More is better – Reviewing the science behind duration of antimicrobial therapy

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Abstract

Antimicrobial resistance concerns have created a renewed interest in antimicrobial stewardship programs in both human and veterinary medicine. Due to the associated logistical and administrative burdens, formal antimicrobial stewardship programs have seen limited adoption outside of large institutional care centers. However, one of the key components of these programs is to optimize antimicrobial therapy – administration: of the right drug, to the right patient, at the right dose, by the right route, for the right duration. Optimizing dosing regimens does not have the same logistical burdens as a formal program, it simply requires evidential support and implementation by individual clinicians; which begs the question, "what is the basis for our current duration of antibiotic therapy recommendations?". To answer this question, a literature search was conducted to evaluate the scientific basis to support current recommendations for duration of therapy in veterinary medicine. Overall, the quantity and quality of scientific studies to support a specific duration of therapy for a specific antimicrobial was underwhelming. However, the limited data generally supports the assumption that shorter durations of therapy can be effective and should be more thoroughly investigated.

Key words: antimicrobial regimen, duration of therapy, antimicrobial stewardship

Résumé

La préoccupation à l'égard de la résistance antimicrobienne a relancé l'intérêt pour les programmes d'antibiogouvernance à la fois en médecine humaine et vétérinaire. En raison de la lourdeur administrative et logistique qui leur sont associés, les programmes officiels d'antibiogouvernance ont été peu adoptés au-delà des grands centres de soins institutionnels. Toutefois, l'une des composantes majeures de ces programmes est l'optimisation des thérapies antimicrobiennes et leur administration : donner la bonne drogue aux bons patients, à la bonne dose, par la bonne voie et pour la bonne durée. L'optimisation des régimes posologiques ne rencontre pas les mêmes embuches logistiques qu'un programme officiel. L'optimisation doit quand même reposer sur des preuves et requière une mise en place par des cliniciens. Cela nous amène à nous poser la question : sur quoi base-t-on les recommandations actuelles concernant la durée de la thérapie antibiotique? Afin de répondre à cette question, une recherche bibliographique a été menée afin d'évaluer la base scientifique des recommandations actuelles sur la durée de la thérapie en médecine vétérinaire. Dans son ensemble, la qualité et la quantité des études scientifiques supportant une durée spécifique pour une thérapie antimicrobienne particulière étaient peu impressionnantes. Néanmoins, le peu de données supporte quand même la supposition que des durées plus courtes de thérapie peuvent être efficaces et que ceci devrait être étudié plus à fond.

Introduction

The increasing threat of antimicrobial resistance has created a renewed interest in antimicrobial stewardship programs (ASP) in both human and veterinary medicine.[2,14] A formal human healthcare ASP would consist of 2 core strategies, prescribing audits with intervention and formulary restriction. A prescribing audit is where the primary physician interacts with an infectious disease specialist and the appropriateness of antimicrobial therapy is determined for the individual case. If deemed necessary, an alternate therapeutic is prescribed. Formulary restriction is an antimicrobial stewardship measure where specific antimicrobials or antimicrobial classes cannot be prescribed without the authorization of an infectious disease specialist. Both of these core strategies can lead to the reduced use of antimicrobials; however, they require significant levels of support in the form of an antimicrobial stewardship team, consisting of an infectious disease physician, clinical pharmacist, clinical microbiologist, information system specialist, infection control professional and hospital epidemiologist.[3] For obvious logistical reasons, this structure has limited the adoption of ASPs in community-based human healthcare settings, as well as private veterinary practices. Additionally, a formal human healthcare ASP is, for the most part, primarily focused on the *reduced* use of antimicrobials, without taking into consideration other factors impacting infectious disease. In veterinary medicine, an emphasis on disease prevention through vaccination, biosecurity, genetics, proper nutrition, etc. is an important component of antimicrobial use reduction.[8] However, there is another component of antimicrobial stewardship – optimized dosing regimens; i.e., those regimens that minimize the potential for antimicrobial resistance development while maintaining adequate efficacy. These regimens could be utilized in nearly every clinical setting

