The why and how of antimicrobial prophylaxis

Perioperative antibiotics have been recommended in small animal surgery for decades. With the increasing importance of antibiotic stewardship in managing antimicrobial resistance, Professor John Williams, of Vets Now 24/7 Emergency Hospital in Manchester, guides Companion readers through when and why they should be used, and what dosages are appropriate.

The premise for using perioperative antimicrobials is to reduce the incidence of surgical site infections (SSI). SSIs account for between 0.8 and 18% of complications in small animal surgery, with evidence from human surgery suggesting that SSIs can be reduced in 30–60% of cases by use of evidence-based guidelines. Although we can take effective steps to reduce SSIs, we cannot completely eliminate them. It is important to remember that using antimicrobials in this way is an adjunct and not a substitute for good surgical preparation and technique. Pasteur, following the publication of his work on germ theory, stated, “Instead of fighting bacteria in wounds, would it not just be better not to introduce them”. The principles of aseptic surgery have contributed greatly to reducing SSIs and it is essential that we adhere to these key principles and not rely on antimicrobials.

Perioperative antimicrobials are used to reduce the bacterial burden so as to reduce the risk of infectious complications. Historically, they have been administered 30–60 minutes prior to making the skin incision, using a time dependent rather than dose dependent bactericidal antimicrobial.

The use of a surgical wound classification table is a useful predictor of contamination during surgery (Tables 1 and 2) and has been advocated as a way of deciding which cases require perioperative antibiotics. Although a wound classification table is a useful guide to prescribing prophylactic antimicrobials, its use has recently been questioned as it may be a poor indicator of the overall risk of SSI developing. As a system, it does not allow for factors such as operative technique, length of surgery and health of the patient, all of which are suggested to be equally important in predicting SSIs. It is now well recognized that length of anaesthesia is a risk factor for SSI, independent of the duration of surgery, with a reported 30% greater risk of wound infection for each additional hour of anaesthesia.1-3 Despite these weaknesses, the wound classification table is a practical tool in deciding whether or not antibiotics should be used for a surgical procedure.

Recent human surgical data suggest that the risk reduction following administration of prophylactic antimicrobials is the same for all procedures but that...
their use is only justified in surgery classified as clean-contaminated or worse. The risk for wound contamination stops once a fibrin seal forms at the wound, some 3–5 hours postoperatively, based on this principle there is no scientific evidence in continuing any antimicrobials beyond this time.4

The use of antimicrobials in clean procedures, starting their use postoperatively or using them beyond 24 hours is not generally recommended in human or veterinary surgery. It is essential that we use perioperative antibiotics wisely and rationally to minimize the risks of both SSI and MDR (multiple drug resistance) developing.

Antimicrobial resistance risk

Historically, antimicrobials have been used to maximize efficacy with no thought given to potential development of resistance. Due to the risk of developing antimicrobial resistance (AMR), newer dosing regimens suggest targeting pharmacokinetic/pharmacodynamic (PK/PD) indices to minimize the risk of developing AMR.5,6 PK/PD indices are defined (Figure 1) as the relationship between the area under the curve (AUC) during a 24-hour period or maximum drug concentration (Cmax), the minimal inhibitory concentration (MIC) and the drug’s efficacy. The aim with targeted PK/PD indices is to improve effectiveness and to help minimize the development of resistance by having a higher AUC/MIC, Cmax/MIC or longer time (T) above the MIC. The optimal response is when the antimicrobial concentration is above MIC for over 40–50% of the dosing interval (Figure 1).

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The optimum timing, frequency, and number of antimicrobial doses that should be administered to achieve this in cats and dogs has been poorly defined as the data is not available. To achieve this, we must understand the pharmacology of the drugs we are using.

