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Review Article

Perioperative antibiotic prophylaxis in paediatric cardiac surgery

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RISK OF INFECTION, AND ANTIBIOTIC PROPHYLAXIS, are topics that have been debated for decades by those involved in the care of children undergoing cardiac surgery. In this review we attempt to analyse what is known and what has been postulated about this subject. Suggestions regarding the best strategies for treatment have been formulated, based on published reports, as well as current practices worldwide.

The burden of infection of the site of cardiac surgery

Cardiac surgery is clean surgery, and should be associated with an incidence of infection less than 5%. Recent studies in adults have demonstrated an incidence of 2 to 6.4% for superficial infections of sternal wounds,[1–3] and an incidence of deep infections or mediastinitis that ranges from 0.77 to 3.3%.[1–5] The National Cardiac Surgical Database of the Society of Thoracic Surgeons revealed an incidence of deep sternal infections of 0.4% in 2002. Lu et al.[6] demonstrated a significantly higher mortality in patients with infected sternal wounds compared to those without such infection during a 4-year follow-up period after coronary arterial bypass grafting.

Postoperative mediastinitis is associated with a mortality of up to 16%.[7] This complication is associated with a marked increase in both in-hospital and long-term mortality.[2,4,5] It also invariably involves additional operations, prolonged stay in the intensive care unit and hospital, increased costs, and an emotional burden not only for the patient, but also for the family, nursing staff, and surgeons. The same can be said of superficial infection at the operative site, though to a lesser degree.

Historically, the most common organisms isolated from patients with infected surgical sites are *Staphylococcus aureus*, *Staphylococcus epidermidis*, and less often gram-negative enteric bacilluses.[7–12] More recently methicillin-resistant *Staphylococcus aureus* has emerged as an important cause of infection at the site of surgery, and has led to the use of glycopeptide antibiotics, such as vancomycin and teicoplanin, as prophylaxis in some institutions.[13,14] In data published from the Cleveland Clinic, methicillin-resistant *Staphylococcus aureus* accounted for one-quarter of such infections in their adult patients.[13]

The incidence of deep infection of the sternal wound and mediastinitis in children is lower than in adults, with a reported incidence from 0.2% to 1.47%.[15–18] The organisms responsible are generally Staphylococcal species.[19] There are, however, no randomized studies specifically focused on perioperative antibiotic prophylaxis in children submitted to cardiac surgery. Prophylaxis, therefore, is often determined on an historical, institutional or personal basis. Moreover, as the incidence of infection at the site of surgery has been low in recent years, there is little incentive to review or study postoperative prophylaxis because of the perception that current

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therapy is effective. With the recent emergence of methicillin-resistant *Staphylococcus aureus*, however, concerns regarding antibiotic resistance and use of resources, along with the choice and duration of prophylaxis, assume important clinical and financial importance.

In conducting this review, we have considered infection at the site of cardiac surgery as the primary outcome. Other postoperative infectious complications, such as pneumonia, bacteremia, or infection of the urinary tract, are not addressed. Many of the conclusions have been drawn on the basis of evidence from adults undergoing cardiac surgical interventions.

The requirement for antibiotic prophylaxis in cardiac surgery

The controversy regarding peri-operative prophylaxis for cardiac surgery began in the 1960s. In a review, from 1961, of adults undergoing extra-corporeal circulation for valvar repair, Kittle and Reed[20] found no advantage to the administration of penicillin and streptomycin. Two additional trials in the same decade also found benefit to the use of semi-synthetic penicillin, or a combination of penicillin G and streptomycin, in preventing postoperative wound infection.[21,22] In 1979, Fong et al.[23] reported results for 105 adults who were randomized in a double-blind fashion to receive either methicillin or a saline placebo for 3 days following coronary arterial bypass grafting. The trial had to be terminated early because of a markedly higher prevalence of infection of the sternal wound in those receiving the placebo, at 21% versus 0%.[23]

In 1992, a meta-analysis[24] of 4 placebo-controlled trials evaluating a total of 405 adults found a marked reduction of infection at the site of surgery in those receiving antibiotics, with an odds ratio of 4.96, and 95% confidence intervals from 2.06 to 9.72. The authors concluded that it would be unethical to perform further placebo-controlled trials to verify the efficacy of antibiotic prophylaxis, and established antibiotic prophylaxis as the standard of practice in cardiac surgery.

The choice of antibiotic therapy

Penicillin versus cephalosporin

The same meta-analysis reported in 1992[24] also examined 6 randomized trials involving 966 adults comparing a cephalosporin versus an antistaphylococcal penicillin with or without aminoglycoside. The analysis showed that 5 of the 6 studies identified fewer total infections of wounds in the patients treated with cephalosporin, with a summary odds ratio of 0.51, suggesting a possible superiority for the use of the cephalosporins.

First generation versus second generation cephalosporins

In the 1980s, 5 randomized trials[25–29] compared first and second generation cephalosporins as prophylactic antibiotics for infections after adult cardiothoracic operations. They all showed either a trend towards significance, or a significant result in favour of either cefamandole or cefuroxime instead of cefazolin. The meta-analysis published in 1992[24] evaluated 2630 patients from 6 randomized trials that compared cefazolin versus either cefamandole or cefuroxime. The incidence of infection of sternal wounds was reduced in 7 of the 8 groups receiving treatment, and the incidence of infections of leg wounds was lower in 5 of the groups receiving second-generation cephalosporins. The total incidence of infection was significantly lower, 5% to 3%, when second generation cephalosporins were used, with a summary odds ratio of 1.51, and 95% confidence intervals from 1.03 to 2.45.

