Surgery And Cephalosporins: A Marriage Made In Heaven Or Time For Divorce?

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Abstract

For many years now, surgeons have used cefuroxime and metronidazole for both prophylaxis and treatment of infections. Times and microbes have changed since the introduction of the cefuroxime in 1978. Cephalosporins are ineffective against the common pathogens causing surgical site infection (SSI) and are associated with superinfection. The argument is made for surgeons and microbiologists to take their local infecting organisms / sensitivity patterns into account when formulating prophylaxis as well as empirical therapy guidelines for individual surgical sites.

REVIEW

For many years now, surgeons have used cefuroxime and metronidazole (often endearingly referred to as "ceph and met") for both prophylaxis and treatment of infections. No doubt many would argue that "ceph and met" have served well and that the incidence of surgical post-operative infection is within expected limits for the degree of infection risk. Times and microbes have changed, though, since the introduction of the cefuroxime by Glaxo in 1978. The majority of organisms causing surgical site infection (SSI) post-operatively are staphylococci including Staphylococcus aureus (including those that are methicillin resistant or MRSA) and Staphylococcus epidermidis (used here as a generic name for coagulase negative staphylococci) the latter being particularly important pathogens in graft infections. In the UK, according to the Nosocomial Infection National Surveillance Service (NINSS) survey (1997-2001) (1), 47% of microorganisms identified as causing SSIs were staphylococci, of which 82% were Staphylococcus aureus. Further, 62% of Staphylococcus aureus isolates were methicillin resistant (MRSA). Nearly two-thirds of St epidermidis isolates are also methicillin resistant (i.e. MRSE). MRSA and MRSE are -by definition- resistant to all the penicillins and the cephalosporins. Other less common but nevertheless important pathogens are enterococci and Pseudomonas aeruginosa. Enterococcal infections (predominantly UTI but also endocarditis) are on the increase and this may well be due to overuse of the cephalosporins to which they are intrinsically resistant. Pseudomonas aeruginosa is also resistant to most

cephalosporins, except for some 3 rd generation drugs such as ceftazidime which is too broad spectrum and expensive for routine surgical prophylaxis.

Cephalosporins, perhaps more so than any other class of drugs, have been associated with superinfection with MRSA (2,3,4), vancomycin resistant enterococci (VRE) (5,6,7), Clostridium difficile enterocolitis $({}_{8,9,10,11})$ and resistant Gram-negative rods, including those producing extended spectrum beta-lactamases (ESBLs) (11,12,13). Furthermore, control of the use of cephalosporins, generally resulted in reduction of the rates of superinfection with the above organisms $(_{4,5,6,7,8,9,11,12})$. Different cephalosporins have different propensities for promoting superinfection including C. difficile diarrhoea $(_{10})$ - with the higher generation drugs $(3^{rd} \& 4^{th})$ being the worst offenders. Demographically, we are witnessing an increasing proportion of hospitalised elderly people who are much more susceptible to the above superinfections, especially C. difficile enterocolitis, than their younger counterparts.

The consequences of deep post-operative infections can be dire. This is especially true of surgical graft infections. Vascular graft infections occur in around 7.8% of patients and prosthetic hip and knee infections in 3.1 and 1.9% respectively (1). Untreated, an infected femoral graft leads to amputation while an infected aortic graft means almost certain mortality. Even with adequate treatment the mortality and amputation rates are high (14). Infected orthopaedic grafts lead to loss of use of the limb, often permanently.

MRSA is often the commonest single organism causing vascular graft infection and this infection has been shown to develop despite cepahlosporin prophylaxis $(_{14})$.

It is thus essential to administer effective antimicrobial prophylaxis according to the accepted scientific principles. In the UK these were laid out by the Scottish Intercollegiate Guidance Network (SIGN) ($_{15}$). The basic principles are:

- 1. The antibiotics selected for prophylaxis must cover the most common pathogens. The chosen antibiotic must reflect local, disease specific information about the common pathogens and their antimicrobial susceptibility.
- 2. The aim is to achieve maximum concentrations of an effective antimicrobial at the target tissues at time of operation. This is because most organisms causing early surgical infection –especially those of prosthetic grafts- are skin organisms (e.g. staphylococci) that land on the open wound at the time of operation.
- 3. With few exceptions (noted in the document), all drugs are given IV as a single dose at induction (roughly 1/2 hour before operation, 1 hour if IM) unless otherwise stated. There is no evidence to support multiple doses beyond the peri-operative period.

The SIGN guidelines (Annex 4) (15) correctly state that Staphylococcus epidermidis and Staphylococcus aureus are most important pathogens following insertion of prosthesis, graft or shunt. They acknowledge that two-thirds of Staphylococcus epidermidis are methicillin-resistant but state that only 10% of Staphylococcus aureus are. This is certainly not the case reported by NINSS (1), not the experience in our institution and probably not the majority of others in the UK. Even more surprisingly, SIGN go on to state that "Prophylaxis with beta-lactam drugs is still appropriate" (for MRSE) and "It is conceivable that betalactam drugs remain effective for the prevention of infections by MRSA or MRSE". This is in direct contradiction of their first principle of surgical antimicrobial prophylaxis -above-, not supported by any microbiological scientific evidence and should be withdrawn.

