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Personal view

Proposed method for estimating clinical cut-off (CO_{CL}) values: An attempt to address challenges encountered when setting clinical breakpoints for veterinary antimicrobial agents☆

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Introduction

Antimicrobial agent susceptibility breakpoints are intended to serve as a tool for guiding therapeutic decisions. When coupled with standardised in vitro susceptibility test methods, clinical breakpoints (BPs) are used by diagnostic laboratories to help guide practitioners in selecting compounds with the highest likelihood of providing a positive clinical outcome. BPs are set on the basis of the relationship between the specific drug, pathogen, dose/dosing regimen and clinical indication. Expressed as a minimum inhibitory concentration (MIC, typically as mg/L or mg/L) or a zone diameter (mm), the interpretive categories include (from VET02-A3[1]), susceptible (S), intermediate, resistant (R) and non-susceptible (NS).

In determining the BP, three 'cut-off' values are considered: (1) the epidemiological cut-off value (ECV or ECOFF); (2) the clinical cut-off (CO_{CL}); and (3) the pharmacodynamic cut-off (CO_{PD}). These cut-off values are factored into deliberations when setting a BP value for a drug and indication. The process for incorporating these three cut-off values into the determination of BPs may vary as a function of the data presented to the standards setting body. For more information on how they are integrated into the decision-making processes, please refer to Turnidge and Paterson (2007) and (as specifically related to the determination of veterinary BPs) the Clinical Laboratory Standards Institute (CLSI) VET02-A3 guideline.

Among the challenges encountered during this process is the difficulty in establishing a CO_{CL} value. Our colleagues in human medicine are typically provided a large amount of information with which to define the relationship between clinical outcomes and antimicrobial susceptibility, thereby allowing for the potential use of several alternative statistical approaches to support their decision making processes. However, within veterinary medicine, the difficulties encountered during efforts to define the CO_{CL} for a given application are magnified by: (1) the small '*n*' values associated with the clinical data sets submitted in support of the CO_{CL} determination (particularly when it comes to companion animal species); (2) fluctuations in the proportion of treatment successes (particularly toward the tails of the MIC distribution); and (3) the very low number of isolates available for assessing efficacy at the tails of the MIC distribution. Because of these issues, a statistical method for setting the CO_{CL} could not be identified.

Consequently, until recently, the determination of CO_{CL} values was made entirely on the basis of a subjective assessment. However, such an approach presents its own range of problems. This 'eyeball' approach can inadvertently be influenced by

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[1] See: VET02-A3: Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters for Veterinary Antimicrobial Agents, Clinical and Laboratory Standards Institute. http://shop.clsi.org/veterinary-medicine-documents/ (accessed 30 June 2017). Note that VET02 is soon to release a modified A4 version which provides a revision to the cut-off decision tree presented in the VET02-A3. The citation provided is for the currently available A3 version.

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spontaneous curesthat confound our ability to ascribe drug response as the cause of the positive clinical response (Rex and Pfaller, 2002). As an example, Forrest et al. (1997) described where, with the use of grepafloxacin for the treatment of acute exacerbations of chronic bronchitis, a 70% clinical response and a 55% bacteriological cure was achieved despite the 'near zero' systemic exposure to grepafloxacin. Subjective assessments are also difficult to reproduce when there are fluctuations in proportional successes at the tails of the MIC distribution.

Given the significance often given to the CO_{CL} estimates during BP deliberations, it was important to identify a method that would reduce the potential bias in its assessment. It is for that reason that we developed what we call the WindoW approach, which constrains the determination of CO_{CL} to values contained within a window (or limited) range of MICs. It is within that WindoW that clinical judgement can then be exercised to render the final determination of the CO_{CL}.

It is our hope that by publishing this Personal View article, we will stimulate discussion on methods for assessing CO_{CL} within the framework of the types of data sets typically seen in veterinary medicine. We encourage readers to provide feedback on strengths and weaknesses associated with the WindoW approach and to provide us with suggestions for method improvement.

The 'WindoW' approach for setting a CO_{CL}

The objective of the WindoW approach is to reduce the subjectivity associated with CO_{CL} assessments by identifying inflexion points in the MIC distribution, signifying mathematically identifiable changes in the rate of therapeutic or microbiological success. This is accomplished using two separate algorithms (i.e. estimation procedures) which, when applied simultaneously, define a range (or 'WindoW') whose boundaries are determined by these two inflection points.

One of the algorithms identifies the MIC at which there is the greatest drop in percent efficacy (the method of maximum difference, MaxDiff). Within the framework of the MaxDiff, the 'Diff' value always uses the entire data set. Thus, at each sequential MIC value, the MaxDiff is influenced by the proportional successes across the entire data set. The second algorithm is the MIC at which there is a maximum shift in the cumulative success rate, designated the cumulative area under the curve (AUC) ratio (CAR). Within this algorithm, proportional successes are considered only from the perspective of the MIC values equal to or less than the segment in question. Unlike the MaxDiff algorithm, what happens downstream is irrelevant for CAR, making it sensitive only to segmental drops in proportional successes at values equal to or less than the MIC being assessed. Given their dissimilarity in perspective, these two perspectives frequently identify different MIC inflection points.

Before describing the method for estimation of the MaxDiff and the CAR, certain 'Expert Rules' are proposed:

1. Establishing data-based restrictions: The CAR should not be set at either the lowest or the highest measured MIC. If CAR values progressively increase over the range of observed MICs such that a drop in the CAR cannot be identified, then the CAR should be set at the second lowest MIC value so long as that MIC is associated with at least four isolates. If that MIC contains less than four isolates, then the MIC values should be incrementally examined until the one with at least four observations is identified. Importantly, the finding of progressively increasing CAR values should raise questions regarding whether it is appropriate to set a CO_{CL} value based on those data.
2. Adjusting for low numbers of observations: Neither metric should be set on a value associated with less than four isolates (i.e. estimable only when $n \geq$ than 4).
3. Total number of isolates: It is important to determine if the data (sample size, range of MIC values) are adequate for supporting an estimate of the CO_{CL}. With the exception of mixed infections (i.e. when the patient harbours two or more unrelated strains of the same bacterial species), each clinical observation should be linked with only a single isolate of the bacterial species in question. Optimally, the data will also reflect therapeutic outcomes derived over multiple clinical sites.

Calculation methods

At any given MIC value, the clinical results can be expressed in terms of success or failure, where success represents the ability to achieve some outcome of interest (e.g. clinical cure, survival). As such, the outcome data represent binomial proportions. Note that the identical hypothetical data set is used in Tables 1–3.

Table 1
Example of estimation of MaxDiff.

MIC (mg/L)	Success	Failure	Total	%Success ≤ MIC	%Success > MIC	MaxDiff	
≤0.001							
0.03	36	4	40	90.00	84.86	5.14	Subset A
0.06	108	13	121	89.44	76.56	12.88	
0.125	34	12	46	85.99	83.33	2.66	
0.25	5	0	5	86.32	76.92	9.40	
0.5	0	0	0	86.32	76.92	9.40	
1	2	1	3	86.05	80.00	6.05	
2	6	0	6	86.43	50.00	36.43	MaxDiff
4	1	1	2	86.10	50.00	36.10	
8	0	1	1	85.71	100.00	-14.29	
16	1	0	1	85.78	100.00		Subset B
32							
64							
≥128							
≥128							

Values in red represent MIC values at which there are less than four isolates.
MIC, minimum inhibitory concentration. MaxDiff, the method of maximum difference. The values included and the calculations associated with subset A and B are provided in the first bullet of the section titled 'Estimation of the MaxDiff'.