In contrast, in 2 randomized trials published a year later, there was no difference between the use of first and second generation cephalosporins. Townsend et al.[30] conducted a double-blind trial evaluating 9 doses of either a first or second-generation cephalosporin. The study was powered to detect a reduction by half in the incidence of infection noted over the previous 2 years, which was 8%. The sites of infection, and the depth of involvement of tissues, were not significantly different across groups. The differences observed between first and second generation cephalosporins was so small that, in order to satisfy the traditional 80% chance of detecting a difference that was 95% likely to be due to the different antibiotic regimens, they would have required 110,718 patients. Curtis et al.[10] evaluated 702 adults in a single-blind trial using a 48-hour regimen, and they too found no difference in the incidence of infection.[10] There does not, therefore, appear to be consistent and conclusive evidence of marked superiority of second over first generation cephalosporins. Cost-effectiveness may be the only variable that influences the choice of cephalosporin.

Vancomycin as antibiotic prophylaxis

In 1992, Maki et al.[31] randomized 320 adults undergoing cardiac or major vascular operations to receive intravenous cefazolin, cefamandole or vancomycin for prophylaxis in a double-blind trial. The incidence of infection, and the duration of hospital stay, were lowest in those receiving vancomycin, with no thoracic infections occurring in those receiving vancomycin. In 1999, Salminen et al.[32] randomized 200 patients undergoing elective heart surgery to receive either a single dose of cefuroxime or 8 doses of vancomycin,

and could find no difference in the incidence of infection. In 2001 Spelman et al.[33] changed their antibiotic policy from cefazolin in 4 doses to vancomycin and rifampicin in 2 doses, after noting a high incidence of infection by methicillin-resistant *Staphylococcus aureus* in their institution. They then compared the incidence of infection in 599 coronary arterial bypass grafting procedures in the 12-month period before the intervention, to the incidence in 515 procedures in the 12-month period after the intervention. They demonstrated a significant decrease in overall infection at the site of surgery, from 10.5% to 4.9%. The relative risk reduction was 55.3%, and the number of patients needed to treat with the new regimen to prevent one infection was 18 in their study. The estimated savings to the hospital over the 12-month period was 576,655 Australian dollars. In 2002, however, Finkelstein et al.,[34] in an institute with a high prevalence of methicillin-resistant *Staphylococcus aureus*, randomized 885 patients undergoing cardiac surgery to receive either 3 doses of cefazolin or 2 doses of vancomycin. The overall incidences of infection were similar in the 2 groups.

In a meta-analysis published in 2004, Bolon et al.[8] evaluated 5761 subjects from 7 randomized trials, of which only 2 were blinded, carried out between 1988 and 2002. All patients received either a glycopeptide or a β-lactam agent such as any penicillin or cephalosporin. The primary outcome evaluated was the incidence of infection at the site of surgery at 30 days. There was no statistically significant difference in the risk of infection between the 2 groups. A pooled sub-group analysis showed that glycopeptides were associated with significantly higher frequency of post-operative superficial, deep, and organ-space infections, deep infection at the site of surgery, and infection at the site of surgery due to gram-positive organisms, with a lower incidence of infection at the site of surgery to the legs and at the site of cardiac surgery due to β-lactam-resistant gram-positive bacteria. The observed inferiority of glycopeptides in preventing infections at the site of thoracic surgery might be explained by their inadequacy, especially teicoplanin, in penetrating fatty tissue and bone.

Two additional problems must also be considered with routine use of vancomycin. First is the development of hypotension, flushing or red-man syndrome, bronchospasm, and even cardiac arrest associated with the administration of vancomycin.[35–49] The mechanism of action is thought to be nonimmunologic release of histamine.[50–52] It requires no previous exposure to vancomycin, and is classified as anaphylactoid. In the randomized study of Maki et al.,[31] 8 adults given vancomycin became hypotensive during administration of a dose despite infusion over a 1-hour period. Romanelli et al.[53] randomized in double blind fashion 58 adults undergoing elective coronary arterial bypass grafting to receive cefazolin and either vancomycin or saline perioperatively, demonstrating that the intra and post-operative administration of vancomycin was associated with significantly lower systemic vascular resistance, mean arterial pressure and systemic arterial pressure and a significantly higher requirement for use of norepinephrine. The second, and probably more important, problem is the emergence of vancomycin-resistant staphylococcal and enterococcal species.[54–57] These potentially devastating infections may well return us to the pre-antibiotic era, and their very spectre should discourage the widespread use of vancomycin without strong supporting evidence.

It appears, therefore, that vancomycin, or teicoplanin, is no more effective then β-lactam agents for the prevention of infection of surgical sites after cardiac surgery, at least in hospitals with low levels of infection by methicillin-resistant *Staphylococcus aureus*. The routine use of vancomycin may be justified in centres with a high prevalence of methicillin-resistant *Staphylococcus aureus*. This, however, carries the risk of encouraging the emergence of vancomycin-resistant *Staphylococcus aureus* or vancomycin-resistant enterococcus.[56] As yet, no institutional thresholds for incidence of infection to trigger the use of vancomycin have been established, and local probability of resistance must be taken into account when choosing prophylaxis. At the Children's Hospital of the University of California, San Francisco, over a 12-month period from January to December 2004, of 469 cases of isolation of *Staphylococcus aureus* throughout the hospital, just over one-quarter demonstrated methicillin-resistance. The incidence of infection in the paediatric cardiac surgical intensive care unit and ward, however, was less than 1%. In this setting, routine antibiotic prophylaxis with vancomycin cannot be justified. Vancomycin can, nonetheless, be used effectively in the setting of penicillin or cephalosporin allergy. It is prudent to monitor for the development of hypotension during its intra and post-operative administration.