regardless of size to *refine* current antimicrobial uses. Optimized dosing regimens are not exclusive of antimicrobial use reduction measures and disease prevention practices, they are, in fact, quite complementary. If our disease prevention practices fail or an appropriate preventive intervention does not exist, wouldn't we want to use our antimicrobial resources in a manner which would promote their long-term efficacy? The primary hindrance to optimized dosing regimens is that the data to design therapeutic protocols that minimize resistance are sparse. While all aspects of the dosing regimen (dose, route, frequency and duration) could be evaluated, this review will focus on optimizing duration of antimicrobial therapy. Specifically, the objective of this review is to summarize and critically appraise the available scientific evidence comparing two durations of antimicrobial therapy.

Methods

In January 2017, a search of the biomedical literature was conducted using the PubMed database.[10] The term string ' "antimicrobial therapy" AND "duration" ' was used to conduct the search with a restricted publication date range of 5 years [only articles published January 2012 through January 2017 were retrieved].

After removing duplicate articles and articles not written in English, a single reviewer (BVL) evaluated all titles/abstracts for relevance. Relevant studies were those that compared 2 specific durations of therapy as the primary outcome. Studies not considered relevant to this review included editorials, manuscripts evaluating diagnostic testing, case reports/case series and review articles/position papers; these were specifically excluded. All relevant studies were included, despite any study limitations (e.g. lack of masking, non-standard treatment assignment); however, the limitations of each study are highlighted in the discussion below.

Results

The initial literature search returned 307 articles. Six articles were duplicates and an additional 18 articles were written in a language other than English. Of the remaining 283 articles, 1 editorial, 29 articles evaluating diagnostic testing, 49 case reports/case series, and 55 review articles/position papers were excluded from this review. After these exclusions, 149 articles remained. Of these, 140 articles did not compare two durations of antimicrobial therapy as the primary study outcome and were excluded from the review. Two of the remaining 9 articles could not be retrieved; therefore, 7 scientific papers are the basis of this review (Figure 1).

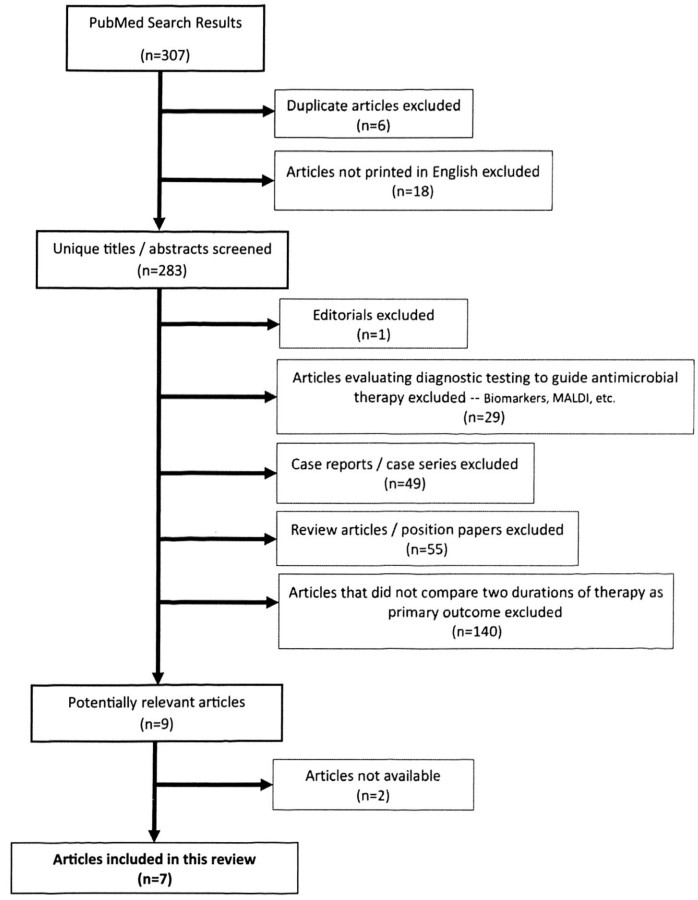

Figure 1. Literature search and publication exclusion strategy.

