Setting clinical breakpoint
Methodological aspects

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Glossary

- Diameters (S,R)
- Risk communication
- Breakpoint
- Risk management
- Cut-off
- Risk assessment
Development of a (clinical) Breakpoint (BP)

Clinical BP

- $CO_{WT}$
- ECOFFs
- $CO_{PK/PD}$
- $CO_{CL}$

Diameter
1-Establishing ECOFFs
Epidemiological/microbiological cut-off
(CLSI=CO_{WT}, EUCAST=ECOFFs)
Epidemiological cut-off values (ECOFFs)

- ECOFFs are related to the distribution of MICs of wild type organisms lacking acquired or mutational resistance to the antimicrobial agent in question.

- The ECOFF is essentially the upper MIC value of the wild type distribution.
MIC distribution: requirement

- An appropriate MIC distribution means
  - MICs determined with accepted methods (ISO)
  - Large numbers (n>100-300, ideally >1000)
  - Representative (EU?)
    - from different locations, investigators....

Tulathromycin
Tulathromycin: The epidemiological cutoff: CO\text{WT}

728 strains of *M. haemolytica* isolated from bovine respiratory disease. Note the “wild-type” population with MIC values $\leq 8 \, \mu g/ml$. 

![Bar chart showing distribution of MIC values for 728 strains of *M. haemolytica*. The x-axis represents MIC values in $\mu g/mL$ (1, 2, 4, 8, 16, 32, 64, >64), and the y-axis represents the percentage of strains. The chart highlights a peak at MIC values of 2 and 4 $\mu g/mL$.](chart.png)
Ciprofloxacin & Acinetobacter baumannii
Statistical method for $\text{ECOFF/CO}_{\text{WT}}$

Statistical characterisation of bacterial wild-type MIC value distributions and the determination of epidemiological cut-off values

J. Turnidge$^1$, G. Kahlmeter$^2$ and G. Kronvall$^3$

**RangeFinder and ECOFFinder**

Normalized Resistance Interpretation as a Tool for Establishing Epidemiological MIC Susceptibility Breakpoints

Göran Kronvall$^*$

*Department of Microbiology and Tumor Biology–MTC, Clinical Microbiology, Karolinska Institutet, Karolinska University Hospital Solna, Stockholm, Sweden*
For more details

Kahlmeter - ECOFFs, ECOFFs, ECOFFs

ECOFFs
ECOFFs
ECOFFs
ECOFFs

MIC wild type distributions and epidemiological cut-off values

Gunnar Kahlmeter
EUCAST, ESCMID and ECDC
Clinical microbiology, Växjö, Sweden

EUCAST workshop, ECOMID 2013
2-The setting of a PK/PD cutoff
The role of pharmacokinetics/pharmacodynamics in setting clinical MIC breakpoints: the EUCAST approach

The setting of a PK/PD CO

Step 1
Selection of a PK/PD index predictive of clinical efficacy and/or prevention of resistance

Step 2
Determination of the critical value (size) of the selected PK/PD index

Step 3
Computation, for a given animal species and for all possible (not probable) MICs of the percentage (proportion) of animals able to achieve the critical value of the selected PK/PD index (computation of so-called Target Attainment Rates (or TAR))
Step 1: Selection of a PK/PD index

Rem: it was shown that for all drugs/formulations having a long half-live that AUC/MIC is the appropriate index (AUC/MIC: universal index?)
Step 2: Determination of the critical value (size) of the selected PK/PD index
The case of tulathromycin in calf: Results obtained from the killing curve assay (RVC/Toulouse)

- PK/PD index: $fAUC_{24h}/MIC$
- Emax model
- The critical value of AUC/MIC for a bactericidal effect (in serum) was about 24h
The setting of a PK/PD CO

Step 1
Selection of a PK/PD index predictive of clinical efficacy and/or prevention of resistance

Step 2
Determination of the critical value (size) of the selected PK/PD index

Step 3
Computation, for a given animal species and for all possible (not probable) MICs of the percentage (proportion) of animals able to achieve the critical value of the selected PK/PD index (computation of so-called Target Attainment Rates (or TAR))
Step 3: Computation of the TAR (%) for the critical value of the selected index for the different possible MICs (TAR are stratified by MIC)

