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ORIGINAL RESEARCH

Modification of empirical antimicrobial regimens in large animal medicine

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Abstract

Background Empirical antimicrobial regimens can be modified following new diagnostic information or when empirical treatment fails. Little is known about the frequency or clinical context in which these modifications occur. We characterised these modifications in a large animal hospital to identify when antimicrobial use could be optimised.

Methods Chart reviews were performed for all inpatients and outpatients administered antimicrobials at a large animal veterinary referral and teaching hospital in 2017–2018 (n=1163 visits) to determine when and why empirical regimens were modified. Multinomial logistic regression was performed to identify factors associated with reasons for modification.

Results Empirical antimicrobial regimens were modified in 17.3 per cent of visits. The main reasons were parenteral-oral conversions in horses and failure of disease prevention or treatment in ruminants. Empirical therapy for disease prevention was more likely to be modified because of complications in ruminants and in animals on the emergency/critical care service. Empirical therapy for disease treatment was more often modified for reasons other than de-escalation in ruminants and in animals with longer lengths of stay.

Conclusions Empirical antimicrobial regimens were modified infrequently and mostly for purposes of parenteral-oral conversion in horses and lack of response in ruminants. De-escalation of antimicrobials administered for disease treatment, when guided by diagnostics, is a major tenet of judicious antimicrobial use. However, more research is needed to determine when and how antimicrobial regimens administered for disease prevention should be modified.

Introduction

The judicious use of antimicrobial agents is broadly defined as the optimal selection of drug, dose and duration of antimicrobial treatment along with reduction in inappropriate and excessive use, with the goal of achieving the best clinical outcome possible and minimising the emergence of antimicrobial resistance.[1 2] In an ideal situation, a clinician would have knowledge of the pathogen(s) causing disease and would choose a narrowly targeted empirical antimicrobial to administer to the patient. However, it is likely that, as in human medicine,[3 4] diagnostic uncertainty leads to empirical use of antimicrobials, often with broad-spectrum antimicrobials or combinations of antimicrobials.[5] Such use is often warranted, especially in the case of polymicrobial infections or life-threatening conditions. However, the risks associated with the potentially unnecessary use of excessively broad regimens, including the emergence of antimicrobial resistance, potential adverse drug effects, greater disruption of the gut microbiome and increased costs due to polypharmacy[2 6] must be weighed against the possibility of choosing the wrong initial antimicrobial (ie, not 'getting it right the first time'[7]).

Modification of empirical antimicrobial regimens can take the form of (1) complete discontinuation of the regimen, (2) de-escalation, defined as a reduction in the number of antimicrobials prescribed or narrowing of the coverage of empirical therapy, (3) parenteral-oral conversion, or (4) escalation, defined

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as broadening of the antimicrobial coverage, following failure of empirical disease prevention or treatment. The goal of de-escalation is to narrow the spectrum of antimicrobial coverage to minimise selection pressure for antimicrobial resistance. The goal of a parenteral-oral transition is to minimise the duration of therapy requiring intravenous access, enable a more rapid discharge from hospitalisation and facilitate client compliance in administering medication.[8] De-escalation should ideally be guided by diagnostic information (including bacterial culture and antimicrobial susceptibility testing results) or in response to clinical progression.[2 9 10] When an empirical regimen fails, it can be modified, ideally with supportive diagnostics to guide the choice. In food animals, label restrictions on duration of therapy can also result in the need to modify the empirical regimen, as the duration of therapy for third-generation cephalosporins and fluoroquinolones is limited in USA.

To the authors' knowledge, no studies have been conducted to describe how often and in what clinical context modification of empirical antimicrobial regimens occurs in large animals (ie, horses, livestock, camelids, cervids). The factors associated with the initiation, discontinuation and modification of empirical antimicrobial regimens must be determined to identify opportunities to reduce unnecessary antimicrobial exposure and thus limit the development of antimicrobial resistance and adverse events.[11] In a cohort of large animal hospital patients, the authors sought to describe empirical antimicrobial regimens, the frequency of and reasons for modification of these regimens, and clinical characteristics associated with different reasons for modification of empirical therapy.

