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REVIEW ARTICLE

Antibiotic prophylaxis in veterinary cancer chemotherapy: A review and recommendations

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Bacterial infection following cancer chemotherapy-induced neutropenia is a serious cause of morbidity and mortality in human and veterinary patients. Antimicrobial prophylaxis is controversial in the human oncology field, as any decreased incidence in bacterial infections is countered by patient adverse effects and increased antimicrobial resistance. Comprehensive guidelines exist to aid human oncologists in prescribing antimicrobial prophylaxis but similar recommendations are not available in veterinary literature. As the veterinarian's role in antimicrobial stewardship is increasingly emphasized, it is vital that veterinary oncologists implement appropriate antimicrobial use. By considering the available human and veterinary literature we present an overview of current clinical practices and are able to suggest recommendations for prophylactic antimicrobial use in veterinary cancer chemotherapy patients.

KEYWORDS

antimicrobial prophylaxis, antimicrobial stewardship, antineoplastic agents, neutropenia, veterinary oncology, veterinary practice guidelines as topic

1 | INTRODUCTION

The aim of antimicrobial prophylaxis is to administer antimicrobials to patients considered to be at risk of infection in order to prevent an infection from developing. Patients at risk of infection include those undergoing surgical procedures or those with immunosuppression for a variety of reasons including cancer chemotherapy. However, as multi-resistant organisms continue to emerge and few new antimicrobials are approved, current antimicrobial use protocols have come under intense scrutiny.[1] This is particularly true in the veterinary setting as evidence mounts on the possibility of transfer of resistant organisms or genes not only between animals but also from animals to humans.[2]

Antimicrobial stewardship among veterinary practitioners is key in reducing the selection pressure for resistant bacteria[3] with the American Veterinary Medical Association urging vets to "commit to stewardship."[4] The British Veterinary Association's 7-point plan for the responsible use of antimicrobials goes a step further to specifically advise minimizing prophylactic antimicrobial use.[5] However, in order to achieve this, effective guidelines on antimicrobial administration are essential. For surgical prophylactic antimicrobial use, numerous recommendations, based on veterinary and human literature, are now available to guide clinicians.[6,7] However, there is evidence from the United Kingdom, Australia, New Zealand and Belgium that despite the availability of antimicrobial usage guidelines there is still poor compliance and suboptimal use of antimicrobials in both prophylactic and disease settings.[6,8–11] This poor compliance may be due in part to the numerous and often slightly conflicting resources available and a subsequent lack of clear message.

In the setting of veterinary cancer chemotherapy antimicrobial prophylaxis is a newer concept, and far fewer resources are available to guide clinicians.[7,12,13] Any recommendations are often minimally evidence based and may not be easy to access. At this stage, there is an opportunity to create clear, unified and evidence-based guidelines and potentially avoid the plethora of data sources and ingrained practice policies that can complicate surgical antimicrobial prophylaxis.

In human oncology there is ongoing debate surrounding prophylactic antimicrobial use. This is due to fears of resistant organism development and the reduction in efficacy of cancer chemotherapeutics counteracting the benefits of infection prevention.[14] One human

literature review and modelling study suggested that for a 30% reduction in antimicrobial efficacy there would be 683 additional deaths per year in patients receiving chemotherapy for haematological malignancies.[15] This suggests that some cancer chemotherapy patients have a marked benefit from antimicrobial use, however, only if antimicrobials are appropriate and efficacious. It is therefore vital that we try to preserve antimicrobial efficacy for these at risk patients by using them appropriately. By assessing evidence from both human and veterinary literature, it is possible to determine whether veterinary patients receiving cancer chemotherapy require prophylactic antimicrobials and to outline defined criteria for their use.

2 | NEUTROPENIA

As neutrophils are a vital component of the innate immune response, any depletion in neutrophil number can predispose the patient to infection and provide an indication for antimicrobial prophylaxis. Neutropenia following chemotherapy administration is a well-characterized adverse event in both human and veterinary oncology. Typical normal reference ranges for absolute neutrophil count (ANC) in complete blood counts (CBCs) in dogs and humans are around 3 x 10^9 to 7 x 10^9/L, although this varies between laboratories. Human studies in the 1960s identified an increased risk of infection when the ANC fell below 2 x 10^9/L, with patients below 0.5 x 10^9/L were considered to be high risk and below 0.2 x 10^9/L were very high risk.[16] More contemporary human studies define a neutropenia of clinical concern as below 1.0 x 10^9/L with most centres focusing on patients with an ANC of less than 0.5 x 10^9/L.[17–19] In veterinary patients, the Veterinary Cooperative Oncology Group has created a grading system to allow classification of the various levels of neutropenia following chemotherapy administration. According to this system an ANC of below 0.5 x 10^9/L is classified as a grade 4, severe neutropenia.[20] For veterinary patients, a grade 3 neutropenia (<1 x 10^9/L) is generally considered clinically significant, particularly if there is likely to be a decline in neutrophil numbers in the next 24 to 48 hours.[12,21,22] Prevalence of grade 3 or 4 neutropenia in humans varies widely from around 10% to over 40% dependant on the centre, type of chemotherapy protocol used and any specific patient risk factors.[15,23] The prevalence in dogs is generally considered to be lower than in humans but varies widely between studies and depends on the chemotherapy protocol used.[24–26]

