REVIEW ARTICLE

Antimicrobial prophylaxis in peripheral vascular surgery: is cephalosporin still the gold standard?

Eduardo Lichtenfels[I]; Márcio L. Lucas[II]; Ronaldo Webster[III]; Pedro A. d'Azevedo[IV]

[I]Vascular surgeon, Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA), Porto Alegre, RS, Brazil. Graduate student, Program of Pathology, Fundação Faculdade Federal de Ciências Médicas de Porto Alegre (FFFCMPA), Porto Alegre, RS, Brazil.

[II]Vascular surgeon, ISCMPA, Porto Alegre, RS, Brazil. Graduate student, Program of Hepatology, FFFCMPA, Porto Alegre, RS, Brazil.

[III]Plastic surgeon, ISCMPA, Porto Alegre, RS, Brazil. Graduate student, Program of Pathology, FFFCMPA, Porto Alegre, RS, Brazil.

[IV]Associate professor, Microbiology, FFFCMPA, Porto Alegre, RS, Brazil. PhD. Professor, Graduate Program in Pathology, FFFCMPA, Porto Alegre, RS, Brazil.

Correspondence

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ABSTRACT

In peripheral vascular surgery, cephalosporins are nowadays regarded as the first choice for operative antibiotic prophylaxis. We have recently observed changes in colonizing patterns, pathogen prevalence and antibiotic susceptibility to antimicrobials. Multiresistant pathogens are becoming more frequent in vascular surgical wound infections, showing regional and local variations as to prophylactic antibiotic susceptibility. Data from the available literature so far have shown no strong evidence for a change in routine surgical antibiotic prophylaxis. We must consider regional and institutional prevalence of pathogen resistance and patterns of antibiotic susceptibility to establish specific guidelines for the use of alternative antibiotics.

Keywords: Antibiotic prophylaxis, surgical wound infection, vascular surgical procedures, surgery.

RESUMO

Nas cirurgias vasculares periféricas, as cefalosporinas têm seu uso consagrado como agente antimicrobiano profilático de escolha. Recentemente, observamos uma mudança nos padrões de colonização, prevalência de patógenos e suscetibilidade geral aos antimicrobianos. Os patógenos

multirresistentes vêm se tornando cada vez mais freqüentes nas infecções de ferida cirúrgica vascular, demonstrando variações regionais e locais quanto à suscetibilidade aos antimicrobianos profiláticos utilizados na rotina cirúrgica. Os dados e a literatura disponível até o momento demonstram que não existe evidência suficiente para uma mudança na rotina profilática perioperatória. Entretanto, devemos levar em consideração os padrões regionais e institucionais de prevalência de patógenos resistentes e padrões de suscetibilidade aos antimicrobianos para estabelecer guias e orientações específicas para a utilização de antimicrobianos profiláticos alternativos.

Palavras-chave: Antibioticoprofilaxia, infecção da ferida operatória, procedimentos cirúrgicos vasculares, cirurgia.

History

Postoperative surgical infections, until the mid-19th century, were the great obstacle to the progress and development of surgery. After the discovery of antiseptics in 1867 by Joseph Lister, surgery experienced its great evolution. Associated with other historical figures and new discoveries, infection rates fell from 90 to 10% until the late 19th century.[1-3]

Postoperative surgical wound infection is considered the main avoidable cause of morbidity and mortality in patients submitted to surgery,[4] accounting for 25% of all infections acquired at hospitals.[5] Despite advances in antiseptics (sterile material, antiseptic solutions, hand washing) in preoperative antimicrobial prophylaxis and in perioperative cares, postoperative surgical infection is still a reason for concern, being responsible for high morbidity and mortality rates and significant costs. The estimated cost per patients with infection is US$ 2.100, generating annual expenses of US$ 4.5 billion[5] in the USA. Introduction of antimicrobials in preoperative prophylaxis brought hope of reduction in infection rates in surgical patients, especially severe infections.[2,3] However, there is currently an increase in cases of severe hospital infections and a growing number of incidence of antimicrobial-resistant pathogens.