Martinez and others (2012) have suggested that the best approach for using perioperative antimicrobials is to “hit hard and fast and get out quick”. Time-dependent killing is characteristic of perioperative antimicrobial classes, such as the β-lactams, and seeks to optimize the duration of exposure of a pathogen to an antimicrobial. Recently, it has been suggested that, where antimicrobial prophylaxis is used during longer procedures, a loading dose and then a continuous rate infusion (CRI) may be a better option for maintaining dosages above MIC.7 Data shows that, during prolonged procedures, drug concentrations remain above the target MIC from incision throughout the surgery, to wound closure. It has also been shown that in order to minimize the risk of MDR using such a protocol, the plasma concentration needs to be four times that of the MIC. The use of CRIs, although logical, has yet to gain traction in human or veterinary surgery, although it has gained some popularity in intensive care units.8 There is currently no data available in veterinary medicine to readily calculate the dose required based on maintaining the concentration at four times MIC for time dependent antibiotics; in humans it is calculated

Table 1: Wound classification. Modified after (Berard & Gandon21).

<table>
<thead>
<tr>
<th>Classification</th>
<th>Veterinary infection rates</th>
<th>Human Infection rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clean</td>
<td>2.0–4.9%</td>
<td>1.3–2.9%</td>
</tr>
<tr>
<td>Clean-contaminated</td>
<td>3.5–4.5%</td>
<td>2.4–7.7%</td>
</tr>
<tr>
<td>Contaminated</td>
<td>4.6–9.1%</td>
<td>6.4–15.2%</td>
</tr>
<tr>
<td>Dirty</td>
<td>6.7–17.8%</td>
<td>7.1–40%</td>
</tr>
</tbody>
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Table 2: Published veterinary and human infection rates based on wound classification system.2,3,22

![Figure 1: Graph representing pharmacokinetic/pharmacodynamic indices. C(max): Maximum concentration. MIC: Minimum inhibitory concentration. AUC: Area under the curve.](image)
from known drug clearance rates and using normograms to aid calculation.

**Perioperative dosing regimes in small animals**

Although antimicrobial prophylaxis is well used and documented in veterinary surgery, there is in fact little hard evidence to support its use, with the results of a number of studies being conflicting. Dosages and regimens are largely extrapolated from human literature, textbooks or surgeons’ opinion, with little or no thought given to MICs or PK/PD indices, and as noted above, the optimum timing, frequency and number of antimicrobial doses that should be administered to achieve this, has been poorly described.

**Intravenous antimicrobials available in the UK**

**Cefuroxime**

Cefuroxime is routinely used in the UK as a perioperative antimicrobial in canine and feline surgery. It is active against Gram-positive bacteria with broader activity against Gram-negative bacteria than first-generation cephalosporins (e.g. cefazolin) especially *Enterobacteriaceae* spp. but is not effective against *Pseudomonas aeruginosa*: it also has activity versus obligate anaerobes. There is, however, very limited data on dosing regimes for this antimicrobial in veterinary use; the BSAVA *Small Animal Formulary* recommends a dose of 10–15 mg/kg intravenously (i.v.) but is not specific on a prophylactic dose. The MIC breakpoint (chosen concentration of an antimicrobial which indicates whether a species of bacteria is susceptible or resistant to the antimicrobial) data for cefuroxime is not available for dogs or cats. Albarellos and others (2016) showed that a dose of 20 mg/kg given intravenously in dogs will give a T above MIC 50% for 3.75 hours (the concentration drops off rapidly after this time), and that the elimination half-life is 60–80 minutes. To maintain a concentration above MIC for longer procedures (over 2 hours) it would be prudent to redose at intervals of 120–160 minutes. The author is not aware of similar work in the cat using cefuroxime, although it has been shown that a single intravenous dose of 20 mg/kg of the first generation cephalosporin, cefazolin in cats achieves a concentration above MIC for at least 4 hours.9

**Co-amoxiclav**

Co-amoxiclav (clavulanic acid potentiated amoxicillin) is also routinely used in the UK as a perioperative antimicrobial. It is active against many Gram-positive and Gram-negative bacteria although *Pseudomonas aeruginosa* and *Klebsiella* spp. are usually resistant. Co-amoxiclav does have activity versus obligate anaerobes. There is surprisingly little published information on its pharmacokinetics in the dog and cat. For perioperative use, the usual recommendation is for 22 mg/kg i.v. and for this to be repeated at 90–120 minute intervals. This regime has been extrapolated from human data, with no veterinary evidence for its use in this way. Recent studies in the dog10 and cat11 show that an oral dose of 25 mg/kg maintains a concentration above MIC in both species for over 4 hours. By extrapolation, a dose of 25 mg/kg repeated every 90–120 minutes may be a better dose, but further work is needed to clarify this.