Use of gentamicin as antibiotic prophylaxis

In 1987, Kaiser et al.,[26] in a double-blind trial, randomized 1030 adults to receive cefamandole or cefazolin with or without gentamicin. All 5 wound infections yielding fungi or gentamicin resistant gram-negative rods occurred in patients who had received gentamicin as the second antibiotic. They concluded that gentamicin has no role for prophylaxis in cardiac surgery. In children as well as adults, cardiopulmonary bypass can modify the usual pharmacokinetics of gentamicin as a result of the greater

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volume of distribution secondary to priming, immature renal function, frequent use of hypothermia, ultra filtration and aprotinin, altered circulatory physiology and transient renal dysfunction.[48,58–63] This results in the lack of a steady state and unpredictable peaks and troughs that, in turn, could have potential renal, vestibular and cochlear toxicity.[64–66] Additionally, there is currently no evidence to suggest a higher rate of infection with gram-negative organisms following paediatric cardiac surgery; even in those undergoing delayed sternal closure.

In a recent study of local wound prophylaxis, Friberg et al.[67] randomized 2000 adults to receive isoxazolyl-penicillin with or without the application of collagen-gentamicin sponges within the sternotomy before closing the wound. At 2 months postoperatively, they demonstrated a lower incidence of infection in those treated with the collagen-gentamicin sponge, at 4.3% versus 9.0%, with no difference in renal function. Hence, there is insufficient evidence to support the routine use of prophylaxis with gentamicin in cardiac surgery, though local application was of some benefit in one study.

The duration of antibiotic prophylaxis

There is general consensus that postoperative prophylactic antibiotics should be stopped within 24 hours of most major surgical procedures.[68–72] There are also important reasons why cardiac surgery may have a higher predisposition to infective complications, which limits the application of studies on the general surgical population to those undergoing cardiac surgery. These have been well summarized in a report from the Society of Thoracic Surgeons Workforce on Evidence Based Surgery on the duration of antibiotic prophylaxis in cardiac surgery.[73] Potential risk factors for infection include cardiopulmonary bypass, which impairs humoral immunologic defences and causes degradation of clotting factors, systemic hypothermia,[74] the longer operation, and the mandatory use of chest tubes and central lines that can serve as external routes for bacterial entry.[74]

Children undergoing cardiac surgery may be at even higher risk than their adult counterparts because of an immature immunologic system, use of deep hypothermic circulatory arrest, which is known to depress immune function,[75] longer duration of operation, practice of delayed sternal closure following complex reconstructions especially in neonates, need for extra-corporeal life support,[76] longer duration of chest tube drainage, especially after construction of the Fontan circulation and bi-directional cavopulmonary procedures, and the delayed return to normal patterns of feeding, necessitating prolonged central venous access for parenteral nutrition.[75,76]

Many cardiac surgeons, rightly or wrongly, consider their patients to be at particularly high risk of infection, and some will employ prolonged antibiotic prophylaxis until all chest tubes and central intravenous lines are removed.

Chest tubes and antibiotic prophylaxis

As stated in the report from the Society of Thoracic Surgeons Workforce on Evidence Based Surgery on the duration of antibiotic prophylaxis in cardiac surgery,[73] there is no scientific evidence from adult cardiac surgery that continuing antibiotics until the chest tubes are removed provides enhanced protection against infective complications.

Maher et al.[77] reviewed their experience with 3 antibiotic prophylaxis regimens over a 6-year period in nearly 4000 children undergoing paediatric cardiac surgery at the University of Michigan (Table 1). The incidence of infection at the surgical site was 2.04%, 6.58% and 1.67% during the first, second, and third protocols, respectively. The second protocol had a significantly higher rate of infection than the other two. Subgroup analysis demonstrated that rates of superficial and deep infections followed a similar pattern. Their study, however, was limited by its retrospective nature. Additionally, a concerning feature is the type of organisms that were isolated from infections both at the surgical site and from the bloodstream. There was a trend towards a greater number of gram-positive infections when changing from the first to the second protocol, which had a decreased duration of treatment with antibiotics. After changing to the third protocol, with an

Table 1. Antibiotic prophylaxis at the University of Michigan, United States of America in children undergoing cardiac surgical procedures from 1993 to 1998.

Protocol	Period	Patients	Antibiotic prophylaxis
1	Jan 1993–Mar 1994	786	Cefazolin 1 hour perioperatively, continued until all central venous catheters, intracardiac lines, chest tubes and mediastinal tubes were removed
2	Apr 1994–Dec 1995	1095	Cefazolin 1 hour perioperatively, discontinued at 48 hours
3	Jan 1996–Dec 1998	2039	Cefazolin 1 hour perioperatively, continued until 48 hours after chest tubes and mediastinal tubes were removed

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increased duration of treatment, there were fewer gram-positive infections, but a higher proportion of gram-negative and fungal infections. Thus, changing to a longer duration of treatment in the third protocol selected toward more gram negative and fungal organisms, and potentially more serious infections.

In contradistinction to the findings from the University of Michigan, Dagan et al.,[78] from the University of Toronto, compared 2 cohorts of children, the first of 310 patients undergoing surgery in 1987 and 1988, and in whom antibiotics were continued until removal of chest tubes, and the second of 455 patients submitted to surgery in 1991 and 1992, and in whom antibiotics were limited to 48 hours or 1 day after chest closure. The incidence of infection at the site of surgery decreased from 7% to 4.3%, and infection at the site of insertion of the chest tubes decreased significantly, from 3.55% to 0.6%. The authors conceded, nonetheless, that there were several other procedural and policy changes in the intensive care unit that could have influenced outcome, for example a new aggressive approach to removal of intravascular and urinary catheters.[78,79] Currently, therefore, there is still no conclusive or consistent evidence in paediatric cardiac surgery to support the administration of prophylactic antibiotics until the removal of chest tubes.