- PK raw data
- Population modeling
- Monte Carlo Simulation (n=5000 animals)
- TAR(%)
Use of Monte Carlo simulation to determine pharmacodynamic cutoffs of amoxicillin to establish a breakpoint for antimicrobial susceptibility testing in pigs

Julien F. Rey, DVM; Céline M. Laffont, PhD; Siska Croubels, Pharm D; Patrick De Backer, DVM; Claudine Zemirline, DVM; Eric Bousquet, DVM; Jérôme Guyonnet; Aude A. Ferran, DVM; Alain Bousquet-Melou, DVM; Pierre-Louis Toutain, DVM
Tulathromycin: Population modeling (healthy & challenged)

**Structural model:**
\[
Y(t) = A \times \exp(-\alpha t) + B \times (-\beta t) - (A + B) \times \exp(-K_{abs} t)
\]

**Random model**
The Between Subject Variability (BSV) was modeled using an exponential model.

**The residual model** which reflects unexplained variability after controlling for other sources of variability (analytical imprecision, departure from the model) was a multiplicative (proportional) model.
Step 2
Generate of a large fictive (simulated) population (n=>1000 calves) using a Monte Carlo simulation tool with PK parameters (typical value and random components (ETA) as estimated at the previous step)
PK/PD cut-offs (ng/mL in serum) for tulathromycin in calves.

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PKPD cut off=83ng/mL in serum or 4.µg/mL in MHB
Step 4

Determination of the population distribution of doses that are able to achieve the critical value of the PK/PD index (AUC/MIC=24h) in the calf population taking into account the actual MIC distribution
Computation of the dose

\[ Dose = \frac{Clearance \text{ (per hours)} \times \left( \frac{AUC}{MIC} \right)_{BP} \times MIC}{F \%} \]

Log normal distribution of CL/F (pop PK)

Observed MIC distributions of MH and PM

BP 24h

Assumption: MIC distribution vs. prevalence of MIC
MIC distributions (MHB)

*M. haemolytica (n=2233)*

*P. multocida (n=2483)*
Distribution of tulathromycin doses required to achieve the critical value of the PKPD (AUC/MIC=24h) over 10 days.
Distribution of doses required to achieve the critical value of the PKPD (AUC/MIC=24h) over 10 days
Clinical cutoff
The clinical CO ($CO_{CL}$)

The $CO_{CL}$ is based upon the collection of isolates obtained during the clinical effectiveness studies.

$CO_{CL}$ reflects the upper limit of the MIC values associated with a high likelihood of clinical success [probability of cure (POC)].

There is no set method for establishing the $CO_{CL}$, and no hard target for POC.
Probability of cure (POC)

• Logistic regression can be used to link MIC values (as independent variable) to the probability of a clinical success

\[ POC = \frac{1}{1 + e^{-(a+bf(MIC))}} \]

- **Dependent variable**: Placebo response
- **Independent variable**: (here collected MICs during clinical trials) + other covariates
- **Sensitivity**

2 parameters: a (ceiling effect) & b (slope of the MIC-effect curve)
Setting the breakpoint

• A risk management exercise
• Not a scientific exercise but should be scientifically acceptable
• CO and others consideration
  – Harmonization (e.g. different dosage regimen across EU, no splitting of the wild distribution...
Decision tree to select a BP from the three CO

When \( CO_{WT} \neq CO_{CL} \), the \( CO_{PD} \) is used as a weighting factor for the final determination of “S.”

Figure C2. Susceptibility Breakpoint (SBPT) Decision Tree
Fig. 1. Ciprofloxacin MIC distribution of *Escherichia coli* isolates (http://www.eucast.org). Epidemiological cut-off (ECOFF) values and clinical susceptible (S) and resistant (R) breakpoints from CLSI and EUCAST committees are indicated. The clinically susceptible population (below the clinical susceptible breakpoint) includes part of the microbiologically resistant population (low-level resistant bacteria, presumably expressing *qnr*-like genes or other PMQR mechanisms or first step *gyrA* mutations) and the wild-type population (below the ECOFF value and presumably without resistance mechanisms). The clinically resistant population (beyond the clinical resistant breakpoint) includes isolates with high-level resistance mechanisms (most probably double-step *gyrA* mutants or a combination of *gyrA* with *parC* mutations).
Clinical breakpoint

• CLSI: vote
• EUCAST: consensus
From BP to diameters
A modelling approach to replace the error-rate bounded method

Modeling Approach to Diameter Breakpoint Determination

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