It is with above evidence and data in mind, that microbiologists and pharmacists in Cumbria have developed a new "standard surgical regime" for prophylaxis. This regime is applicable where broad-spectrum cover including anti-anaerobic, MRSA and pseudomonas spp. is required. The regime and example indications for surgical prophylaxis are given in table I. It can equally be used for empirical therapy pending culture and sensitivity results, when narrower spectrum agents may be employed. We concur with SIGN that glycopeptides are not suitable for routine surgical prophylaxis as they are expensive and require up to 48 hours for serum levels to achieve a steady state. Further, vancomycin requires IV infusion over at least 100 minutes. Thus the glycopeptides are best kept as "reserve" drugs. However, glycopeptides have been successfully used in surgical prophylaxis involving prosthetic implants in Europe and the USA $(_{16,17})$. Gentamicin on the other hand, has broad-spectrum Gram-positive and negative activity (including Pseudomonas aeruginosa, -100% sensitive at our institution-), is rapidly bactericidal, has a useful postantibiotic effect and is cheap. Widespread resistance or superinfection problems have not been reported and levels need not be monitored if given for less than 48 hours since toxicity is very unlikely following a single dose. Both coamoxiclav and clindamycin have good anti-anaerobic activity, which obviates the need for using metronidazole, as well as reasonable activity against enterococci. To illustrate this, local Gram-positive (since these are the most common pathogens in surgical graft infection) sensitivity patterns of blood culture isolates are given in table II. Though clindamycin has been associated with C. difficile enterocolitis, as have the cephalosporins, it is only recommended for those patients allergic to penicillin or known to be MRSA colonised, so numbers are expected to be relatively small.

We are not recommending this regime for every institution and other European and UK regions are also advised to take their local infecting organisms and their sensitivity patterns into account when formulating prophylaxis as well as empirical therapy guidelines. It has to be remembered, however, that prophylaxis does not prevent the late haematogenous infection of prosthetic joints and antibiotics should be administered prior to bacteraemia inducing procedures such as dental extraction and urinary catheterisation. Audit of early and late postoperative infections pre- and post- introduction of any new regime such as this one is desirable. However, as prosthetic joint infections are low incidence diseases (see above), large numbers of patients would have to be recruited and monitored and this is perhaps more suited to a multi-centre study.

In conclusion, there is compelling evidence that cephalosporins are ineffective against the common pathogens causing SSIs and that they are associated with superinfection; strong grounds for divorce indeed. Thus it is time for the surgeons to break their long-lasting relationship with the cephalosporins and court "new" antibiotics effective against today's pathogens, both for prophylaxis and empirical therapy.

Figure 1

Table 1: Surgical Antimicrobial prophylaxis

Standard Surgical Regime

Co-amoxiclav 1.2 g + Gentamicin 160 mg (240 mg if weight >80 Kg)

If Penicillin allergic or known to be MRSA colonised give

Clindamycin 600 mg + Gentamicin 160 mg (240 mg if weight >80 Kg)

Upper Gl including: Oesophago- gastrectomy	 Prophylaxis is not given routinely. If obstruction or malignancy is present, then prophylaxis is given, as the upper GI tract may become heavily colonised with bacteria under these circumstances.
Lower GI including: Appendicectomy, Colo-rectal surgery, Exploratory Iaparotomy	 Prophylaxis is given to ALL patients
Vascular surgery	 Prophylaxis is given for patients undergoing amputations, vascular implants and arterial grafts. High-risk patients, e.g. diabetics, may be given a further dose at 24 hours. Pre-operative screening & eradication of <i>Staph</i> <i>aureus I</i> MRSA carriage (as per Infection Control Protocol) desirable.
Prosthetic joint replacements (Arthroplasties: THR, TKR) Internal fixation of fractures with pins, screws, etc. around pelvic area (e.g. fracture neck of femur)	 Pre-operative screening & eradication of Staph aureus / MRSA carriage (as per Infection Control Protocol) desirable. If a tourniquet is used (e.g. for total knee replacement) then antibiotic prophylaxis must be given 10 to 15 minutes before the tourniquet is applied.

Figure 2

Table 2: Gram-positive blood culture isolates in Cumbria 2001-2002 (% senstivity rate)(Antibiotics are: penicillin, amoxicillin, co-amoxiclav, flucloxacillin, cefuroxime, ceftazidime, ciprofloxacin, meropenem, gentamicin, clindamycin, vancomycin & teicoplanin)

Organism	Tot	%	PEN	AMX	AUG	FLU	CXM	стх	CAZ
Staphylococcus epidermidis (CNS)*	361	54.7	14%	14%	39%	45%	45%	45%	45%
Staphylococcus aureus	74	11.2	21%	30%	85%	100%	100%	100%	100%
MRSA	31	4.7	0%	0%	0%	0%	0%	0%	0%
Enterococcus faecalis	36	5.5	0%	100%	100%	0%	0%	0%	0%
Enterococcus faecium	7	1.1	0%	33%	100%	0%	0%	0%	0%
Streptococcus pneumoniae	15	2.3	93%	100%	100%		100%	100%	
Haemolytic Streptococci Group A,B,G	14	2.1	100%	100%	100%		100%	100%	
Other Gram-positive cocci	122	18.5							
Total	660	100							

Organism	Tot	%	CIP	MER	GEN	CLI	VAN	TEI
Staphylococcus epidermidis (CNS)*	361	54.7	64%	58%	79%	84%	100%	100%
Staphylococcus aureus	74	11.2	79%	94%	100%	100%	100%	100%
MRSA	31	4.7	67%	57%	100%	86%	100%	100%
Enterococcus faecalis	36	5.5	53%	57%	0%	40%	100%	100%
Enterococcus faecium	7	1.1	17%	7%	0%	40%	100%	100%
Streptococcus pneumoniae	15	2.3	67%	100%	0%	100%	100%	100%
Haemolytic Streptococci Group A,B,G	14	2.1	50%	100%	0%	100%	100%	100%
Other Gram-positive cocci	122	18.5						
Total	660	100						

Most are skin contaminants but some related to long line and prosthetic graft infection

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