Physiopathology

Postoperative surgical infections always occur when the combination of microorganism number and virulence in the surgical wound is large enough to beat local defense mechanism in the host and establish an invasion of tissues.[1,2] A study in the 1960's identified that practically all surgical wounds have, at least, a small number of bacteria, but few develop infection.[6]

Surgical wound infection rates published in the literature are, respectively, 1.5-2.9% for clean wounds; 2.8-7.7% for clean and contaminated wounds; 6.4-15.2% for contaminated wounds; and 7.1-40% for dirty wounds.[7,8]

The main factors involved in the development of surgical wound infection are bacterial, wound and the patient's own factors. Bacterial deposition and growth are requirements for infection, as well as type of pathogen and toxins produced by it. Many pathogens have specific components that increase their virulence: *Klebsiella* spp and *Streptococcus pneumoniae* capsules, endotoxins of gram-negative bacteria, streptococci exotocins, *Staphylococcus aureus* and *Staphylococcus*

epidermidis biolfims. Several studies on surgical wounds demonstrated that, in healthy patients, it is necessary to have a contamination with a number higher than 10^5 bacteria to have infection at a given frequency. Local factors include surgical material, surgical technique, graft implantation, hematomas, dead space and wound care. Factors associated with the patient are all systemic alterations that can influence the surgical wound. Among them are age, reduced blood flow to the wound., hypothermia, uremia, corticosteroid, neoplasms and trauma.[1-3,8-11]

Classification of surgical wounds

Classification of surgical wounds according to risk of infection:

-Clean wound: reduced potential of infection; no opening of hollow viscera or infraction of aseptic technique; risk of infection between 1.5-2.9% (example: arterial vascular surgery).

-Clean-contaminated wound: opening of hollow viscera, with minimal content extravasation or small technical infractions; risk of infection between 2.8-7.7% (example: cholecystectomy).

-Contaminated wound: opening of hollow viscera with gross content extravasation; acute inflammation without pus, gross infractions in aseptic technique and traumatic lesions with less than 6 hours; risk of infection is between 6.4-15.2% (example: colectomy).

-Dirty/infected wound: presence of pus, perforated hollow viscera and traumatic lesions with more than 6 hours of evolution; risk of infection is between 7.1-40% (example: abscess draining).[7,8]

Prophylactic methods

The four basic principles of prophylaxis for surgical wound infections are patient's preoperative preparation, surgical technique, perioperative antimicrobial prophylaxis and postoperative care with the surgical wound.[5] Surgical antimicrobial prophylaxis is currently accepted as routine in surgical practice in clean-contaminated surgeries, as well as in some clean surgeries. In contaminated and dirty wounds, antimicrobials are always therapeutic, and not prophylactic.[4] Surgical antimicrobial prophylaxis should obey the principles and indications established to be successful; otherwise, development of multi-resistant pathogens that are not susceptible to usual antimicrobials will be the natural course. Indication of prophylactic antimicrobials in simple and clean surgeries occurs only in special cases, as in surgeries requiring grafts and synthetic material. Due to a low risk of infection, around 1%, the potential to reduce this low rate does not justify expenses and collateral effects of their administration.[1,12]

Antimicrobial prophylaxis is more efficacious when started in the preoperative period and maintained during the surgery, with the aim of maintaining therapeutic blood levels during the whole procedure. In most procedures, antimicrobials should be intravenously administered immediately before the surgery, at anesthetic induction. It is not necessary and harmful to administer it 1 hour after the surgery, as well as maintaining it after the surgery is over. Single dose is the standard prophylaxis, but it is dependent on the antimicrobial. In long surgeries, the dose of prophylactic antimicrobials should be repeated at intervals of one to two half-lives of the chosen agent. Administration for more than 12 hours is hardly ever indicated. Prophylactic agents administered some hours after contamination are much less effective, and started after the surgery is over are totally useless.[1-3]

Antimicrobial prophylaxis: current status

Recent studies have suggested that the actual incidence of postoperative infections after clean surgeries without use of grafts is larger than that reported in the literature. It is estimated that more than 50% of complications occur after the patient is discharged, which are underdiagnosed.[13-15] Such cases do not affect hospital institutions, but affect the community and the health system. Other studies showed that patients submitted to clean procedures using prophylactic antimicrobials had lower postoperative infection rates.[16-19]