Of additional importance in conjunction with the ANC is the clinical status of the patient. In particular, pyrexia accompanying a neutropenia is of far more clinical concern than if a patient is afebrile and clinically well, as it indicates the probable presence of infection. Febrile neutropenia is a medical emergency for both veterinary and human patients, necessitating immediate medical attention and administration of empirical broad spectrum antimicrobials to prevent progression of infection.[27] Human chemotherapy protocols are classified as high, intermediate or low risk for inducing febrile neutropenia, with high-risk protocols resulting in a febrile neutropenia rate of greater than 20%.[28] Most current human protocols are classified as intermediate risk with one recent retrospective cohort study in the United States identifying a 16.8% rate of febrile neutropenia in patients receiving chemotherapy for a solid tumour or non-Hodgkins lymphoma.[19,28] In this study, 83.2% of febrile neutropenic patients were hospitalized and hospital mortality rate was 8.1%.[19] The risk of febrile neutropenia appears to be lower in veterinary patients, with most studies reporting rates of less than 10%.[21,26,29] However, higher rates are reported with some chemotherapy protocols[30,31] and mortality among hospitalized canine patients is similar to the human studies with rates around 8%.[32]

3 | HUMAN TRIALS ASSESSING ANTIMICROBIAL USE

There are now several randomized control trials assessing prophylactic antimicrobials in human cancer chemotherapy patients. Two large trials assessed the efficacy of levofloxacin compared to a placebo given prophylactically to patients receiving chemotherapy for various malignancies. In these trials there was a statistically significant reduction in fever, microbiologically documented infections and hospitalization, although there was no significant difference in mortality between the two groups.[18,33] Meta-analysis of multiple randomized control trials did indicate a reduction in mortality for neutropenic patients on antimicrobial prophylaxis although some trials in these analyses were inadequately powered to accurately predict mortality.[34,35]

Even without strong evidence for a reduction in mortality with antimicrobial prophylaxis in humans there is reasonable evidence in humans for a reduction in febrile neutropenias and hospitalization rates.[36] This reduction has multiple positive outcomes including a reduction in the cost of the overall treatment (an extremely important factor for organizations such as the National Health Service [NHS]). In addition, one human study found that patients with hospitalization because of febrile neutropenia in their first chemotherapy cycle were 4.4 times more likely to terminate their chemotherapy protocol prematurely than those who were not hospitalized.[37]

4 | VETERINARY LITERATURE

There are far fewer studies assessing the efficacy of antimicrobial prophylaxis in dogs. One, much cited, double-blinded placebo-controlled study assessed prophylactic trimethoprim sulfadiazine (TMPS) administration during doxorubicin chemotherapy in dogs with lymphoma and osteosarcoma. Seventy-three dogs were investigated, 34 with osteosarcoma and 39 with lymphoma. Dogs receiving prophylactic TMPS experienced a significant reduction in non-hematologic toxicity (gastrointestinal toxicity, hospitalization, suspected infection) compared to the placebo group. However, the occurrence of sepsis was not specifically assessed in this study and the chemotherapy protocol was low risk with only 3 out of 73 animals developing febrile neutropenia.[24] Several other studies in dogs have used TMPS prophylaxis, particularly when investigating protocols with a higher dose intensity and where more severe haematological toxicity was expected.[38–40] It is difficult to compare infection and hospitalization rates between studies particularly as different protocols and hospital

populations are involved. In this context, some studies reported a higher incidence of myelosuppression than with other more standard protocols but no associated increase in hospitalization or febrile neutropenia among the dogs, suggesting a possible protective role for TMPS used in this setting.[41,42]

A few veterinary papers have conflicting evidence about the efficacy of antimicrobial prophylaxis. One case series assessing the toxicity associated with epirubicin in dogs found no difference in the percentage of vomiting, diarrhoea, pyrexia or hospitalization between dogs receiving antimicrobials and those without. However, as assessing antimicrobial prophylaxis was not the primary aim of the study it is difficult to interpret the significance of this.[29] A study evaluating factors associated with prolonged hospital stay assessed 70 dogs that developed febrile neutropenia following cancer chemotherapy. About 22% of these dogs had received prophylactic antimicrobials and there was no significant difference in the length of hospitalization or survival compared to dogs that had not received prophylaxis.[32]

The reduction in cost of treatment and hospitalization rates noted in human trials would also be key benefits for veterinary chemotherapy patients if present. Clients may be more willing to proceed with chemotherapy if there is a lower risk of adverse effects and a reduction in the overall cost of treatment. With these factors in mind, it is tempting to prescribe antimicrobials prophylactically in the hope that they will be protective and reduce adverse effects.