Antibiotic resistance

The ability of microorganisms to develop antibiotic resistance has recently caused considerable concern because of the emergence of staphylococcus and enterococcal species that are resistant to vancomycin.[54–57] The Center for Disease Control and Prevention reports that vancomycin-resistant enterococcus encountered in the intensive care unit has increased in the United States of America from 0.3% in 1989 to over 25% in 1999.[80] There is consistent evidence that prolonged administration of antibiotics encourages the development of antimicrobial resistance.[81–90] In addition, mediastinitis caused by these organisms is truly devastating. Other well-described drawbacks of prolonged antibiotic prophylaxis include *Clostridium difficile* colitis, drug fever, fungal infections and increased costs.[91]

In 2000, Harbarth et al.,[88] in an observational study involving 2641 adults undergoing coronary arterial bypass grafting and/or valvar surgery, compared 1502 patients having prophylaxis for less than 48 hours, and 1139 patients receiving prophylaxis for more than 48 hours. Administration was at the discretion of the surgeon. Patients receiving more than 48 hours of antibiotics were found to have 1.6 times higher probability of harbouring resistant organisms. Other than this study, there is no evidence directly linking duration of prophylactic antibiotics in cardiac surgery to antibiotic resistance. There is no scientific evidence, furthermore, that prophylactic antibiotics used for less than 48 hours after cardiac surgery are associated with development of antibiotic resistance.

Single-dose prophylaxis

The Society Of Thoracic Surgeons Workforce on Evidence Based Surgery recently reviewed all the important single-dose randomized trials involving adults undergoing cardiac surgery published in the last 20 years.[73] Of these studies, 6 involved at least one antibiotic in the multiple-dose arm that was different from the antibiotic used in the single-dose arm, thereby limiting their utility.[9,32,92–95]

In 1994, Nooyen et al.[96] randomized 844 adults undergoing coronary arterial bypass grafting surgery to receive either a single dose of cefuroxime or cefuroxime for 72 hours. No significant difference was found in infection at the site of surgery between the 2 groups, though 2 patients in those receiving a single dose developed the potentially fatal complication of mediastinitis. There are 2 major drawbacks with this study. The first is the fact that the analysis for the incidence of infection was underpowered. The second is that the wounds were examined only on the 7th post-operative day, though infected sternal wounds can often present later than 2 weeks post-operatively.[3,88] In a non-randomized prospective Australian study published in 2000,[97] 151 patients who received 48 hours of prophylaxis were compared with 202 patients who received a single dose.[97] Patients considered to be at high risk from methicillin-resistant *Staphylococcus aureus* received teicoplanin and timentin instead of cefazolin. No difference was found in the incidence of infection in the 2 groups. In addition to being underpowered, however, the proportion of patients receiving methicillin-resistant *Staphylococcus aureus* prophylaxis was very different in the 2 groups. Moreover teicoplanin has poor penetration of fatty tissues and bone, and is a sub-optimal agent as compared to vancomycin.

McDonald et al.[98] performed a systematic review of prospective randomized trials to determine the overall efficacy of single versus multiple-dose antimicrobial prophylaxis for major surgery across surgical disciplines. All trials had the same antimicrobial in each treatment arm. Combined odds ratios indicated no clear advantage of either single or multiple-dose regimens in preventing surgical infection. Of the 28 trials that met the requirements for inclusion in their study, only 2 involved cardiac surgical patients.

With the exception of the 2 non-randomized studies discussed above,[77,78] there are no trials specifically

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examining the issue of duration of antibiotic prophylaxis in paediatric cardiac surgery. After careful examination of the evidence, the Society of Thoracic Surgeons Workforce on Evidence Based Surgery[73] concluded that single-dose antibiotic prophylaxis may be effective in cardiac surgery, but there is inconclusive data to confirm this effectiveness. There is insufficient evidence to recommend the routine use of single-dose prophylaxis in cardiac surgery.

Twenty-four-hour prophylaxis

Neiderhauser et al.[11] evaluated 53 high-risk cardiac surgical patients who could not be weaned from cardiopulmonary bypass without an intra-aortic balloon pump. Patients were randomized to receive either cefazolin for 24 hours versus cefazolin for 24 hours followed by ticarcillin/clavulanate for 48 hours together with vancomycin until removal of the balloon. They observed no difference in the incidence of post-operative infections including sepsis, infection, colonization of intra-vascular catheters and tracheal or bronchial aspirates. Finkelstein et al.,[34] in an institute with a high prevalence of methicillin-resistant *Staphylococcus aureus* in Tel Aviv, randomized 885 patients undergoing cardiac surgery to receive either 3 doses of cefazolin or 2 doses of vancomycin over 24 hours. The overall incidence of infection at the surgical site, and superficial and deep sternal infection, was similar in the 2 groups. This study is most notable for the 1.6% incidence of major sternal complications seen in the group receiving cefazolin, indicating that the regime of 24-hours cefazolin provided acceptable prophylaxis against infection in this population at high risk. Thus, 24-hours of antibiotic prophylaxis may be effective in cardiac surgery. These results must be interpreted with caution as the trials did not specifically examine the duration of antibiotic prophylaxis and the antimicrobial agents were different in both arms of both trials. Moreover there are no trials specifically examining the issue of 24-hour antibiotic prophylaxis in paediatric cardiac surgery.

Forty-eight-hour prophylaxis

Adult cardiothoracic surgery

Three randomized studies from the 1980s evaluated the effectiveness of 48-hour prophylaxis compared to longer regimens. In 1983, Hillis et al.[99] compared either a 48-hour course of kanamycin and cephalothin or the same regimen followed by 3 days of oral cephalexin in 160 randomized patients undergoing aortocoronary bypass grafting. In 1986, Geroulanos et al.[100] compared 48 hours of cefuroxime or 96 hours of cefazolin in 569 randomized patients undergoing cardiac surgery. In 1988, Jewell et al.[101] compared 48 hours of intravenous cephalothin or 72 hours of oral cephalexin in 200 randomized patients after aortocoronary bypass. No difference was found in infection at the site of surgery in all 3 studies. Non-identical antimicrobial agents in the 2 arms were an important limitation of all 3 studies. Ariano et al.[102] reviewed the literature to determine the optimal prophylactic antimicrobial regimen for patients undergoing aortocoronary bypass. They noted a trend towards greater effectiveness with cefuroxime, followed by cefamandole, and then cefazolin. Despite the many limitations of the studies evaluated, they concluded that there was insufficient data at the time to recommend less than two days of antimicrobial prophylaxis for this type of surgery. The addition of an aminoglycoside also appeared to provide no added benefit.