There are many antimicrobials used as prophylaxis in surgical infections, and it is important to observe the pathogens likely to cause postoperative infection and determine whether there will be penetration of parts of the organism carrying anaerobic bacteria, especially intestinal (*bacteroid species*). The drug of choice in surgeries in which there is no contact with contaminated sites by anaerobic bacteria is cefazolin (first-generation cephalosporin), which aims at covering especially staphylococci, the main agents causing infections in noncavitary surgeries.[20,21] Some authors report that some second-generation cephalosporins (cefuroxime, for example) could be more effective in the treatment of methicillin-sensitive staphylococci, both *in vitro*[22] and in clinical practice,[23] but they have a significantly higher cost.[5] In cases in which there is contact with intestinal flora, an antimicrobial drug with activity against gram-negative and anaerobic bacteria should be associated (aztreonam and aminoglycosides). Gynecological and obstetrical, biliary and gastroduodenal surgeries, which have specific flora (Table 1), are benefited from antimicrobials alternative to cefazolin, such as, for example, cefoxitin, piperacillin, ampicillin/sulbactam and amoxicillin/clavulanate.[20] In cases of allergy to beta-lactams, erythromycin, clindamycin or vancomycin can be used, and the latter should be reserved, whenever possible, for the treatment of methicillin-resistant *Staphylococcus aureus* .[1]

Table 1 - Type of surgery and most frequent pathogens*

Type of surgery	Most frequent pathogens
Clean	Staphylococci
Cardiovascular with graft	*Staphylococcus aureus, coagulase-negative* Staphylococcus
Biliopancreatic	Gram-negative, anaerobic bacilli, enterococci
Colorectal	Gram-negative bacilli, *Bacteroides fragilis, Escherichia coli*, Bacteroides*species*, enterococci
Gynecological/obstetrical	*Escherichia coli*, Bacteroides*species*, enterococci
Head and neck	*Staphylococcus*, oropharyngeal anaerobic bacteria

* Adapted from Lalla.[4]

Nowadays, 1/3 of all prescriptions for antimicrobials for outpatients are unnecessary. A study carried out in Turkey showed that in 23% of patients the antimicrobials were being incorrectly used.[24] A review including 44 hospitals in New York, USA, showed that 44 different types of antimicrobials were used in preoperative prophylaxis and, despite being used in 81-94% of patients, 27-54% were administered at the wrong moment.[5]

Antimicrobial resistance

Due to the occurrence of multi-resistant pathogens, general reduction in susceptibility to

antimicrobials and change in profile of community and hospital colonizing pathogens, the most important question currently is whether the classical antimicrobials, used with surgical prophylaxis, are still the gold standard to prevent postoperative surgical infections, especially when compared to vancomycin and teicoplanin. The American Center for Disease Control and Prevention (CDC) does not indicate routine use of vancomycin as antimicrobial prophylaxis for any type of surgical procedure.[21] Certainly there are exceptions, especially in cases in which the hospital or institution has rates higher than 20% of postoperative infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA).[25] In these cases, surgical antimicrobial prophylaxis should be carried out with the use of vancomycin or teicoplanin.

Nowadays, with execution of increasingly more complex and prolonged procedures, transplantation in immunodepressed patients, surgeries in patients with multiple comorbidities and surgeries with implantation of prosthetic material, preoperative antimicrobial prophylaxis aiming at protection against resistant pathogens has become a challenge.

Main antimicrobial drugs used in prophylaxis

First-generation cephalosporins

Cefazolin is a first-generation cephalosporin with short half-life and parenteral administration that is part of the family of beta-lactam antibiotics. It primarily acts by inhibiting one step in the synthesis of the bacterial cell wall (transpeptidation), which results in spontaneous bacterial cell lysis. The most important resistance mechanisms are production of beta-lactamases, which cause hydrolysis of the beta-lactam ring, genetic change in penicillin-binding proteins (PBP), bacterial receptors for beta-lactam drugs. The most common adverse effects are hypersensitivity, gastrointestinal discomfort and development of bacterial resistance.[26,27]

The concept of perioperative prophylaxis was introduced in the 1960's, revolutionizing the criteria of antimicrobial treatment existing so far. Such method allowed reduction in phenomena of perioperative sepsis and in the high cost of hospital treatment due to infectious complications. At that time, advantages regarding cost-benefit ratio of using cefazolin were demonstrated. Prospective clinical assessment showed that antimicrobial prophylaxis using 1 g of intravenous cefazolin in a single dose before the surgery was efficacious in reducing infection levels in surgeries that had infectious complications in a rate higher than 7%.[28-30] Nowadays, the practice of using antimicrobial drugs prophylactically is widespread, being present in more than 90% of surgical procedures.[31]