5 | ANTIMICROBIAL RESISTANCE

In spite of the possible benefits of antimicrobial prophylaxis there are considerable concerns regarding their use, in particular, the development of antimicrobial resistance. There are two main factors in the development and spread of antimicrobial resistance: antimicrobial selection pressure and clonal dissemination or spread of resistant species.[36] Administering antimicrobial prophylaxis can exert a selection pressure within the microbial flora of an individual patient and can result in the emergence of antimicrobial-resistant strains. There are increasing reports in the human literature of fluoroquinolone-resistant organisms isolated from patients receiving chemotherapy prophylaxis. One literature review reported resistance to standard prophylactic antimicrobials in 26.8% of pathogens causing infections after chemotherapy in the United States.[15] Many centres report an increase in the number of patients colonized by fluoroquinolone-resistant organisms in rectal cultures obtained after fluoroquinolone-based prophylaxis[43,44] and bacteria with increased mutation frequency and antimicrobial resistance are present in higher levels in the commensal flora of patients receiving several courses of antimicrobials.[45] In addition, fluoroquinolone administration has been cited as a risk factor for the progression from intestinal colonization with extended spectrum beta-lactamase producing Enterobacteriaceae to blood stream infection, with a fluoroquinolone resistance rate of greater than 50% among *Escherichia coli* bloodstream isolates in some cancer patients.[44,46] In one study, levofloxacin administration also tended to increase the minimum inhibitory concentration for viridans group streptococci in the bowel and throat microflora of patients with haematological malignancies.[46]

Specific veterinary studies assessing resistance in chemotherapy patients are not available. However, prior antimicrobial use has been identified as a risk factor for resistance in *Staphylococcus pseudointermedius* ear and skin isolates in dogs.[47] Increasing number of antimicrobial courses was also associated with increased risk of development of methicillin-resistant *Staphylococcus aureus* (MRSA) in a case control study involving 150 veterinary practices.[48] One study in 7 healthy dogs found that faecal *E. coli* species exhibited resistance to multiple antimicrobials after 4 to 7 days of amoxicillin administration.[49] Resistant organisms also tended to return to pre-antimicrobial administration levels and resistance profiles following cessation of antimicrobials in some studies.[44,49]

One meta-analysis did not find any significant increase in infections caused by resistant pathogens in patients receiving prophylactic antimicrobials compared to placebo.[50] In addition, it can be difficult to determine whether the increasing number of resistant bacteria isolated from oncology patients are because of patient-specific antimicrobial prophylaxis or whether they are a symptom of the general increase in incidence of resistant nosocomial infections.[2] However, the reality of a global rise in resistant infections is inescapable and therefore careful consideration must be given to the benefits vs risks of prophylactic antimicrobial use.[2]

6 | THE MICROBIOME

Systemically administered antimicrobials have been reported to have a dramatic impact on the composition and function of the gastrointestinal microbiome, a key factor in increasing gastrointestinal colonization by pathogenic and resistant bacteria.[51] There is also significant evidence in humans that disruption of the intestinal microbiome during chemotherapy because of prophylactic antimicrobials as well as immunosuppression and mucositis can predispose to infections with *Clostridium difficile*.[52]

Worryingly, there is now increasing evidence that disruption of the microbiome may reduce the efficacy of chemotherapy treatment. A study in mouse models of colon carcinoma and melanoma has revealed that tumour necrosis and immune responses after treatment with platinum chemotherapy were reduced in mice treated with antimicrobials prior to therapy.[53] In addition, melanoma, sarcoma and colon cancers failed to respond to CTLA-4 blockade immunotherapy in antimicrobial-treated mice, and antimicrobials with Gram-positive spectrum reduced the efficacy of cyclophosphamide when administered to mice with lymphoma.[54,55] Based on these studies it is suspected that the commensal microbiome (particularly in the small intestine) is essential for an optimal response to chemotherapy. This is likely to be because of the effects such as bacterial translocation and activation of helper T cells, induction of reactive oxygen species and modulation of cell functions in the tumour microenvironment.[51]