Materials and methods

Patient population

Hospital administrative and billing records were used to characterise antimicrobial use in all animals (ie, inpatients and outpatients) seen at a large animal veterinary referral and teaching hospital from January 1, 2017 to August 1, 2018 as previously described.[12 13] Empirical antimicrobial regimens, defined as antimicrobial regimens initiated upon admission to the hospital in the absence of bacterial culture and susceptibility testing, were characterised and tabulated by species. Next, to identify patients that had their empirical regimen modified, a three-step data extraction process was performed. First, the authors identified animals that received at least two classes of antimicrobials other than penicillin and gentamicin, as this combination is the most commonly used antimicrobial combination at the authors' hospital and therefore essentially never indicative of an antimicrobial switch. The authors extracted detailed information on the signalment and diagnoses of these patients, the types and quantities of antimicrobials dispensed, and the clinical service. Secondly, manual review of the medical record of each patient visit was performed to determine whether the antimicrobials were administered concurrently or sequentially. Thirdly, if the antimicrobials were given sequentially, the initial choice of antimicrobials was characterised as administered for purposes of disease prevention or disease treatment,[14] and the reason for modifying the regimen was recorded. Administration of antimicrobials for purposes of disease prevention was defined as administration to prevent an infection perioperatively or for advanced reproductive procedures. Administration for purposes of disease treatment included treatment for diagnosed or suspected bacterial infection or contaminated wounds. Reasons for modifying the empirical regimen were classified as (1) de-escalation or a parenteral-oral conversion; (2) development of complications from either the procedure or the empirical antimicrobial or development of a new clinical condition; (3) lack of response to empirical therapy (eg, failure to defervesce, worsening clinical condition, lack of response in acute phase protein concentrations); (4) culture ±susceptibility testing results-driven; or (5) duration modification due to label restrictions that limit the duration of therapy with third-generation cephalosporins and fluoroquinolones in food animals in USA. The classification of cases was performed by two investigators (HG and LR), and a random selection of cases was classified by both investigators to assess agreement, which was high (95 per cent). Any disagreements on classification were resolved by discussion.

Analysis

Descriptive analyses were performed, including computation of means with 95 per cent confidence intervals, standard deviations, medians, interquartile ranges of continuous variables and tabulation of categorical variables. Categorical variables were compared among the different reasons for modifying the empirical regimen using the chi-squared test.

To determine which factors were associated with different reasons for modification of empirical regimens, multinomial logistic regression was performed. First, univariable analysis was conducted to determine the unadjusted association between potential risk factors (patient species, age, length of stay, affected body system and clinical service) and the reasons for modification of the empirical regimen. Variables trending to be associated with different reasons for modification ($P<0.20$) were added to the model in a stepwise fashion and retained if they were significantly associated ($P<0.05$) with the outcome on multivariable analysis according to the Wald test.

All descriptive statistics and analyses were conducted with Stata V.15 (StataCorp, College Station, Texas, USA), with two-sided tests of hypotheses and a value of $P<0.05$ as the criterion for statistical significance.

Table 1 Characteristics of animals receiving at least one antimicrobial at a large animal referral and teaching hospital in north-eastern USA from January 1, 2017 to August 1, 2018

	Horses (n=2455 visits)	Cattle (n=327 visits)	Small ruminants (n=432 visits)	Other* (n=116 visits)
Median (IQR) age (years)	8.0 (3.2–14.3)	1.0 (0.08–3.0)	2.0 (0.48–5.0)	1.3 (0.4–6.4)
Median (IQR) length of stay (days)†	3 (1–7)	5 (2–8)	5 (2–12)	3 (1–7)
Service – n (per cent)				
Surgery	1011 (41.2)	166 (50.8)	133 (30.8)	50 (43.1)
Emergency/critical care	568 (23.1)	85 (26.0)	156 (36.1)	32 (27.6)
Medicine/ophthalmology	737 (30.0)	65 (19.9)	125 (28.9)	32 (27.6)
Other	139 (5.7)	11 (3.4)	18 (4.2)	2 (1.7)

*Includes camelids, pigs, cervids.
†A length of stay of 0.5 days was assigned for outpatients. For inpatients, the length of stay was defined as the number of days between discharge and admission.
IQR, interquartile range.