Kreter and Woods[24] performed a meta-analysis of 28 randomized trials involving 6759 cardiothoracic patients over the preceding 30 years. Of these, 4 trials involving 466 patients compared a shorter duration of less than 2 days to a longer duration of 3 or more days of antibiotic prophylaxis. The incidence of infection at the site of surgery was lower in those treated for a short duration, although the differences were not statistically significant. Kriaras et al.[103] also performed a meta-analysis of 4 randomized controlled trials between 1980 and 1995, involving 2970 patients undergoing cardiovascular surgery. Though the use of several different regimes limit the interpretation of the results, the overall infection at the site of surgery in all patients was 1.1%, and no statistical difference was observed between any groups. They concluded that, if a cephalosporin would be administered properly at the induction of anaesthesia, a low rate of infection would occur, that could not be lowered further by longer duration of antimicrobial administration.

As already discussed, Harbarth et al.[88] compared 1502 patients having short periods of prophylaxis with 1139 patients receiving prophylaxis for more than 48 hours. They found no statistically significant differences between the groups in either an unadjusted or a risk-adjusted analysis, and concluded that the maximum clinical benefit of prophylaxis is realized by 48 hours, with administration for more than 48 hours being ineffective in further reducing infection. We have already discussed the 2 important limitations of this study.

In January 2003, the leadership of the Medicare National Surgical Infection Prevention Project hosted the Surgical Infection Prevention Guideline Writers Workgroup meeting with the objective of reviewing the most recently published guidelines for surgical antimicrobial prophylaxis.[69] The recommended antimicrobials for cardiothoracic and vascular

operations included cefazolin or cefuroxime. The consensus of the workgroup was that administration of prophylaxis for less than 24 hours or for 24 hours was acceptable and that there was no evidence that providing antimicrobials for longer periods reduced surgical site infection. In 2005, the National Surgical Infection Prevention Project published baseline results from a national retrospective cohort study with medical record review of a systematic random sample of 34,133 Medicare inpatients from 2965 hospitals.[104] Surgeries surveyed included aortocoronary bypass, thoracic surgery, vascular surgery, colorectal surgery, hysterectomy and replacement of the hip and knee. The conclusion was that prophylaxis of short-duration, as little as one dose, is equally effective as longer-duration prophylaxis in preventing infection, and that newer antibiotics are no more effective than older options. Following a systematic review of the literature by its Committee on Evidence-based Medicine, the Society of Thoracic Surgeons currently recommends that antibiotic prophylaxis should not be continued for more than 48 hours postoperatively.[73]

Paediatric cardiothoracic surgery

As discussed above, there are only 2 trials that evaluate the effectiveness of 48 hours versus longer duration of antibiotic prophylaxis. Currently there still is no conclusive or consistent evidence in paediatric cardiac surgery to support the administration of prophylactic antibiotics for longer than 48 hours.

Intraoperative redosing of antibiotics

Ultrafiltration

There is limited data on the effects of ultrafiltration on concentrations of antibiotics in the serum. Haessler et al.,[66] using venovenous ultrafiltration, showed minimal effects on concentrations of cefazolin and gentamicin. O'Rullian et al.[59] compared the concentration of cefazolin in 2 groups of adults undergoing cardiac surgery, and also found no significant differences between those who did or did not receive ultrafiltration. Both sets of authors concluded that ultrafiltration has negligible effects on concentrations of antibiotics in the serum.

Extracorporeal circulation

Extracorporeal circulation alters both the volume of distribution and elimination of commonly administered prophylactic antibiotics. Multiple studies in adults and children undergoing cardiopulmonary bypass show significant decreases in concentrations of vancomycin, cephalosporins, and gentamicin at the onset of extracorporeal circulation, followed by a period of no change or slight increase in levels in the serum.[66,105–107] Elimination has been shown to remain unchanged or decrease during cardiac surgery compared to preoperative and postoperative clearance.[66,105–107] Surgery and cardiopulmonary bypass may lower cardiac output and organ perfusion, which decreases the volume of distribution of antibiotics.[105,108] Protein binding is decreased by hypothermia, haemodilution, and binding competition with heparin-induced free fatty acids. Decreased binding leads to increased free concentrations and increased apparent volume of distribution of highly protein bound medications. Drugs with high serum protein binding, such as cefazolin, have larger changes in the volume of distribution compared to drugs with lower protein binding, such as vancomycin.[105–109] Additional factors in children, such as a greater degree of hypothermia during surgery, potentially immature renal function and altered circulatory pathways in congenital heart disease, can further alter the absorption, distribution, metabolism, and elimination of antibiotics.[59,60,66]

Zanetti et al.[110] compared the risk of infection at the site of surgery in 1546 adults undergoing cardiac surgery for more than 240 minutes after preoperative administration of cefazolin. Overall infections were similar in patients with or without intraoperative redosing of antibiotics. Redosing was beneficial in procedures lasting for longer than 400 minutes. Haessler et al.[66] analyzed concentrations of cefazolin and gentamicin in the serum of 19 children all weighing less than 10 kilograms. Concentrations of cefazolin at the completion of surgery and during the postoperative period were all greater than the suggested minimum inhibitory concentration of 8 micrograms/milliliter for common potential pathogens implicated in infection at the site of surgery.