Antimicrobial prophylaxis is indicated in clean and clean-contaminated procedures, preferentially using only one type of antimicrobial drug, administering the drug of choice in the preoperative period.[32]

A multi-centered study was performed to detect how much time was necessary to obtain an efficient perioperative prophylaxis using cefazolin. The efficacy of a single dose of prophylaxis was compared with other combinations of multiple doses. A total of 527 patients was treated for skin neoplasms and in areas likely to be contaminated. Groups were divided into: A) no prophylaxis; B) cefazolin 1 g, every 12 hours, starting 48 hours before the surgery and continued for 48 hours after the surgery; C) cefazolin 1 g, every 12 hours, intramuscular and starting 2 hours before the surgery and continued for 24 hours after the surgery; and D) intramuscular cefazolin, 1 g at a single dose, 2 hours before the surgery. Rate of postoperative infections was 12% in group A; 4.6% in group B; 0.77% in group C; and 2.96% in group D. The study confirmed the usefulness of antimicrobial prophylaxis to prevent postoperative infections and showed that short regimes are better than longer ones. In particular, a single dose of antimicrobial drug significantly reduced

infection rate, being cheaper and better tolerated by patients.[33] Previous findings were confirmed by other studies involving multiple types of procedures, confirming that a single dose of cefazolin before the surgery could reduce treatment costs and maintain efficacy in preventing infectious events.[34]

With the aim of verifying the effect of prophylaxis with cefazolin on infection rate in surgical wound in clean wounds according to preoperative clinical status, a randomized, double-blind clinical trial was performed including 303 patients. Cases were grouped according to a classification by the American Society of Anesthesiologists (ASA). Patients ASA 2 and ASA 3 benefited from antimicrobial prophylaxis, showing that patients who were not given the antimicrobial drug were 4.3 and 4.8 times, respectively, more likely to have infection than the control group (relative risk 0.91; confidence interval 0.83-0.99; p = 0.02).[35]

In procedures restricted to soft and superficial tissues, a case control study was designed to identify risk factors for surgical wound (SW) infection. The control group was comprised of patients who underwent esthetic surgeries and did not develop SW infection. Twelve patients in the control group and four patients who developed SW infection (by *Staphylococcus aureus)* were included in the study. Risk factors associated with SW infection were mean procedure time (5 h*vs.* 2 h; p = 0.02); general anesthesia (p = 0.004); and placement of drains (p = 0.004). In that same study, after reintroduction of antimicrobial prophylaxis with cefazolin for procedures estimated to last more than 3 hours, SW infection rate was zero.[36] On the other hand, there is evidence that, in certain types of intervention, antimicrobial prophylaxis does not seem to bring any benefit.

A study carried out to determine the usefulness of prophylactic antimicrobial drugs in arteriovenous fistulas for dialysis showed that the only local postoperative infection occurred in a patient who had received prophylaxis. The authors concluded that antimicrobial prophylaxis is not necessary in arteriovenous fistulas for dialysis. With or without antimicrobial drugs, infection rate is almost zero.[37]

There is a concern over the development of bacterial resistance to cefazolin. There is an estimated prevalence of 30% in patients with *Staphylococcus aureus*, and more than 96% of them are methicillin resistant.[38] The SENTRY program, in 1997, showed a 16.7% incidence of methicillin-resistant *Staphylococcus aureus* .[39]

Newer studies are needed to verify rate of cefazolin resistance in clean and clean-contaminated SW infections, including those restricted to soft tissues and skin, using local and worldwide programs, so that the current status of cefazolin efficacy as a prophylactic agent is established and new options of antimicrobial drugs are standardized.[40-43]

Alternative antimicrobial drugs used in prophylaxis

Widespread use of some antimicrobial drugs, such as first- and second-generation cephalosporins, for prophylaxis or therapy resulted in a dramatic increase in the prevalence of bacterial resistance.[44] In this context, there was an increase in the prevalence of multi-resistant organisms, such as MRSA .[45] At environments or institutions that have a high prevalence of methicillin-resistant bacteria, alternative antimicrobial drugs, i.e., which do not have a routine or established use, such as glycopeptides, are the first choice as prophylactic agents.[46,47]