Other detrimental effects to patient health have been reported with disruptions to the microbiome including alterations in metabolites and cytokine profiles and inflammatory immune responses. One study found that alterations in the intestinal microbiome of patients

receiving fluoroquinolone prophylaxis after haematopoietic stem cell transplantation were predictive of pulmonary complications such as lung infiltration.[56] A "catch 22" situation has been described in human medicine where chemotherapy induces mucosal injury and inflammatory response, antimicrobials are given prophylactically at this stage to try to prevent infection but induce microbial dysbiosis leading to potential pulmonary complications, reduced responses to chemotherapy, inflammatory colitis, *C. difficile* and resistant infections.[51]

There are several studies indicating that prophylactic antimicrobials may have similar effects on microbial diversity and disruption of the microbiome in dogs. One study reported that administration of the macrolide antimicrobial tylosin altered microbial composition and had prolonged effects with changes continuing for over 28 days after completion of a 14-day antimicrobial course.[57] Another study demonstrated that oral administration of metronidazole markedly decreased bacterial diversity in the gut microbiome with an increase in potentially pathogenic bacteria such as Enterococcaceae, Enterobacteriaceae and *Streptococcus*.[58]

7 | PATIENTS AT RISK

With mounting evidence of the disadvantages of antimicrobials, it is important to try to refine their use in cancer chemotherapy patients. The National Institute for Health and Care Excellence (NICE) provides clinical guidelines for the management of neutropenic sepsis in human patients with cancer treated in the United Kingdom. These guidelines are based on systematic reviews of the literature but also consider cost effectiveness. They recommend fluoroquinolone prophylaxis for adult patients most at risk of developing sepsis. These are patients with acute leukaemias, stem cell transplants, those on high dose chemotherapy and those in the first cycle of chemotherapy.[36,59]

Risk of infection is a key concept on which many human antimicrobial prophylaxis guidelines are based.[60,61] Many human hospitals use the multi-national association for supportive care in cancer (MASSC) index to stratify patients at risk of sepsis and allow them to prescribe prophylaxis in a more targeted way. This index found that patients were more likely to have septic complications if they presented with hypotension, respiratory failure, altered mental status, congestive cardiac failure, arrhythmias, renal failure, were over the age of 60 or had severe symptoms of their disease or high disease burden.[61]

In dogs, a case control study by Sorenmo et al investigated risk factors for development of febrile neutropenia and revealed several similar risk factors to the human studies.[62] Thirty-nine dogs that developed febrile neutropenia while undergoing standard cancer chemotherapy protocols for various malignancies were compared to randomly selected controls that did not develop febrile neutropenia but were receiving similar chemotherapy protocols. This study found that dogs with lymphoma and dogs with lower body weights were significantly more likely to develop febrile neutropenia than larger dogs or those with solid tumours. The increased risk in smaller dogs has also been observed in another study where a significant increase in myelosuppression was noted in dogs weighing under 14 kg compared to dogs weighing greater than 14 kg.[63] In the study on TMPS prophylaxis, the greatest benefit of prophylaxis was seen in dogs with lymphoma, supporting the finding that dogs with lymphoma seem to be more at risk of sepsis.[24] Lymphoma was also the most common tumour in cats with febrile neutropenia in one paper.[64] The Sorenmo et al study also found that dogs were more likely to develop febrile neutropenia if they had received doxorubicin or vincristine, and in the Pierro et al study, cats were at higher risk if they had received lomustine or vinka alkaloids.[64] However, as these drugs are used most frequently in lymphoma protocols it is difficult to determine whether they are truly causative agents of the increased risk or if this finding is due to confounding.[62] An additional finding of the Sorenmo et al study was that 71.8% of dogs were in the induction phase of their protocol when they developed febrile neutropenia, with 48.7% developing it after receiving the chemotherapeutic drug for the first time.[62]

In addition, there is now an increasing evidence that certain breeds of dog, in particular, Collies and herding breeds, are at increased risk for toxicity, such as neutropenia, from certain cancer chemotherapeutics. This is because there is a high frequency of a germline mutation, the ABCB1Delta polymorphism (formerly known as MDR1) in these breeds. This gene encodes a P-glycoprotein drug efflux pump that excretes drugs from the cell in normal dogs. In dogs with a heterozygous or homozygous mutation, there is decreased excretion of drugs transported by the pump (such as vincristine and doxorubicin) and thus increased exposure of the patient to drug toxicity.[21,65,66] Genetic testing should be considered for dogs of breeds with a known risk of the mutation prior to initiation of treatment with drugs transported by the pump.