Discussion

Of the 7 relevant publications, only one article compared two durations of therapy in a veterinary species. In a prospective trial of horses undergoing exploratory celiotomy, patients were assigned to either short duration (72 hr) or long duration (120 hrs) of perioperative procaine penicillin G (22,000 IU/kg, q12 hr) and gentamicin sulphate (6.6 mg/kg, q24 hr).[5] The primary study outcome was development of incisional complications, which the investigators defined as any incisional drainage present 12 hours post-surgery. In total, 92 horses met criteria for inclusion in this study. In the short duration (72 hr) group, 14 of 42 horses developed an incisional complication, while 25 of 50 horses in the long duration (120 hr) group had incisional complications; a difference between groups that was not significant (p=0.17). The investigators concluded that a 72 hr duration of perioperative antimicrobial therapy was as effective at preventing incisional infections as 120 hr regimens in horses undergoing colic surgery. The investigators also suggested that 72 hrs may not be the minimum effective duration and that subsequent studies should be conducted to evaluate treatment durations less than 72 hrs. There are some limitations to the study design that deserve consideration. The most significant limitation is that the investigators did not report any methods of masking treatment assignment, potentially lead to investigator bias.[1] Another limitation is that the patients were assigned to treatment groups on a simple alternating basis, which could (unknowingly) lead to selection bias; however,

the investigators did not identify any significant differences between treatment groups regarding: patient characteristics on hospital admission, types of procedures performed, duration of anesthesia, postoperative clinicopathology test results, duration of hospital stay or duration of intravenous fluid support. Another limitation to this study is that there was no patient outcome data collected post-hospital discharge, thus the long term impacts of shorter duration antimicrobial therapy could not be evaluated.

The remaining 6 publications report findings from studies in human patients or animal models of human disease. While some extrapolation is required in applying the results of human medical studies to veterinary patients due to differences in dosing frequencies and treatment exposure (individual vs population), there are many similarities in the antimicrobial classes, pathogens, antimicrobial resistance mechanisms, pathophysiology and disease severity that make such extrapolations feasible. For these reasons, the findings and limitations of these studies are discussed here briefly.

In a clinical trial of 40 patients with diabetic foot osteomyelitis, Tone et al (2015) randomly assigned patients to receive either: 1) short duration (6 weeks) or 2) long duration (12 weeks) antimicrobial therapy.[13] The primary outcome was remission of diabetic osteomyelitis, defined as: the absence of local and/or systemic signs of infection, stabilized/improved radiographic abnormalities at the end of treatment and 1 year post-treatment, and complete healing of the wound responsible for underlying osteomyelitis. Remission was obtained in 60% of patients in the short duration group and 70% of patients in the long duration therapy group; a non-statistically significant difference in patient outcomes. These findings led the study authors to conclude that short duration (6 weeks) was as effective as long duration (12 weeks) antimicrobial therapy in resolving diabetic osteomyelitis of the foot in humans. The authors also noted that the incidence of (antibiotic associated) gastrointestinal adverse events was statistically lower in the short duration therapy group. One of the weaknesses of this study is that the antibiotic selection was not standardized, but rather based on antimicrobial susceptibility test results and the individual patient characteristics. While overall, the infecting bacterial species and antimicrobials prescribed were not statistically different between treatment groups, conclusions regarding the efficacy of short vs long duration therapy for individual drugs/classes could not be evaluated for such a small study population.

In another randomized clinical trial, patients with complicated intraabdominal infections were assigned to either a short, fixed duration (4 day) treatment regimen or a variable duration based on resolution of fever, leukocytosis and ileus (median treatment duration of 8 days).[12] In total, 518 patients at 23 sites throughout the US and Canada were randomized to treatment in this study. The primary outcome in this study was a composite measure consisting of any of the following negative outcomes: surgical site infection, recurrent intraabdominal infection or death within 30 days. There was no statistical difference between treatment groups in either the composite measure or the individual specific outcomes of surgical site infection, recurrent infection or death. The investigators, therefore, concluded that shorter (fixed) duration of antimicrobial therapy did not negatively impact patient outcome. In fact, shorter duration therapy reduced the time to diagnosis of surgical site infection and recurrent intraabdominal infection. While baseline patient demographics, disease severity and type of surgical procedures performed were not statistically different between treatment groups, this study is limited by the fact that treatment assignment was not masked and antimicrobial selection was not standardized, but based on individual pathogen and patient characteristics.

