgical wound infections: a 5-year prospective study of 20,193 wounds at the Minneapolis VA Medical Center. Ann Surg 1984; 199: 253–9.
7. Howes EL. Prevention of wound infection by the injection of nontoxic antibacterial substances. Ann Surg 1946; 124: 268–76.
8. Jones RN, Slepack JM, Wojeski WV. Cefotaxime single-dose surgical prophylaxis in a orthopedic group practice: comparison with other cephalosporins and ticarcillin/clavulanic acid. Drugs 1988; 35 (Suppl 2): 116–23.
9. Richards WR. An evaluation of the local use of sulfonamide drugs in certain gynecological operations. Am J Obstet Gynecol 1943; 46: 541–5.
10. Gaudin HJ, Zide HA, Thompson GJ. Use of sulfanilamide after transurethral prostatectomy. JAMA 1938; 110: 1887–90.
11. Conte JE Jr. Antibiotic prophylaxis: non-abdominal surgery. Curr Clin Top Infect Dis 1989; 10: 254–305.
12. Plorde JJ, Kennedy RP, Bourne HH, Ansell JS, Petersdorf RG. Course and prognosis of prostatectomy with a note on the incidence of bacteremia and effectiveness of chemoprophylaxis. N Engl J Med 1965; 272: 269–77.
13. Cortecchia V, Randone D, Corti G, *et al.* Profilassi antibiotica con aztreonam nel paziente cateterizzato dopo interventi chirurgici urologici. Farm Ter (Int J Drugs Ther) 1991; 8 (Suppl 4): 189–93.
14. Cortecchia V, Randone D, Corti G, *et al.* Profilassi antibiotica con aztreonam nel paziente sottoposto a manovre strumentali urologiche. Farm Ter (Int J Drugs Ther) 1991; 8 (Suppl 4): 194–8.
15. Kittle CF, Reed WA. Antibiotics and extracorporeal circulation. J Thorac Cardiovasc Surg 1961; 41: 34–48.
16. Dempsey R, Rapp RP, Young B, Johnston S, Tibbs P. Prophylactic parenteral antibiotics in clean neurosurgical procedures: a review. J Neurosurg 1988; 69: 52–7.
17. Archer GL, Tenenbaum M. Antibiotic-resistant *Staphylococcus epidermidis* in patients undergoing cardiac surgery. Antimicrob Agents Chemother 1980; 17: 269–72.
18. Jensen NK, Johnsrud LW, Nelson MC. The local implantation of sulfanilamide in compound fractures. Surgery 1939; 6: 1–12.
19. Mollan RAB, Haddock M, Webb CW. Teicoplanin vs cephamandole for antimicrobial prophylaxis in prosthetic joint implant surgery. Proceedings of the 17th International Congress of Chemotherapy, Berlin, June 23–28, 1991. Munich: Futuramed-Verlag, 1991; (Abstract 548).