A second study by Britton et al, from the same institution as the Sorenmo study assessed factors associated with prolonged hospital stay in febrile neutropenic dogs receiving chemotherapy. This study assessed 70 dogs receiving various cancer chemotherapy protocols for various malignancies. They found that tachycardia on admission, gastrointestinal signs, decreasing neutrophil count after admission and documented infection (pneumonia or urinary tract infection) were all factors associated with a prolonged hospital stay. In addition, hypotension and granulocyte colony stimulating factor (GCSF) use were significantly associated with death in hospital although the result for GCSF was suspected to be because of bias.[32] Several of these factors are also present in the MASSC index, in particular, hypotension. Utilization of these risk factors to guide therapy has obvious potential.

8 | TIMING AND DURATION OF TREATMENT

If prophylactic antimicrobials are indicated, it is important to consider when they should be administered. In febrile neutropenia cases, prompt treatment with empirical antimicrobials is recommended by both veterinary and human texts. British human guidelines recommend starting antimicrobial therapy within 1 hour of documenting pyrexia and neutropenia.[61] However, several studies have not found any improvement in mortality or overall outcome based on quicker initial administration of antimicrobials and this is currently under review in the human literature.[67,68] Despite some conflicting evidence on the exact timing of initial administration of antimicrobials, waiting for blood or urinary culture results to inform antimicrobial choice is

contraindicated.[12,13,61] A rational empirical choice must therefore be made in the first instance.[12,13,61]

In patients that are not septic, antimicrobials may be administered prophylactically at the time of cancer chemotherapy protocol initiation or on first documentation of a neutropenia. There are no randomized control trials investigating a difference between these times of administration and meta-analysis has not identified a significant difference between the two groups, so typically they are combined for analysis in human studies.[35] Starting prophylaxis at the time of chemotherapy protocol initiation is more common in human studies while administration of antimicrobials on documentation of a neutropenia is more common in veterinary patients. This may be because neutropenia is far more likely to occur with human chemotherapy protocols so prophylaxis is administered in anticipation.

An additional complicating factor in deciding when to administer antimicrobials comes in defining a significant neutropenia. As already discussed, an ANC of below 0.5 x 10^9/L is considered high risk for infection.[16] However, the "cut off" ANC at which to start antimicrobial prophylaxis seems to vary widely among institutions. Human guidelines in the United States recommend starting antimicrobial prophylaxis only in patients with an ANC of less than 0.1 x 10^9/L for longer than 7 days.[69] Other studies and British guidelines recommend initiation of prophylaxis for suspected neutropenia of less than 0.5 x 10^9/L.[33,61]

In veterinary patients, the ANC cut off tends to be higher than in people and most veterinary texts recommend antimicrobials for any ANC lower than 1.0 x 10^9/L, although this is an empirical value.[12,13,21] The reported reasons for a higher cut off are multiple and include a less predictable neutrophil nadir and lower tolerance of adverse effects in pets by clinicians and owners. For most chemotherapy drugs, the neutrophil nadir is at 5 to 7 days post-administration and typically CBC is performed 1 week post-chemotherapy administration to assess the ANC. This blood sample is very much a "snapshot in time" and does not reflect whether the animal's ANC is rising or falling on that particular day.[13] In addition, some cancer chemotherapy drugs such as lomustine or carboplatin, have been documented to have a prolonged or late neutrophil nadir.[70,71] As serial blood tests are rarely a viable option, because of patient compliance and costs, if a borderline low ANC is documented many clinicians will err on the side of caution and prescribe prophylactic antimicrobials. In a survey of veterinarians attending the 2009 Veterinary Cancer Society Annual Conference, 9% of vets started antimicrobial prophylaxis for any neutrophil count lower than the laboratory reference range and 29% of vets started antimicrobial prophylaxis for any ANC below 1.5 x 10^9/L in dogs with lymphoma.[72] This suggests that a concerning number of clinicians are prescribing antimicrobials even more frequently than suggested in current veterinary texts. The ANC cut off for antimicrobial prophylaxis used at the authors' institution is 0.75 x 10^9/L with recent data suggesting that this may be reasonable for clinical use.[73]

The length of antimicrobial administration also varies widely between centres and protocols, with mean duration of antimicrobial administration ranging from 10 to 151 days in one recent human meta-analysis.[35] Typically, duration of prophylactic antimicrobials is dependent on the time point at which they were initiated. For instance, in studies where antimicrobials are administered because a neutropenia is expected that they are administered for the length of the anticipated neutropenia (typically around 7 days). One study found that 40% of febrile neutropenic episodes occurred outside the expected period of neutropenia (the period of prophylaxis in this study) suggesting that timing based on the anticipated neutropenia may not be optimal.[33] Other studies recommend antimicrobial administration for the entire time that the patient is receiving cancer chemotherapy. Most veterinary texts advise a 3 to 7-day course of antimicrobials on documentation of a neutropenia, although this is not evidence based.[12,13,21] An alternative approach is to administer prophylactic antimicrobials until the ANC has increased back to above the original cut off value used to initiate the therapy. This is an approach adopted by our institution and in several human studies and seems an appropriate approach as long as there is no documented infection.[35]