In a rodent model of induced intraabdominal infection investigators compared 3 day to 5 day durations of therapy with imipenem-cilistatin.[7] The primary outcome measure was 28 day mortality. Secondary outcomes were peritoneal bacterial load, clinicopathology profiles and cytokine profiles (as a surrogate marker for inflammation). There were no statistical differences in mortality, peritoneal bacterial counts or clinicopathology results and only 1 of 12 measured cytokines were significantly elevated in the short duration therapy group. Results of this study demonstrated that a 40% reduction in therapy duration did not decrease survival in a murine intraabdominal infection model. As an induced model, the time of disease insult and subsequent timing of treatment are known factors; this is most likely not the case in a clinical setting and thus, limits application of these results to clinical patients. While these investigators did show that shorter durations of therapy did not negatively impact patient outcome, they also only evaluated 3 and 5 days of therapy, when in fact, an even shorter duration may have produced equivalent results.

In a retrospective case-control study, Riccio et al evaluated the association between extended durations of therapy for intraabdominal infections and the subsequent development of extraabdominal infection (EAI) and mortality.[11] These investigators evaluated all intraabdominal infections occurring in a single hospital over a 14 year period with 549 cases developing secondary EAI. These 549 cases were matched (1:2) on the basis of disease severity score with control patients that did not develop secondary infection. In the final analysis, longer duration of therapy was statistically associated with development of secondary EAI and mortality. Although this study included a large population of patients, the evaluation period was quite long and the impacts of changing patient care and characteristics over time could not be evaluated. And while patients with EAI were at increased risk of mortality, duration of antimicrobial therapy was not the only predictor of EAI. Disease severity on admission, hospital (vs community) onset of intraabdominal infection, intensive care unit status at the time of intraabdominal infection, organ transplantation and days from hospital admission

to treatment of intraabdominal infection were also statistical predictors of subsequent EAI.

In a retrospective review of 33,336 male urinary tract infections (UTI), Drekonja et al evaluated the impact of short (≤7 day) vs long (>7 day) duration of antimicrobial therapy on recurrence of UTI.[4] Urinary tract infections were defined as patient visits that included: a corresponding *International Classification of Diseases* (ICD) code from a relevant care provider (dietitians, respiratory therapists, *etc.* were excluded) and a UTI-relevant antimicrobial prescription filled within 72 hours of diagnosis. The primary outcomes were the early (≤30 days) and late (>30 days) recurrence of UTI. There was no statistical difference between short and long durations of therapy in reducing early recurrence of UTI. However, longer duration therapy was significantly associated with an increase in late recurrence of UTI. Longer courses of therapy were also associated with increased *Clostridium difficile* infections. The considerable variability in patient co-morbidities and non-standardized antimicrobial selection limit the ability of this retrospective analysis to define the optimal duration for any specific antimicrobial / pathogen combination. And although duration of therapy was significantly associated with late recurrence of UTIs, it was not the only variable that predicted recurrent infection.

Muñoz et al conducted a retrospective analysis of the effect of short (<21 days) and long (≥21 days) durations of therapy on outcomes of patients undergoing surgery for infective endocarditis.[9] The measured outcomes included: development of renal failure, development of hepatic failure, total length of hospital stay, length of hospital stay post-surgery, mortality, relapse and reinfection. Mortality, relapse and reinfection rates were not significantly different between patients receiving short and long courses of therapy; leading the authors to conclude that short durations of antimicrobials for post-surgical therapy of infective endocarditis were safe. Given the serious limitations of this particular study, such a conclusion should be questioned. The primary limitation of this study is that some important patient characteristics were statistically different between the short and long duration groups. Significantly more patients in the long duration group had an endocavitary device and positive valve cultures, while more patients in the short duration group had congenital heart disease and infections due to *Streptococcus viridans.* These differences bring into question whether shorter duration therapy was truly as effective as longer duration therapy or whether short duration therapy was selected for cases with less severe co-morbidities.