Results

Patient population

From January 1, 2017 to August 1, 2018, a total of 5820 patients were seen as either an inpatient or an outpatient at the hospital across 8111 visits, including 4538 horses (78.0 per cent), 475 goats (8.2 per cent), 408 cattle (7.0 per cent), 175 sheep (3.0 per cent), 164 pigs (2.8 per cent), 54 camelids (0.9 per cent) and 6 cervids (0.1 per cent). At least one antimicrobial was administered in 3367 (41.5 per cent) of these visits. More specifically, antimicrobials were prescribed in 38.6 per cent of visits for horses, 68.5 per cent for cattle, 55.2 per cent for small ruminants and 49.7 per cent for other species (pigs, camelids, cervids). Patient demographics by species of the animals that were prescribed at least one type of antimicrobial are shown in table 1. The patient's length of stay was calculated as the number of days between admission and discharge for inpatients, and a length of stay of 0.5 days was assigned to outpatients.

Empirical antimicrobial regimens

The distribution of empirical regimens is displayed by species in figure 1. The ranking of the most common

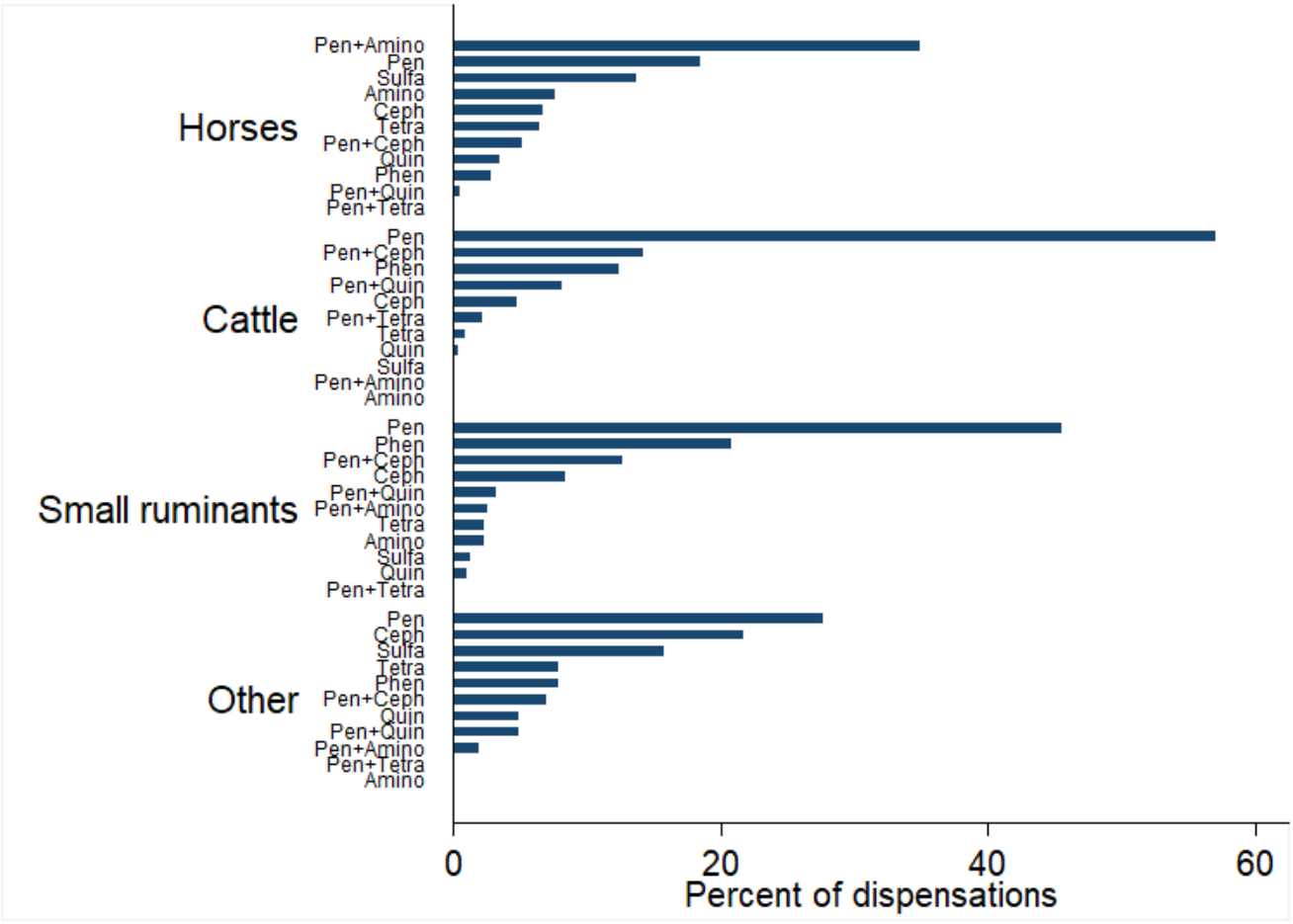

Figure 1 Most commonly administered empirical antimicrobial regimens at a large animal referral and teaching hospital in north-eastern USA from January 1, 2017 to August 1, 2018. 'other' species, swine, camelids, cervids; Pen, penicillin; Amino, aminoglycoside; Tetra, tetracycline; Sulfa, sulfonamide; Ceph, cephalosporin; Quin, fluoroquinolone; Phen, phenicol.

Table 2 Reasons for modifications of antimicrobial regimens by species in a large animal referral and teaching hospital in north-eastern USA from January 1, 2017 to August 1, 2018