There is limited data comparing antimicrobial courses of 2 to 3 vs 7 days. However, increasing data comparing longer vs shorter antimicrobial courses is available. A human systematic review found that mechanically ventilated patients with hospital-acquired pneumonia receiving a 7-day course of antimicrobials had the same clinical outcomes as similar patients receiving a 10 to 15-day course, with some evidence that those receiving a 7-day course were less likely to develop multi-resistant infections.[74] However, neutropenic patients were excluded from several of the studies in this review.[74] The findings are similar to those of a retrospective, multi-centre, cohort study which found that human patients with Enterobacteriaceae bacteraemia treated with a short antimicrobial course (median 8 days) had the same mortality and infection recurrence rates as those treated with a longer antimicrobial course (median 15 days).[75] Around 34% of patients in the study were immunocompromised, for a variety of reasons including chemotherapy, split evenly between the short and long course groups.[75] Fewer multi-drug resistant infections were described with the shorter antibiotic course in this study.[75] A recent veterinary, prospective, observational study in 47 dogs with uncomplicated pneumonia did not find any significant difference between dogs treated with a short course of antimicrobials (<14 days) compared to those treated with a longer course (>14 days) in radiographic resolution or relapse rate. However, these data can only be considered as preliminary as the dogs were not randomized and only 3 had confirmed bacterial pneumonia.[76] Dogs in this study were excluded if they had received chemotherapy.[76] While further studies are needed in patients that have received chemotherapy, withdrawing prophylaxis on resolution of clinical signs and severe neutropenia appears to be a more appropriate choice than an empirical 7-day course, as the dogma of "completing the course" is increasingly challenged.[77] This is supported in the ACVIM consensus on antimicrobial use in animals where they advise that antimicrobials should never be continued once there is clinical and microbiological evidence that an infection has been eliminated.[78]

In addition to the appropriate length of treatment consideration should also be paid to the pharmacokinetics and pharmacodynamics of the antimicrobial used with particular care taken to consider the dose, dosing interval and site of desired action of the drug.[79] It is vital to use antimicrobials at an appropriately high dose as there is increasing evidence that subtherapeutic doses of antimicrobials may increase bacterial resistance.[78]

9 | CHOICE OF ANTIMICROBIAL

An additional important factor to consider is the choice of drug. In most infections in cancer chemotherapy patients, the source of septicaemia is bacterial translocation from the patient's own gastrointestinal tract. Other sources or sites of infection such as the urinary tract, respiratory tract or skin are also possible.

For patients that are febrile neutropenic, veterinary texts advise broad spectrum intravenous coverage for both Gram-positive and Gram-negative organisms and anaerobic and aerobic bacteria. This would involve a combination of drugs such as a penicillin and aminoglycoside combination or a cephalosporin and fluoroquinolone.[12] Significantly, human guidelines are moving away from this type of recommendation, with a clear shift away from extensive antimicrobial cover even in patients with suspected sepsis.[61] Use of a single antimicrobial is recommended with no addition of aminoglycosides unless there is a patient-specific indication such as a confirmed aminoglycoside responsive infection.[61] Meta-analysis of several human randomized control trials has found that oral antimicrobials (quinolones alone or combined with another antimicrobial) were as effective in preventing mortality and treating sepsis as intravenous antimicrobials in febrile neutropenic patients considered to be "low risk" of septic complications (as decided by the MASCC index).[80]

In a prophylactic setting, it is therefore even more important not to prescribe extensive and unnecessary antimicrobial coverage. In human oncology, the most frequently used antimicrobial for prophylaxis is levofloxacin, a second generation fluoroquinolone. Quinolones are generally favoured because of their broad spectrum of action, high concentration in faeces and minimal side effects. They also have very little activity against anaerobic bacteria, this spares the anaerobic gastrointestinal flora and can help to prevent overgrowth of pathogenic bacteria.[35] TMPS have similar broad spectrum and anaerobe sparing qualities, although they have been found to cause more adverse effects than quinolones including myelosuppression and *C. difficile* colitis.[60] Meta-analysis has not revealed any significant difference between quinolones and TMPS in mortality, febrile episodes or bacteraemia, yet it did find that the occurrence of Gram-negative infections and adverse effects were less in the quinolone group as opposed to the TMPS group.[35]