While the studies reviewed here would generally support the use of shorter durations of antimicrobial therapy (Figure 2), the evidence is neither overwhelming nor does it provide guidance for specific antimicrobial/disease indications encountered in veterinary practice. It should also be noted that not *all* publications support a finding of no difference between short and long durations of therapy. In a randomized, prospective trial Hoberman et al compared 5 days vs 10 days of amoxicillin/clavulanic acid for therapy of acute otitis media in young children.[6] The primary outcome measure was clinical failure, defined as worsening symptoms, otoscopic signs of infection or lack of complete resolution of symptoms by the completion of therapy. A clinical failure rate of 34% in the 5 day group and 16% in the 10 day group was statistically significant. These results should be inter-

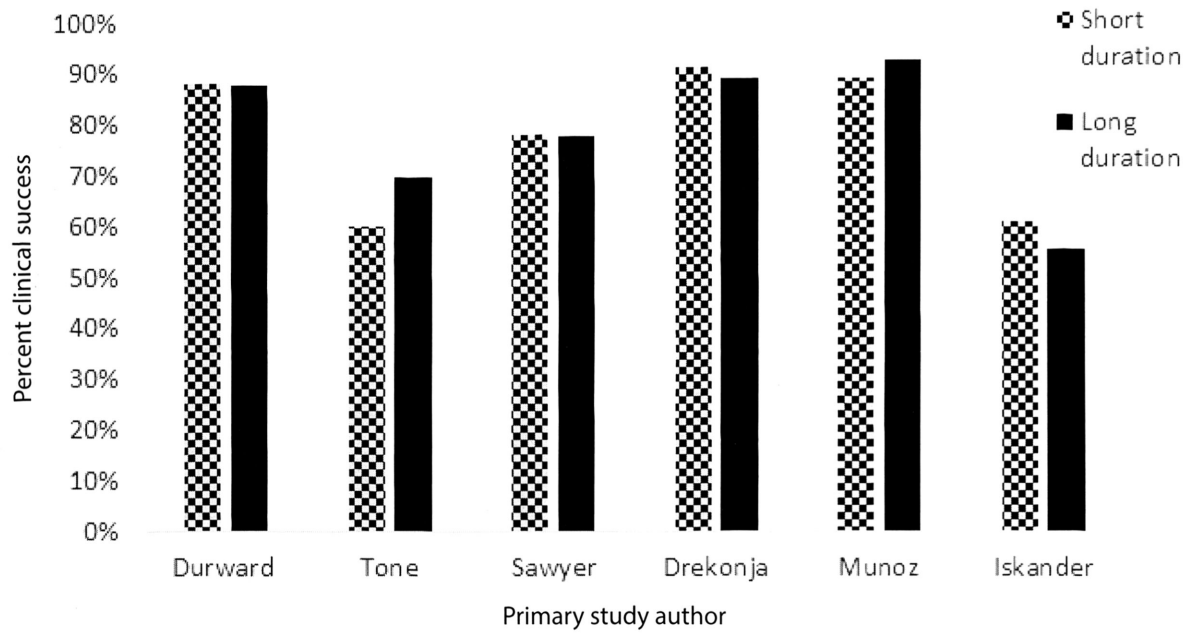

Figure 2. Comparison of clinical success for long vs. short duration antimicrobial therapy.
Clinical success defined as the percentage of patients in the study that were successfully treated according to the investigator's primary study outcome. Long and short duration as defined by the study investigator for the particular study.

preted cautiously as there was a difference in the number of unfavorable characteristics (infection in both ears, exposure to other children) between treatment groups, with the long duration study population having fewer unfavorable clinical characteristics.

Conclusions

This search of the recent literature for evidence to support durations of antimicrobial therapy in veterinary medicine revealed that there is a paucity of data to guide clinicians. Generally, studies demonstrate that shorter durations do not negatively impact patient outcomes; however, clear guidance on specific durations of therapy for specific antimicrobials is lacking. With the present emphasis on antimicrobial stewardship in veterinary medicine, this is an alarming knowledge gap that should be considered a priority research area.