	Empirical regimen given for purposes of disease prevention (n=213)		Empirical regimen given for purposes of disease treatment (n=380)	
Species	Reason	N (per cent)	Reason	N (per cent)
Horses	Parenteral-oral conversion	172 (89.6)	Parenteral-oral conversion	233 (79.5)
	Complications	20 (10.4)	Cuture/susceptibility-guided	32 (10.9)
			Lack of response	19 (6.5)
			New condition	9 (3.1)
Cattle	Complications	5 (83.3)	Lack of response	17 (34.0)
	De-escalation	1 (16.7)	Cuture/susceptibility-guided	13 (26.0)
			New condition	11 (22.0)
			Duration restriction*	5 (10.0)
			De-escalation	4 (8.0)
Small ruminants	Complications	9 (75.0)	Lack of response	10 (40.0)
	De-escalation	3 (25.0)	Cuture/susceptibility-guided	5 (20.0)
			De-escalation	4 (16.0)
			New condition	4 (16.0)
			Duration restriction*	2 (8.0)
Other species†	De-escalation	3 (100.0)	De-escalation	7 (58.3)
			Cuture/susceptibility -guided	4 (33.3)
			Lack of response	1 (8.3)

*In food animals, labelling restrictions limit the duration of therapy for cephalosporins and fluoroquinolones
†Includes camelids, pigs, cervids.

empirical regimens differed by species. Horses most often received a combination of a penicillin and aminoglycoside (usually gentamicin). All other species most commonly received penicillin alone. The second most commonly administered empirical regimens for horses, cattle, small ruminants and other species were penicillin alone, penicillin and a cephalosporin (mostly ceftiofur), a phenicol (florfenicol) and a cephalosporin (ceftiofur), respectively.