Vuorisalo et al.[111] measured levels of cefuroxime and vancomycin levels in 60 patients undergoing coronary arterial bypass grafting who were randomized to six groups, with 10 patients in each. Each was given a one-day course, or an additional dose during cardiopulmonary bypass or a single dose.[111] Levels of the antibiotics were measured at various times throughout the operative procedure and until 48 hours after the start of prophylaxis. Patients in each of the six groups maintained levels in the serum adequate for prophylaxis throughout the operative procedure. The levels remained above 2 milligrams per litre for more than 8 hours postoperatively, even in those receiving a single dose of cefuroxime, and above 4 milligrams per litre for more than 24 hours with all the doses of vancomycin. Thus a single dose of cefuroxime, either of 3 grams or 1.5 grams, or 1.5 grams of vancomycin, seems to achieve, and maintain, levels of the antibiotic in the serum sufficient for

prophylaxis against infection for at least 8 hours after coronary arterial bypass grafting procedures. Miglioli et al.[107] studied the effects of cardiopulmonary bypass on the levels of vancomycin in the serum of 10 adults. All had received one dose of 15 milligrams per kilogram prior to induction of anaesthesia. During cardiopulmonary bypass, the levels of the antibiotic in the serum invariably decreased, but remained in a potentially effective range for antimicrobial prophylaxis for at least 8 hours postoperatively. Thus, athough studies on the intraoperative pharmacokinetics of antibiotics are limited, available evidence suggests that concentrations of cephalosporins and vancomycin in patients submitted to cardiac surgery remain high enough to ensure adequate prophylaxis for at least 8 hours after a single preoperative dose.

Antibiotic prophylaxis at the University of California in San Francisco

In the 12 months preceding this review, specifically from July, 2004, through June, 2005, the incidence of infection at the site of cardiac surgery in the paediatric heart centre at University of California in San Francisco was 1.4%, with the methicillin-resistant *Staphylococcus aureus* accounting for half of these infections. We currently use one preoperative dose of intravenous cefazolin, 25 milligrams per kilogram, to a maximum of 1 gram, at the induction of anaesthesia, or vancomycin, 15 milligrams per kilogram, again to a maximum of 1 gram, in those patients with an allergy to penicillin. This is followed by cefazolin given intravenously at 25 milligrams per kilogram every 8 hours, but every 12 hours in neonates younger than 7 days, or else vancomycin at 15 milligrams per kilogram every 12 hours postoperatively. Patients receive intraoperative redosing if surgery lasts longer than 8 hours. Antibiotics are continued for 48 hours post-operatively for routine operations involving a sternotomy or thoracotomy. Patients who require delayed closure of the sternum receive cefazolin for 24 hours following closure of the chest. Although delayed sternal closure can be considered to be a procedure in its own right, given the fact that no cardiopulmonary bypass is used, we believe that it is reasonable to continue cefazolin for only 24 hours subsequent to the procedure. Patients undergoing an emergency sternotomy are also subject to the same regimen, provided there has been no break in sterile technique at the start of the procedure. Should the sterile field be compromised, antibiotic prophylaxis is decided at the discretion of the individuals involved. Patients on extra-corporeal life support receive the same antibiotic prophylaxis. In these patients, however, we draw blood for culture daily, and we have a low threshold for broadening coverage. Patients already receiving antibiotics, such as those with chest infections, necrotizing enterocolitis, or endocarditis, and who require surgery as an emergency procedure, continue to receive the same antibiotics, provided the spectrum of antimicrobial cover is as inclusive as cefazolin.

Worldwide survey of antibiotic prophylaxis regimens in paediatric cardiac surgery

In order to evaluate the practice of antibiotic prophylaxis in other centres, we conducted a cross-sectional survey of a sample of paediatric cardiac surgical units around the world. Staff members from 50 units, known personally to the senior author, were sent a questionnaire by email, seeking responses to the following:

- The choice and duration of antibiotic prophylaxis for a routine operation.
- Alteration, if any, in antibiotic prophylaxis for patients undergoing delayed sternal closure.
- Alteration, if any, should extra-corporeal support be required postoperatively.

Responses were received from 42 units, and are shown in Table 2. Units have been sorted in ascending order of the duration of antibiotic prophylaxis for a routine sternotomy or thoracotomy. Of the units, 15 (36%) used antibiotic prophylaxis for less than 24 hours or for 24 hours, with 10 units (24%) continuing prophylaxis for 48 hours, 4 units (9%) for 72 hours, and 13 units (31%) for longer than 72 hours or until removal of central lines and/or chest tubes.

Limitations of the available data

Currently, there are no randomized trials in children undergoing cardiac surgery. Conclusions, therefore, have been extrapolated from trials conducted in adults. As stated earlier, there are important differences in the paediatric population, which may influence the incidence of infection at the site of cardiac surgery. Even the randomized studies in adults were usually poorly controlled to examine specifically the issue of duration of prophylaxis. Moreover, there were often confounding factors, such as the use of different antibiotics in each arm of the study. Additionally, many randomized trials were underpowered. Although a meta-analysis does partially correct for inadequate size of the samples, results must still be interpreted with caution. The incidence of infection at the site of surgery can vary widely from unit to unit, as does the prevalence of microorganisms, especially methicillin-resistant *Staphylococcus aureus*. In addition, the potential impact of different surgical techniques and medical management other than

Table 2. Antibiotic prophylaxis in paediatric cardiac surgery in 40 units around the world as revealed in the response to a questionnaire.