Some concerns have been raised that quinolones may not provide adequate cover for Gram-positive organisms such as viridans streptococci and coagulase negative staphylococci and the addition of Gram-positive cover with antimicrobials such as rifampin or amoxicillin has been trialled. Meta-analysis of these trials reveals that while there was a decrease in the number of Gram-positive bacteraemia episodes there was no significant difference in mortality and a significant increase in side effects in the patients receiving additional cover compared to quinolones alone.[35,81] An additional study found that patients receiving cyclophosphamide for chronic lymphocytic leukaemia who received antimicrobials with a Gram-positive spectrum had significantly reduced progression free and overall survival times compared to those receiving primarily Gram-negative spectrum antimicrobials or no antimicrobials at all. This finding is suspected to be related to alterations in the microbiome as discussed above.[82]

For antimicrobial prophylaxis in afebrile neutropenic animals veterinary texts advise oral antimicrobials similar to those used in humans, such as enrofloxacin or TMPS.[12,13,21] The only trial assessing prophylactic antimicrobials in dogs receiving cancer chemotherapy used TMPS. In this study, there was no obvious toxicity attributed to TMPS and as discussed above there was reduced morbidity in dogs that received it compared to placebo receiving controls.[24] TMPS also have the advantage of not being considered a critically important antimicrobial class for human use; but they are associated with a number of adverse effects in dogs including blood dyscrasias, keratoconjunctivitis sicca, hypothyroidism, hyperkalaemia, cholestasis, acute hepatic necrosis and skin disease.[83] This association has made them a less popular clinical choice. There is no specific literature regarding prophylactic quinolones in veterinary medicine. However, they have a similar spectrum of action to TMPS and generally seem to be better tolerated in dogs; although adverse effects can still occur including cartilage damage in young, growing animals, retinal toxicity in cats and reduced seizure thresholds.[84]

Yet unlike TMPS, fluoroquinolones are listed by the World Health Organization as critically important for human medicine and should therefore be safeguarded with any prophylactic use discouraged.[85] Also, quinolones are notorious in driving evolution of resistant bacteria and have been suggested to be a crucial factor in the evolution of hospital MRSA.[2] The NICE guidelines recommend that cancer centres in which patients are receiving fluoroquinolones for antimicrobial prophylaxis should monitor rates of antimicrobial resistance.[61] In addition, 2010 guidelines from the Infectious Diseases Society of America do not recommend routine use of fluoroquinolone prophylaxis in low risk (according to MASCC index) patients because of the low likelihood of sepsis in this group.[60] In veterinary patients the use of quinolones, particularly in a prophylactic setting has to be considered very carefully. A recent survey of Belgian general practice vets found that fluoroquinolones were the second most frequently prescribed antimicrobial after amoxicillin-clavulanic acid in dogs, in a recent UK study they were the fifth most frequently prescribed and studies in Italy and New Zealand also describe frequent use.[9–11,86] All of these studies commented that there was a tendency for overuse of fluoroquinolones, particularly for treatment of common diseases where broad spectrum cover is not required.[9–11,86] There is an obvious disparity between fluoroquinolone usage guidelines and clinical use, and the responsibility for reducing their use and using them only for appropriate clinical indications lies with veterinary clinicians.[9]

10 | GRANULOCYTE COLONY STIMULATING FACTOR

A possible alternative to prophylactic antimicrobials for neutropenia is the administration of GCSF. GCSF is a haematopoietic growth factor that promotes the proliferation and maturation of neutrophil precursors in the bone marrow thus increasing the neutrophil count.[87] There are several synthetic, injectable versions available such as filgrastim and pegfilgrastim. In human patients, prophylactic administration of these drugs has been shown to reduce the duration of grade 3 or 4 neutropenias and decrease the incidence of febrile neutropenias.[23] Some studies have suggested that use of GCSFs may decrease

TABLE 1 Recommendations for prophylactic antimicrobial use in clinically well dogs undergoing cancer chemotherapy