References

1. Chalmers TC, Celano P, Sacks HS, Smith Jr., H. Bias in treatment assignment in controlled clinical trials. *N Engl J Med* 1983; 309: 1358-1361.
2. DeDonder KD, Apley MD. A literature review of antimicrobial resistance in pathogens associated with bovine respiratory disease. *Anim Health Res Rev* 2015; 16: 125-134.
3. Dellit TH, Owens RC, McGowan JE, Gerding DN, Weinstein RA, Burke JP, Huskins WC, Paterson DL, Fishman NO, Carpenter CF, Brennan PJ, Billeter M, Hooton TM. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007; 44: 159-177.
4. Drekonja DM, Rector TS, Cutting A, Johnson JR. Less is more: urinary tract infections in male veterans. *JAMA Intern Med* 2013; 173: 62-68.
5. Durward-Akhurst SA, Mair TS, Boston R, Dunkel B. A comparison of two antimicrobial regimens on the prevalence of incisional infections after colic surgery. *Vet Rec* 2013; 172:287.
6. Hoberman A, Paradise JL, Rockette HE, Kearney DH, Bhatnagar S, Shope TR, Martin JM, Kurs-Lasky M, Copelli SJ, Colborn DK, Cohen NL, Haralam M, Pope MA, Nagg JP, Green MD, Shaikh N. Shortened antimicrobial treatment for acute otitis media in young children. *N Engl J Med* 2016; 375: 2446-2456.
7. Iskander KN, Vaickus M, Duffy ER, Remick DG. Shorter duration of postoperative antibiotics for cecal ligation and puncture does not increase inflammation or mortality. *PLOS ONE* 2016; 11: e0163005.
8. Morley PS, Apley MD, Besser TE, Burney DP, Fedorka-Cray PJ, Papich MG, Traub-Dargatz JL, Weese JS. Antimicrobial drug use in veterinary medicine. *J Vet Intern Med* 2005; 19: 617-629.
9. Muñoz P, Giannella M, Scoti F, Predomingo M, Puga D, Pinto A, Roda J, Marin M, Bouza E. Two weeks of postsurgical therapy may be enough for high-risk cases of endocarditis caused by *Streptococcus viridans* or *Streptococcus bovis*. *Clin Microbiol Infect* 2012; 18: 293-299.
10. PubMed – US National Library of Medicine. National Institutes of Health. Available at: https://www.ncbi.nlm.nih.gov/pubmed. Accessed 28 March 2017.
11. Riccio LM, Popovsky KA, Hranjec T, Politano AD, Rosenberger LH, Tura KC, Sawyer RG. Association of excessive duration of antibiotic therapy for intra-abdominal infection with subsequent extra-abdominal infection and death: a study of 2,552 consecutive infections. *Surg Infect* 2014; 15: 417-424.
12. Sawyer RG, Claridge JA, Nathens AB, Rotstein OD, Duane TM, Evans HL, Cook CH, O'Neill PJ, Mazuski JE, Askari R, Wilson MA, Napolitano LM, Namias N, Miller PR, Dellinger EP, Watson CM, Coimbra R, Dent DL, Lowry SF, Cocanour CS, West MA, Banton KL, Cheadle WG, Lipsett PA, Guidry CA, Popovsky K. Trial of short-course antimicrobial therapy for intraabdominal infection. *N Engl J Med* 2015; 372: 1996-2005.
13. Tone A, Nguyen S, Devemy F, Topolinski H, Valette M, Cazaubiel M, Fayard A, Beltrand E, Lemaire C, Senneville E. Six-week versus twelve-week antibiotic therapy for nonsurgically treated diabetic foot osteomyelitis: a multicenter open-label controlled randomized study. *BMJ Open Diabetes Res Care* 2015; 38: 302-307.
14. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. 2013. Antibiotic resistance threats in the United States. Available at: http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf. Accessed 30 March 2017.