No.	Hospital	Country	Routine sternotomy/thoracotomy	Delayed sternal closure	ECLS
1	Royal Children's Hospital, Melbourne	Australia	Cefazolin 3 hourly until the last stitch, no postoperative antibiotics	Cefazolin 3 hourly until the last stitch, no postoperative antibiotics	Cefazolin 3 hourly until the last stitch, no postoperative antibiotics
2	Children's Hospital, University of Zurich, Zurich	Switzerland	Cefazolin one dose (25 mg/kg) during anesthesia induction, single dose at 12 hours	Cefazolin once daily until chest closure	Cefazolin once daily until chest closure/decannulation
3	Starship Children's Hospital, Auckland	New Zealand	Cefazolin 50 mg/kg at induction, after coming off CPB, additional dose of 25 mg/kg if bypass >3 hours	Cefazolin 50 mg/kg at induction, after coming off CPB, additional dose of 25 mg/kg if bypass >3 hours, no interval antibiotics, vancomycin at the time of chest closure/exploration	Cefazolin single dose for ECLS cannulation, vancomycin pre chest closure/exploration
4	Institut Hospitalier Jacques Cartier, Massy Cedex	France	Cefamandole 25 mg/kg every 2 hours during the operation	Cefamandole 25 mg/kg every 2 hours during the operation, no post operative prophylaxis	Cefamandole 25 mg/kg every 2 hours during the operation, no post operative prophylaxis
5	Children's Hospital of Philadelphia, Philadelphia	USA	Cefazolin 24 hours	Cefazolin 24 hours post chest closure	Cefazolin until decannulation
6	Escorts Heart Institute and Research Center, New Delhi	India	Cefotaxime/Gentamicin 3 doses each	Cefotaxime/Gentamicin/Teicoplanin 5–7 days	
7	Hospital for Sick Children, Great Ormond Street, London	United Kingdom	Flucloxacillin/Gentamicin 24 hours	Augmentin continuously until chest closure	Augmentin continuously until chest closure or decannulation; Teicoplanin to cover any surgical intervention
8	Children's National Medical Center, Washington D.C.	USA	Cefazolin until 1st postoperative morning	Broad spectrum coverage, no fixed protocol	Broad spectrum coverage, no fixed protocol
9	Texas Children's Hospital, Houston	USA	Cefazolin 4 doses (24 hours)	Cefazolin	Cefazolin
10	Denver Children's Hospital, Denver	USA	Cefazolin 24 hours	Cefazolin until chest closure	Cefazolin until chest closure/ decannulation
11	Lund University Hospital, Lund	Sweden	Cefuroxime 4 doses (24 hours)	Cefotaxime, Vancomycin single dose at the time of chest closure	Cefotaxime
12	Alfred I DuPont Hospital for Children, Wilmington	USA	Oxacillin 24 hours (<2 months), Cefazolin 24 hours (>2 months)	Oxacillin or cefazolin until 24 hours post chest closure	Oxacillin or cefazolin until 24 hours post chest closure
13	Gasthuisberg University Hospital, Leuven	Belgium	Cephalosporin 24 hours (12 hours if no CPB)	Cephalosporin 24 hours	Cephalosporin 24 hours
14	Phoenix Children's Hospital, Phoenix	USA	Cefuroxime 24 hours (48 hours if long complicated operation)	Cefuroxime 72–96 hours	Cefuroxime 72–96 hours
15	Hospital 12 Octubre, Madrid	Spain	Cefazolin 24 hours	Vancomycin/Gentamicin until chest closure	Vancomycin/Gentamicin until chest closure/decannulation
16	Ospedali Riuniti, Bergamo	Italy	Cefazolin 48 hours	Cefazolin 48 hours	Teicoplanin/Amikacin
17	Stanford University, Palo Alto	USA	Cefazolin 48 hours	Cefazolin	Cefazolin
18	Doernbecher Children's Hospital, Portland	USA	Cefuroxime 48 hours	Cefuroxime until chest closure	Cefuroxime until decannulation

19	Rijkshospitalet, Copenhagen	Denmark	Cefuroxime 48 hours	Cefuroxime until chest closure	Cefuroxime until decannulation
20	Calvo McKenna Children's Hospital, Santiago	Chile	Cefazolin 48 hours	Cefazolin until chest closure	Cefazolin until chest closure/ decannulation
21	Emory University, Atlanta	USA	Cefazolin 48 hours	Cefazolin until chest closure	Cefazolin until chest closure
22	Ospedale Bambino Gesu, Rome	Italy	Amoxicillin/Clavulinic acid 48 hours	Teicoplanin/Gentamicin until 48 hours post chest closure (add fluconazole in 23 Tet with PA/MAPCAs, 22 q deletion)	Vancomycin/Amikacin/Meropenem until 48 hours post decannulation/ chest closure
23	Cleveland Clinic, Cleveland	USA	Cefuroxime 24–48 while the chest tubes are in place (redo sternotomy: zinacef 5 days)	Vancomycin until chest closure	Vancomycin until chest closure/ decannulation
24	Duke University Medical Center, Durham	USA	Cefuroxime 48 hours	Vancomycin/Cefotaxime until 24 hours post chest closure	Vancomycin/Cefotaxime until 24 hours post closure
25	Pediatric Heart Center, UCSF Children's Hospital, San Francisco	USA	Cefazolin 48 hours	Cefazolin until 24 hours post chest closure	Cefazolin until 24 hours post chest closure
26	Tokyo Women's Medical University, Heart Institute of Japan, Tokyo	Japan	Ampicillin/Amikacin 72 hours	Ampicillin/Amikacin until chest closure	Ampicillin/Amikacin until chest closure/decannulation
27	Deutsches Herzentrum, Berlin	Germany	Cefazolin 72 hours or earlier if central lines are removed	Cefazolin/Vancomycin until chest closure	Cefazolin/Vancomycin until chest closure
28	Dong-A University Hospital, Pusan	South Korea	Cephazedone sodium 72 hours	3rd generation cephalosporin 7 days/ Teicoplanin 3 days	3rd generation cephalosporin 7 days/ Teicoplanin 3 days
29	National Cardiovascular Center, Osaka	Japan	Cefazolin or ampicillin 72 hours	Vancomycin until chest closure	Vancomycin until chest tube removal
30	Children's Hospital of Wisconsin, Milwaukee	USA	Ampicillin/Oxacillin until central venous line removal (Vancomycin/Cefipime if any signs of infection)	Ampicillin/Oxacillin until central venous line removal (Vancomycin/Cefipime if any signs of infection)	Ampicillin/Oxacillin until central venous line removal
31	Hospital de Ninos Dr. Ricardo Gutierrez, Buenos Aires	Argentina	Cefazolin until central venous line removal	Vancomycin/Meropenem until chest closure	Vancomycin/Meropenem until chest closure
32	Primary Children's Medical Center, Salt Lake City	USA	Cefazolin until chest tube removal	Cefuroxime until 72 hours post chest closure	Cefuroxime until 72 hours post chest closure
33	Mayo Clinic, Rochester	USA	Cefazolin until chest tube/pacing wire removal	Cefazolin until chest tube/pacing wire removal	Cefazolin until chest tube/pacing wire removal
34	C.S. Mott Children's Hospital, University of Michigan, Ann Arbor	USA	Cefazolin until chest tube removal	Vancomycin/Gentamicin until chest closure	Vancomycin/Gentamicin until decannulation/chest closure
35	St Christopher's Hospital for Children, Philadelphia	USA	Cefazolin until chest tube/invasive line removal (Nafcillin/Gentamicin in neonates)	Cefazolin until chest tube/invasive line removal (Nafcillin/Gentamicin in neonates)	Cefazolin until chest tube/invasive line removal (Nafcillin/Gentamicin in neonates)
36	Children's Memorial Hospital, Chicago	USA	Cefazolin until chest tubes/arterial line removal	Cefazolin until chest tubes/arterial line removal	Cefazolin until chest tubes/arterial line removal
37	The Congenital Heart Institute of Florida (CHIF), Saint Petersburg and Tampa	USA	Cefazolin until chest tube removal	Cefazolin until chest tube removal (Vancomycin/Ceftazidime if any signs of infection)	Cefazolin until chest tube removal (Vancomycin/Ceftazidime if any signs of infection)