Modification of empirical regimens

A modification of the empirical regimen occurred in 583 visits, representing 17.3 per cent of the 3367 visits where any antimicrobials were prescribed. When the initial regimen was given for purposes of disease prevention (n=213 visits), the most common reason for the modification of the regimen was a parenteral-oral conversion in horses and the development of complications (ie, a failure of disease prevention) in all other species (table 2). The majority of animals that underwent parenteral-oral conversion had presented with signs affecting the respiratory system (n=100, 55.9 per cent) (table 3). The majority of animals that experienced failure of disease prevention had presented with signs affecting the gastrointestinal system (n=14, 41.2 per cent) or the urogenital system (n=11, 32.4 per cent) (table 3), and these proportions were significantly different from each other (P<0.001).

When the initial regimen was given for purposes of disease treatment (n=380 visits), the most common reason for modification of the regimen was a parenteral-oral conversion in horses and other species (ie, swine and camelids), and a lack of response to the empirical therapy in ruminants (table 2). In a small number of food animal cases (7, 1.8 per cent) a modification occurred because of duration restrictions associated with third-generation cephalosporins and fluoroquinolones. The ranking of reasons for modification of empirical therapy differed significantly by species (p<0.001) (table 2).

De-escalation in horses, which accounted for 73.7 per cent of cases in this study, generally consisted of a parenteral-oral transition to trimethoprim-sulfonamide or a tetracycline (doxycycline or minocycline) (figure 2). De-escalation in hospitalised food animals, which are generally not given oral antimicrobials, consisted of a transition to a long-acting parenterally administered antimicrobial such as florfenicol that requires less frequent administration by the owner. When modifications of empirical therapy occurred for reasons other than de-escalation or parenteral-oral conversion, there were many different combinations of

Table 3 Distribution of affected body systems in patients receiving a modification of their prophylactic empirical antimicrobial regimen at a large animal referral and teaching hospital in north-eastern USA

	Reason for modification of empirical therapy N (per cent)	
Affected body system	De-escalation	Complications/new condition
Oropharyngeal/nasal	8 (4.5)	1 (2.9)
Ocular	2 (1.1)	0 (0.0)
Respiratory	100 (55.9)	3 (8.8)
Cardiovascular	1 (0.6)	0 (0.0)
Gastrointestinal	7 (3.9)	14 (41.2)
Urogenital	28 (15.6)	11 (32.4)
Musculoskeletal	9 (5.0)	3 (8.8)
Integument	6 (3.4)	2 (5.9)
Other	18 (10.1)	2 (5.9)
Total	**179 (100.0)**	**34 (100.0)**

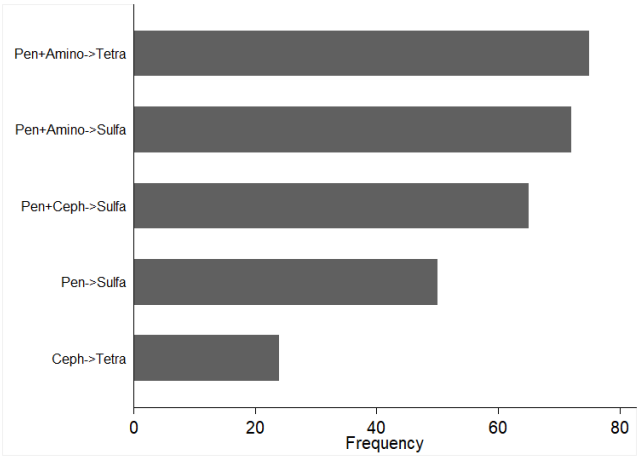

Figure 2 Most common combinations of antimicrobials prescribed when a parenteral-to-oral de-escalation occurred at a large animal referral and teaching hospital in north-eastern USA from January 1, 2017 to August 1, 2018. Pen, penicillin; Amino, aminoglycoside; Tetra, tetracycline; Sulfa, sulfonamide; Ceph, cephalosporin.

antimicrobials that were used, and no dominant pattern occurred.