Vancomycin

Vancomycin was introduced in clinical practice in the 1950's, and over the 3 following decades

bacterial resistance to it has been rarely reported.[44] However, in the 1980's, there is the occurrence of vancomycin-resistant coagulase-negative staphylococci, especially *Staphylococcus epidermidis*, *Staphylococcus hominis*, *Staphylococcus warneri*, *Staphylococcus haemolyticus* and *Staphylococcus xylosus*.[48,49] The American CDC recommends vancomycin to be used only as a prophylactic agent in cases of MRSA strains or coagulase-negative methicillin-resistant staphylococcus in SW infection or when there is high prevalence of isolated MRSA at the site or institution.[21] Unfortunately, CDC guidelines do not attribute any value to the prevalence of methicillin resistance that could justify prophylaxis with glycopeptides. Zanetti et al.[50] demonstrated that a better performance of cefazolin in relation to susceptible organisms would be required, unless the prevalence of methicillin resistance was lower than 3%. Comparing antimicrobial prophylaxis with vancomycin and cefazolin in femoral neck fracture, Merrer et al.[51] obtained a similar incidence of SW infections in patients who were given cefazolin (4%) and vancomycin (2%). In addition, the same authors observed that the impact of both antimicrobial agents on occurrence of glycopeptide-resistant enterococci and staphylococci stains was similar. It is believed that use of vancomycin causes the development and transmission of that resistance.[52] Moreover, vancomycin is also more expensive and hard to be administered when compared with cefazolin, being the first choice only to prevent MRSA and coagulase-negative methicillin-resistant staphylococci.[52] However, Zanetti et al.[50] demonstrated that routine prophylaxis using vancomycin was more effective than cefazolin in patients submitted to myocardial revascularization surgery, preventing a higher number of SW infections or deaths caused by methicillin-resistant staphylococci and enterococci. Furthermore, routine use of vancomycin was less expensive than cefazolin; not even higher purchase and administration costs, neither absence of protection against gram-negative bacilli reduced the final positive balance. The authors concluded that use of vancomycin in the USA could prevent 110 deaths and 3,184 SW infections when compared with use of cefazolin. On the other hand, it is hard to recommend universal use of vancomycin due to insufficient data as to the possible consequences of a routine use of vancomycin and its impact on the development of bacterial resistance.

Sometimes, systemic administration of antimicrobial agents is not enough to prevent graft infection, since the antimicrobial concentration in the tissue surrounding the graft is very low. Hirose et al.[53] recently developed a system of sustained antimicrobial release by using caprolactone (biodegradable material), which maintains an effective tissue concentration around the prosthetic graft. The same authors demonstrated that sustained release of vancomycin reduced infection rate in animal model grafts.

Teicoplanin

The most frequent microorganisms causing SW infection in orthopedic and vascular surgeries are gram-positive cocci, with prevalence of *Staphylococcus*spp, accounting for 70-90% of isolated pathogens. The main reason for such prevalence is the ability those pathogens have to adhere and multiply in polymers by producing biofilm.[54] Glycopeptides have been considered a reasonable alternative, especially at a time of high prevalence of methicillin-resistant staphylococci.[55] Many studies have compared effectiveness and toxicity of teicoplanin and cephalosporins as preoperative antimicrobial prophylaxis, but results were not inconclusive. Kardakas et al.[55] conducted a meta-analysis comparing efficacy and safety of teicoplanin and first- (cefazolin) and second-generation cephalosporins in preoperative antimicrobial prophylaxis for orthopedic and vascular surgeries. We identified two studies involving vascular procedures and four involving orthopedic procedures between January 1950 and November 2004, in a total of 510 patients submitted to vascular surgery and 2,376 submitted to orthopedic surgery. The authors did not observe any difference between teicoplanin and cephalosporins as to development of SW infection or in other sites. In addition, there was no difference as to adverse effects or mortality.

Teicoplanin has a half-life of 45-70 hours, and can be administered at a single dose. In contrast, first- and second-generation cephalosporins require multiple-dose regimes.[56] Furthermore, the

antimicrobial spectrum of teicoplanin covers the methicillin-resistant staphylococci, which is part of the normal flora in 25% of patients submitted to surgery with placement of total articular graft.[57] Such properties support selection of glycopeptides as preoperative prophylactic agents in orthopedic and vascular surgeries with use of prosthetic material. Therefore, it is not surprising that both vancomycin and teicoplanin are being used at a large scale in several countries with that purpose. However, the findings described above suggest that there is no superiority of one antimicrobial agent over another in terms of prevention of infections, development of adverse effects and total mortality.