(*Continued*)

Table 2. (Continued)

No.	Hospital	Country	Routine sternotomy/thoracotomy	Delayed sternal closure	ECLS
38	Marie-Lannelougue Hospital, Le Plessis Robinson	France	Penicillin G until chest tube removal	Cephamandole/Gentamicin until chest tube removal	Cephamandole/Gentamicin until chest tube removal
39	Seattle Children's Hospital, Seattle	USA	Cefazolin until chest tube removal	Cefazolin until chest tube removal	Cefazolin until chest tube removal
40	Ospedale San Vincenzo, Taormina, Sicily	Italy	Ceftazidime until chest tube removal	Vancomycin/Imipenem until chest closure	Vancomycin/Imipenem until chest closure/decannulation
41	Children's Hospital, Boston	USA	Cefazolin until chest tube removal	Cefazolin until chest tube removal	Cefazolin until chest closure decannulation
42	Alderhey Children's Hospital, Liverpool	United Kingdom	Neonates: Gentamicin/Teicoplanin (intubated <48 hours – 2 doses, intubated >48 hours – until extubation or POD 5) Children older than 1 month: Gentamicin (intubated <36 hours – 2 doses, intubated >36 hours – until extubation or POD 5)/ Teicoplanin (intubated <48 hours – 3 doses, intubated >48 hours – until extubation or POD 5)		

Abbreviations: CPB: cardiopulmonary bypass; ECLS: extra corporeal life support

antibiotics, and factors such as the use of bone wax, the use of topical antibiotic preparations, and techniques for the preparation of the patients, can never fully be evaluated. Delayed sternal closure is almost unique to paediatric cardiac surgery, and there is limited data to guide therapy in this subgroup. In addition, there are no trials to guide therapy in patients undergoing extracorporeal life support.

Summary and conclusions

Based on our extensive review of the literature, we suggest that

- Perioperative antibiotic prophylaxis in cardiac surgery should be the standard of care.
- Currently there is no consistent and conclusive evidence of marked superiority of second-generation cephalosporins over first-generation cephalosporins. Cost-effectiveness may be the best way to decide.
- Vancomycin, and teicoplanin, are no more effective then β-lactam agents for the prevention of infection at the site of cardiac surgery. The routine use of vancomycin for perioperative antibiotic prophylaxis in cardiac surgery carries the risk of encouraging the emergence of vancomycin-resistant *Staphylococcus aureus*, or vancomycin-resistant enterococcus, particularly in hospitals with low levels of infection with methicillin-resistant *Staphylococcus aureus*. As yet, no threshold for incidence of infection has been established for institutions to mandate the use of vancomycin. Local probability of resistance must be taken into account when choosing prophylaxis. Vancomycin can be used effectively in the setting of allergy to penicillin or cephalosporin. Intra and post-operative administration of vancomycin requires monitoring for the development of hypotension.
- Single dose and 24-hour antibiotic prophylaxis may be effective in cardiac surgery. Patients undergoing cardiac surgery, however, may be considered to be at higher risk of infection than the general surgical population, and there is consistent evidence indicating that antibiotic prophylaxis of 48 hours duration is effective, a low incidence of infection at the site of surgery being found in all studies using 48 hours of prophylaxis. There is no evidence that prophylaxis administered for longer than 48 hours is more effective than the regime lasting 2 days.
- The duration of a prophylactic antibiotic regimen is directly related to the probability of developing resistant microorganisms, and there is no doubt that resistance increases as the duration of the regime increases. There is limited data

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demonstrating that antibiotic prophylaxis for longer than 48 hours increases antibiotic resistance.
- The duration of antibiotic prophylaxis should not be dependent on catheters, lines, nor drains of any type.
- Currently there is no consistent or conclusive evidence to support the administration of antibiotic prophylaxis in paediatric cardiac surgery for more than 48 hours.
- Intraoperative redosing of antibiotics is probably warranted after 8 hours.
- As children cannot be considered as small adults, a well-conducted study is warranted in children undergoing cardiac surgery.

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