Characteristics associated with different reasons for modification of empirical therapy

When an empirical regimen was administered for purposes of disease prevention, cattle and small ruminants were significantly more likely than horses to experience a modification due to failure of disease prevention, as were patients on the emergency/critical care service and on 'other' services (reproduction, cardiology, sports medicine, podiatry) compared with patients on the surgery service (table 4). Neither the patient's age, length of stay or affected body system were significantly associated with the regimen being modified due to failure of disease prevention.

When the empirical regimen was administered for purposes of disease treatment, species and length of stay were significantly associated with the likelihood of the regimen being modified for reasons other than de-escalation (table 5). Specifically, compared with horses, cattle were 51.6, 23.6 and 71.7 times more likely to experience a modification due to a lack of response to empirical therapy, culture/antimicrobial susceptibility testing-guided change or development of a new condition, respectively. Small ruminants were 25.4, 7.1 and 14.6 times more likely to experience such modifications, respectively, compared with horses (table 5). Longer lengths of stay were significantly associated with modifications of empirical regimens for reasons other than parenteral-oral conversion or de-escalation: for each one week increase in length of stay, the risk of experiencing a modification due to lack of response, culture/antimicrobial susceptibility testing results or development of a new condition increased by 31 per cent, 40 per cent and 47 per cent, respectively. Neither the patient's age, affected body system, nor clinical service were significantly affected with the likelihood of experiencing a change in regimen due to factors other than de-escalation.

Table 4 Factors associated with the likelihood of experiencing a modification in a prophylactic empirical antimicrobial regimen due to failure of disease prevention compared with de-escalation at a large animal referral and teaching hospital in north-eastern USA

	Relative risk ratio	95 per cent CI	P value
Species*			
Horses	[Referent]	[Referent]	[Referent]
Cattle	32.9	2.4 to 349.6	0.008
Small ruminants	17.4	2.9 to 83.7	0.001
Clinical service*			
Surgery	[Referent]	[Referent]	[Referent]
Emergency/critical care	17	6.1 to 47.7	‹0.001
Other services†	6.6	1.3 to 33.5	0.023

*Other species and the medicine/ophthalmology service were omitted because of complete separation.
†Includes reproduction, podiatry, sports medicine, cardiology services, accounting for less than 15 per cent of all visits.

Table 5 Factors associated with the likelihood of experiencing a modification in an empirical therapeutic antimicrobial regimen for various reasons compared with de-escalation at a large animal referral and teaching hospital in north-eastern USA

Reason for modification of empirical regimen	Factor	Relative risk ratio	95 per cent confidence interval	P value
Lack of response to empirical therapy	Species			
	Horses	[Referent]	[Referent]	[Referent]
	Cattle	51.3	15.6 to 168.6	‹0.001
	Small ruminants	25.9	7.3 to 92.0	‹0.001
	Other species*	2	0.23 to 17.2	0.53
	Length of stay (weeks)	1.3	1.1 to 1.6	0.014
Culture/susceptibility results	Species			
	Horses	[Referent]	[Referent]	[Referent]
	Cattle	23.4	7.1 to 76.9	‹0.001
	Small ruminants	7.4	1.8 to 29.6	0.005
	Other species	5	1.4 to 18.4	0.015
	Length of stay (weeks)	1.4	1.2 to 1.7	0.001
	Species			
New condition	Horses	[Referent]	[Referent]	[Referent]
	Cattle	70.9	7.1 to 76.9	‹0.001
	Small ruminants	15.1	1.8 to 29.6	0.005
	Other species	Omitted because of complete separation		
	Length of stay (weeks)	1.5	1.2 to 1.9	0.001

*Other species includes swine, camelids and cervids.