**Metronidazole**

Metronidazole, a concentration dependent antibiotic, has been advocated where anaerobes are a particular concern.12 Recent work in cats13 shows that a dose of 5 mg/kg given intravenously achieves a concentration above the MIC for most anaerobes for 6–8 hours. This suggests that a single dose of 5 mg/kg would be suitable for cats every 12 hours. Similar data for dogs does not exist; although its terminal half-life is statistically similar to that in cats it is not possible to extrapolate a dose.13,14 The BSAVA *Small Animal Formulary* gives a dose of 15–25 mg/kg i.v. Metronidazole has become an important tool in the management of *Clostridium difficile* in human medicine, for that reason it should be used sparingly in veterinary species.

If there are concerns regarding perioperative infection control procedures, the use of postoperative antimicrobials may be prudent

Should postoperative antimicrobials be used after clean orthopaedic implant surgery?

There has been much debate in the veterinary literature as to whether post-operative antibiotics are necessary for clean procedures where an implant is used.1,2,15–17 A number of studies have been published with conflicting results and conclusions; the evidence from these papers is inconclusive as they are level 418 prospective or retrospective studies with only one control study published.19 In human orthopaedic surgery, current guidelines including those for total hip replacement recommend that antibiotics are not used beyond 24 hours after surgery, the evidence level for this is 1–3.20

A number of veterinary papers have suggested that there is a protective effect in prescribing post-surgical antimicrobials for between 5 and 10 days, for clean procedures where an implant is used.15,16 However,
two other recent papers suggest that there is no protective effect in using postoperative antibiotics on infection rates. Nazarali et al. (2014) suggest that the protective effect of postoperative antibiotics may be present due to deficiencies in perioperative infection control procedures.

Based on the current, albeit weak, evidence, cefuroxime can be considered as a perioperative antimicrobial for clean orthopaedic implant surgery which is only administered during the surgical procedure. However, this is not conclusive and if there are concerns regarding perioperative infection control procedures, the use of postoperative antimicrobials may be prudent.

Conclusion

Perioperative antimicrobials should not be used on any clean surgical procedures. For clean-contaminated and contaminated procedures the choice of antimicrobial is harder and is based on some veterinary evidence together with extrapolation from human data. Current guidelines indicate administration should be 30–60 minutes before the first skin incision.

Cefuroxime has a suitable spectrum of activity and pharmacokinetic/pharmacodynamic index and should be administered intravenously in both the dog and the cat at 20 mg/kg and the dose repeated during long procedures at 120–180 minute intervals.

Where co-amoxiclav is chosen, a dose of 22–25 mg/kg i.v. should be used and repeated every 90–120 minutes during long procedures.

If anaerobes are a concern (e.g. for colonic surgery), metronidazole can be administered intravenously as a single dose at 5 mg/kg in the cat and 15–25 mg/kg in the dog.

In non-orthopaedic procedures there is no evidence that giving antimicrobials beyond the surgical procedure has any benefit for the patient, and it is likely to increase the risk of MDR developing.

For clean orthopaedic procedures where an implant is used the evidence is inconclusive and if there are concerns regarding the SSI control procedures, the use of postoperative antimicrobials may be sensible.

For dirty wounds (pre-existing infection), antimicrobial choice should be based on the results of culture and sensitivity testing. When the results of culture and sensitivity are pending, it would be prudent to use cefuroxime and metronidazole (where suitable), using the criteria noted above, until those results are available.

More work is required on pharmacokinetics and MIC breakpoints in veterinary species to allow for better informed use, both prophylactically and therapeutically.

References and further reading are available at www.bsavalibrary.com and in e-Companion.