With regard to the glycopeptide to be used, initial choice for surgical prophylaxis is teicoplanin due to its excellent tissue penetration, demonstrated by excellent distribution, low toxicity and prolonged half-life. Many clinical trials using teicoplanin as preoperative prophylactic agent in clean orthopedic, cardiac, vascular and oral surgeries demonstrate its efficacy.[58]

Antimicrobial agents that bind to prosthetic grafts

As an additional prophylactic measure, in cases in which a vascular graft will be specifically used, use of antimicrobial agents that bind to the prosthetic graft has been proposed in high concentrations.[59-61] Regarding vascular surgery, many antimicrobial agents have been proposed as associated prophylaxis.[62,63] Clinical trials have used Dacron grafts impregnated with rifampicin with the aim of preventing their colonization and infection.[62] Other types of graft impregnated with antimicrobial agents have been used only in experimental studies.[45] Vicaretti et al.[64] established an animal model of infection by *Staphylococcus epidermidis* in vascular graft, suggesting that an increase in concentration of rifampicin bound to the graft (Dacron) could significantly reduce incidence of vascular graft infection caused by resistant staphylococci. On the other hand, development of rifampicin resistance, with large-scale use of impregnated grafts, could result in the need of developing new and complex prophylactic methods.[65]

Mupirocin produced by *Pseudomonas fluorescens* is a topic antimicrobial agent used in the treatment of superficial skin infections caused by staphylococci (*Staphylococcus aureus and Streptococcus pyogenes*) and to eradicate the nasal (colonizing) *Staphylococcus aureus* .[66] Mupirocin was introduced in clinical practice in 1985, in the United Kingdom, but the development of resistance was described soon after it started being used clinically.[67] Giacometti et al.[44] investigated, in animal models, the efficacy of mupirocin to prevent vascular graft infection by *Staphylococcus epidermidis* stains with different resistance patterns (methicillin-susceptible, methicillin-resistant and intermediate resistance to vancomycin). The authors demonstrated that use of Dacron graft impregnated with mupirocin could result in a significant inhibition of staphylococcic growth, even when they are multi-resistant. Other authors demonstrated superiority of mupirocin over rifampicin to prevent MRSA infections.[65]

More recently, studies involving use of streptogramins (quinupristin/dalfopristin) have been conducted in animal models, with the aim of assessing its ability to prevent infections by methicillin-resistant *Staphylococcus epidermidis* and with intermediate resistance to glycopeptides. In the study by Giacometti et al.,[68] there was a significant reduction in bacterial growth in grafts impregnated with the new drug, *in vitro*.

Another recent study evaluated the efficacy of grafts impregnated with an association of vancomycin, teicoplanin and fusidic acid to prevent graft infections in an animal model. The authors demonstrated that the association of fusidic acid with glycopeptides resulted in a significantly higher inhibition of bacterial growth of MRSA, even when the multi-resistant strains were inoculated directly in the graft.[45]

The development of infection-resistant grafts has a strong commercial appeal, but so far any

studies have confirmed *in vitro* the results obtained *in vitro*. However, use of grafts impregnated with antimicrobial agents can be an important measure in the future for antimicrobial prophylaxis in surgeries requiring synthetic material.

Conclusion

Although cephalosporins are well established as a preoperative antimicrobial prophylactic agent, we should be aware for the recent change in colonization patterns and susceptibility to antimicrobial agents. Nowadays, multi-resistant pathogens have become increasingly more frequent in SW infections, showing regional and even local variations regarding susceptibility to prophylactic antimicrobial agents routinely used. We conclude that there is not enough evidence to justify change in classical surgical antimicrobial prophylaxis. However, regional and institutional patterns of prevalence of resistant pathogens and antimicrobial susceptibility should guide individual decision making to the use of alternative antimicrobial agents in preoperative prophylaxis.

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Correspondence:
Eduardo Lichtenfels
Rua Honório S. Dias, 1500/305
CEP 90540-070 – Porto Alegre, RS, Brazil
Tel.: (51) 3325.5379
Email: elichtenfels@uol.com.br

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