Discussion

In this study, the authors characterised empirical antimicrobial regimens administered for purposes of disease prevention and treatment and the frequency of and reasons for modifications of these regimens in a large animal referral and teaching hospital. Empirical antimicrobial regimens were modified in 17.4 per cent of visits where an antimicrobial was prescribed. In horses, parenteral-oral conversions accounted for the majority of cases where the empirical regimen was modified. Modifications for reasons other than de-escalation/parenteral-oral conversion (eg, culture/susceptibility results, lack of response, development of complications) were significantly more likely to

occur in ruminants and patients with longer lengths of stay. This may be because ruminants are less likely to undergo elective procedures than horses and are often sicker and hospitalised later in a course of illness.[15] Similarly, animals with more complicated illnesses are more likely to experience greater lengths of stay, which can increase the possibility of a nosocomial infection. All of these factors are likely to prompt a modification in the empirical regimen or require such a change in the case of drugs with duration restrictions in food animals. Moreover, given the turnaround time associated with culture/antimicrobial susceptibility testing (typically two to three days), animals undergoing a modification in their regimen due to testing results will necessarily have a longer length of stay.

De-escalation from an empirical antimicrobial regimen administered for purposes of disease treatment, ideally guided by knowledge of the pathogen and an antimicrobial susceptibility report, is a major tenet of judicious antimicrobial use.[2 8] Both de-escalation and parenteral-oral conversions can accelerate discharge from the hospital, which decreases the likelihood of hospital-acquired infections, and reduces the likelihood of potential complications associated with venous access.[8 16 17]

The conversion from parenteral to oral therapy following the administration of antimicrobials for disease prevention is a different story. There are very few evidence-based guidelines on this conversion in large animals. In human medicine, comprehensive guidelines on surgical antimicrobial prophylaxis recommend limiting prophylaxis to no more than 24 hours duration for most procedures (ie, no de-escalation to oral therapy),[18] and it has been suggested that prophylactic antimicrobial use in horses beyond 24 hours is likely unnecessary in most patients.[19] In the authors' hospital, the administration of antimicrobials for disease prevention almost always occurred in the context of surgeries in the form of perioperative antimicrobials. Less commonly, antimicrobials were also administered for disease prevention when patients underwent general anaesthesia for non-surgical reasons (eg, to prevent anaesthesia-associated pneumonia) or for advanced reproductive techniques such as oocyte aspiration or embryo transfer. Conversion from parenteral to oral administration occurred in a small proportion of surgical patients receiving antimicrobials for disease prevention (161/1362, 11.8 per cent). Animals with respiratory signs (ie, most often undergoing airway surgery) appeared to be overrepresented, though it is unclear why that was the case. A great deal more research on when prolongation of antimicrobial regimens administered for disease prevention should occur is necessary, including clinical trials to compare durations of therapy and studies to evaluate the number of animals needed to treat to prevent adverse outcomes.

De-escalation and parenteral-oral conversion frequently involved a switch in drug classes, which can result in enhanced selection pressure for the development of antimicrobial resistance.[20] Ideally, oral agents should be in the same class as the parenteral agents or at least provide a similar spectrum of antimicrobial activity as the parenteral antimicrobial.[21] In this study, parenteral-oral transitions were mostly from a penicillin+aminoglycoside or a penicillin+cephalosporin combination to a tetracycline (minocycline or doxycycline) or trimethoprim-sulfonamide. The antibacterial activities of these drugs have some overlap, but monotherapy with drugs such as tetracyclines generally offer narrower antimicrobial coverage than combination therapy such as penicillin+gentamicin,[22] and some studies have shown that common equine pathogens such as *Streptococcus equi zooepidemicus* are less susceptible to tetracyclines than penicillin.[23 24] However, large animal veterinarians are limited in their choice of antimicrobials available for parenteral-oral conversion. Bioavailability of commonly used classes of antimicrobials such as β-lactams is poor in horses,[25] and legal restrictions on the types and duration of therapy of antimicrobial drugs that can be used in food-producing animals and the chemical reduction of antimicrobials by ruminal microflora and fauna limit what can be used in ruminants.[26 27] These limitations make choosing the 'ideal' oral antimicrobial to convert very difficult for large animals. Possible solutions include placing animals on oral antimicrobials before and immediately after a planned procedure so that no switch in drug class occurs; choosing parenteral drugs that are also available in oral formulations (eg, sulfonamides, fluoroquinolones, tetracyclines); and for food animals, which are generally not administered oral antimicrobials in a hospital setting, starting with a broad-spectrum drug that can be easily administered at home by the owner following discharge (eg, florfenicol). Reasons these practices are not currently being done may include costs of drugs, potential for drug-drug interactions (eg, intravenous sulfonamides and α-2 agonists), concerns about antimicrobial-associated diarrhoea and drug label restrictions. More research is needed to investigate these possibilities.