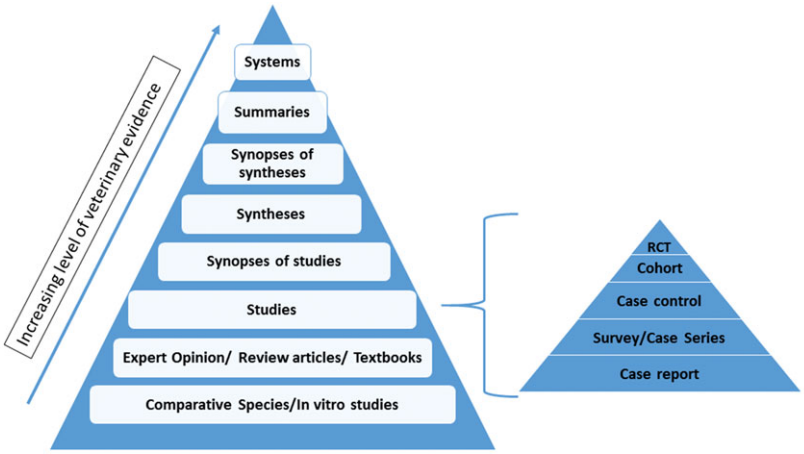
Prophylactic antimicrobial use	Choice of antimicrobial	Duration of treatment
Use indicated		
Neutrophil count: <0.75 × 10^9/L	Anaerobe sparing, broad-spectrum antimicrobial Do not prescribe additional Gram-positive cover	If no infection is documented: Measure CBC 3 days after antimicrobials are started Stop antimicrobials when the neutrophil count is >0.75 × 10^9/L
Use should be considered		
Neutrophil count: >0.75 × 10^9/L and <1 × 10^9/L and one or more of the risk factors below: • Haematological malignancies • Concomitant disease • Collie or herding breed that has tested positive for the ABCB-1delta mutation and is being treated with doxorubicin or a vinca alkaloid • Weight less than 14 kg	Anaerobe sparing, broad-spectrum antimicrobial Do not prescribe additional Gram-positive cover	If no infection is documented: Measure CBC 3 days after antimicrobials are started Stop antimicrobials when the neutrophil count is >1 × 10^9/L
Do not use		
Neutrophil count: >1 × 10^9/L		
Neutrophil count: >0.75 × 10^9/L and no risk factors		

hospitalizations and reduce the need for intravenous antimicrobials.[88] They are generally well tolerated in humans; the main side effect is bone pain although other less common adverse effects such as myalgia, psoriasis, vasculitis, pain on injection and headache have been reported.[89] This appears promising, yet their use in human oncology remains controversial, partly because several studies have been unable to demonstrate a reduction in mortality for patients receiving GCSFs.[88,89] These drugs are also expensive and economic analysis has suggested that administration of GCSFs in human chemotherapy patients is highly unlikely to be cost effective.[61,90] The NICE guidelines for UK practice recommend against offering GCSF for most patients unless they are undergoing a chemotherapy protocol with particularly high dose intensity.[61] US guidelines only recommend primary prophylaxis with GCSF for patients on a high risk chemotherapy protocol (one with a febrile neutropenia risk of greater than 20%).[23] Meta-analysis of two randomized control trials comparing the use of GCSF to prophylactic antimicrobials was unable to draw any useful conclusions to inform clinical practice because of low patient numbers, although there was no obvious difference between the 2 groups in mortality or febrile neutropenias.[88]

There is very limited evidence on the use of GCSF in dogs; canine recombinant GCSF is not readily available and is extremely expensive, human alternatives are available but are also costly.[21] With human GCSF there is a risk of cross species antibody production which may neutralize not only the human GCSF but also the endogenous canine GCSF and has been reported to lead to severe neutropenias.[91] One study found that canine GCSF did accelerate the recovery and decrease the severity of neutropenias in dogs treated with cyclophosphamide.[91] Since the study only looked at 6 healthy research beagles it cannot be used to guide treatment in canine cancer patients of varying breeds. Most veterinary texts therefore do not currently advise the use of GCSFs in veterinary patients except in cases of very severe neutropenia that is expected to be prolonged or if a known chemotherapy overdose has occured.[12,21,92]

11 | RECOMMENDATIONS

Because of the paucity of a veterinary-specific evidence base in this area, recommendations must be formulated relying heavily on extrapolation from human guidelines with the addition of minimal and



Within Table 1 evidence is ranked according to this evidence pyramid and represented as below; for each tier of evidence reached the corresponding tier of the pyramid is shaded in:

Represents systems level evidence

Represents no evidence at all

FIGURE 1 A revised evidence pyramid for veterinary clinical resources. Based on the recent evidence-based veterinary medicine association (EBVMA) symposium by Fricke[93]

anecdotal veterinary evidence. Multi-centre veterinary trials are required to generate the evidence on which to build veterinary-specific guidance. With the current climate of increasing antimicrobial resistance and the drive to reduce antimicrobial use, particularly within the veterinary sector it is vital that centres begin to investigate antimicrobial prophylaxis in more detail. On this basis we have constructed the following guidance as shown in Table 1.

The evidence has been ranked using the revised evidence pyramid for veterinary clinical resources suggested at a recent evidence-based veterinary medicine association (EBVMA) symposium by Fricke (Figure 1).[93]

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Conflict of interest

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