While the authors did not find the initial choice of antimicrobial(s) to be significantly predictive of treatment failure, choices of antimicrobial drug regimens do influence clinical outcomes and the development of antimicrobial resistance.[28] Combinations of antimicrobials that result in redundant or antagonistic coverage can produce unnecessary selection pressure for antimicrobial resistance or ineffective therapeutic results and should be avoided. For example, penicillin+ceftiofur was the most common combination of parenterally administered antimicrobials other than

penicillin and gentamicin, and ceftiofur and florfenicol were also administered concurrently in certain cases. Especially when administered for disease prevention rather than disease treatment, these drug combinations provide coverage that is likely to be redundant, as few organisms that would not already be targeted by a broad-spectrum antimicrobial such as ceftiofur or florfenicol would be susceptible to penicillin.[29] In other cases, bacteriostatic and bactericidal drugs such as penicillin and oxytetracycline, or penicillin and florfenicol were administered concurrently, which could have resulted in antagonism.[30] Antimicrobial regimens should be carefully considered, if necessary with the consultation of a microbiologist or pharmacologist, to avoid unnecessary antimicrobial resistance selection pressure.

This study had some limitations. First, the authors did not always know whether animals were receiving antimicrobials before admission, which could have influenced a clinician's decision-making regarding choice of antimicrobials. A course of therapy that was initiated before admission could have been discontinued, in which case the modification of the empirical regimen would not have been captured, resulting in misclassification of the patient visit.

Secondly, there were cases where the authors' assigned reasons for modification of the empirical regimen may have failed to capture the clinical picture, where clinical uncertainties, dynamic clinical progression and competing factors such as owners' financial resources may have influenced prescribing decisions. Additionally, in a small number of cases, multiple modifications of the antimicrobial regimen occurred for different reasons (eg, an initial lack of response to clinical therapy followed by a culture/susceptibility-guided switch in therapy), but these cases were classified by the first modification that occurred.

Finally, as a referral and teaching hospital that sees animals that are often referred from a primary care veterinarian, the results of the present study may not be entirely generalisable. The authors' hospital likely also has access to a greater inventory of antimicrobial drugs and more staffing to facilitate administration of drugs with short dosing intervals than general or ambulatory practices, which might result in different prescribing practices.

In conclusion, modifications of empirical antimicrobial regimens occurred relatively infrequently and for different reasons in horses (parenteral-oral conversion) compared with ruminants and other species (complications, lack of response). Empirical regimens were generally appropriate, though refinement could be made in a small number of cases where redundant or antagonistic antimicrobial coverage may have occurred. Limitations on the type of drugs available for large animals for purposes of de-escalation makes choosing the 'ideal' antimicrobial to de-escalate too difficult. Options for antimicrobial regimens that do not involve exposure of the patient to many different classes of antimicrobials should be investigated.

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Competing interests None declared.

Ethics approval Ethical approval was not deemed necessary by the Institutional Animal Care and Use Committee and the Institutional Review Board of the University of Pennsylvania.

Data availability statement Data available upon request from the corresponding author.

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