Antibiotic susceptibility test reports under NetAcquire system

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Introduction

Reports state S = susceptible, I = intermediately susceptible, R = resistant as well as the minimum inhibitory concentration (MIC) in μg/mL for each organism and antimicrobial agent tested

To encourage prudent prescribing practice and as per standard practice in human hospitals, reporting comprises a 2- tier system:

- Susceptibility results will be reported for a primary list of antibiotics that will include first choice agents for the particular organism / condition in question.
- Only if there is resistance resulting in there being no suitable product for treatment on the primary list, will susceptibility results to agents on the secondary list be released.
- In the event of isolation of a highly MDR organism, additional susceptibility testing using disk diffusion may be carried out.
- Susceptibility results to drugs that are reserved exclusively for human use will never be released (e.g. vancomycin, carbapenems).
- Some organisms are intrinsically resistant to a number of antimicrobial agents and thus these agents are never reported for such organisms - commonly =
    - Enterococci are intrinsically resistant to all cephalosporins and potentiated sulphonamides
    - *E. coli* is intrinsically resistant to clindamycin
    - *Pseudomonas aeruginosa* is intrinsically resistant to many antimicrobial classes and thus the choice of antimicrobials is very limited

- Clinical breakpoints for antimicrobial agents used **topically** have not been defined. Therefore the susceptibility results reported for organisms isolated from ear and eye samples relate only to antimicrobials administered systemically. Results cannot be extrapolated for topical use.

- On a technical note, the date of birth is a *required* field. When the date of birth is not provided, a default date will be entered.

LISTS OF AGENTS TO BE REPORTED

The following table (Table 1) lists the agents to be reported in the primary and secondary lists for companion, farm and equine species. Some agents will not be reported depending on the pathogen being tested as different agents are tested on VITEK cards for Gram-positive and Gram-negative pathogens. Some agents are not reported because the pathogen is intrinsically resistant to those agents (see Table 2).

Table 1. Agents to be reported on primary and secondary lists for small animal, farm animal and equine*.

Primary list Small Animal	**Secondary list SA**	**Primary list Farm Animal**	**Secondary list Farm Animal**	**Primary list Equine**	**Secondary list Equine**
Amoxicillin	Amikacin	Ampicillin	Amikacin	Ampicillin	Amikacin
Cefalexin	Amoxycillin/ clavulanate	Benzylpenicillin	Amoxycillin/ clavulanate	Benzylpenicillin	Amoxycillin/ clavulanate
Tetracycline (Doxycycline)	Cefovecin	Cephalothin	Ceftiofur	Cefalexin	Ceftiofur
Trimethoprim/ sulphameth-oxazole	Enrofloxacin	Gentamicin**	Enrofloxacin	Gentamicin**	Enrofloxacin
Clindamycin	Marbofloxacin	Kanamycin	Marbofloxacin	Tetracycline	Marbofloxacin
Fusidic acid	Minocycline	Neomycin	Tylosin	Trimethoprim/ sulphamethox-azole	
Gentamicin**	Florfenicol (for MRSA/MRSP)	Streptomycin			
		Florfenicol			
		Tetracycline			
		Trimethoprim/ sulphamethox-azole			

*Note: Testing anaerobes for metronidazole susceptibility by disc diffusion is available on request. (Use of metronidazole is prohibited in food animals)

** Note: Enterococci are intrinsically resistant to aminoglycosides. However, enterococci with low levels of resistance to penicillin or ampicillin may be susceptible to gentamicin or streptomycin in combination with a penicillin if a high level gentamicin/streptomycin resistance test is negative. This will be indicated on reports where relevant.

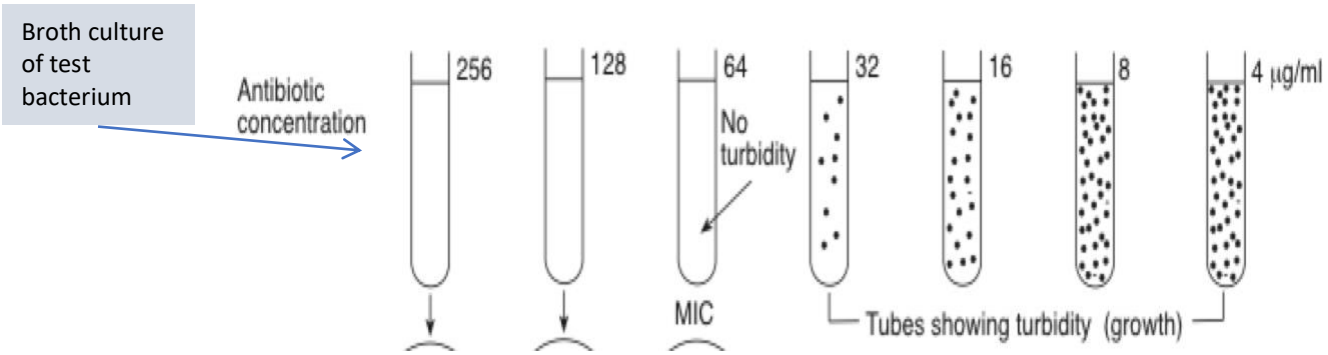
Table 2. Intrinsic resistance of veterinary pathogens against selected veterinary antimicrobial agents.

Organism	Resistant to:
Enterobacteriaceae *Proteus* spp.	Benzylpenicillin, macrolides, lincosamides, rifampicin, fusidic acid Resistant to all of above plus tetracyclines and Polymixin B/colistin. *Proteus vulgaris* is also resistant to ampicillin and first /second generation cephalosporins
Acinetobacter baumannii	Benzylpenicillin, ampicillin, many cephalosporins, macrolides, lincosamides, rifampicin, trimethoprim, fusidic acid
Burkholderia cepacia	Benzylpenicillin, ampicillin, amoxicillin clavulanate, 1st generation cephalosporins, macrolides, lincosamides, rifampicin, ciprofloxacin, aminoglycosides, trimethoprim, Polymixin B/colistin, fusidic acid
Pseudomonas aeruginosa	Benzylpenicillin, ampicillin, amoxicillin clavulanate, cephalosporins, macrolides, lincosamides, rifampicin, kanamycin and neomycin, trimethoprim-sulphamethoxazole, fusidic acid, chloramphenicol
Campylobacter species	Lincosamides, trimethoprim
Staphylococci	Polymixin B/Colistin
Streptococci	Polymixin B/Colistin, aminoglycosides
Enterococci	Fusidic acid, Polymixin B/Colistin, cephalosporins, low level resistance to aminoglycosides, erythromycin, clindamycin, sulphonamides
Listeria monocytogenes	Cephalosporins

Utilisation of Minimum Inhibitory Concentration Values.

What is the minimum inhibitory concentration?

The minimum inhibitory concentration (MIC) of an organism is the lowest concentration of an antimicrobial that will inhibit growth of that organism.



The MIC of the organism in this example is 64µg/ml of the antibiotic in question.

What is the relationship between MIC and clinical resistance?

MIC alone does not determine the effectiveness of an antibiotic in a clinical case
Clinical breakpoints are calculated to determine if an isolate is clinically susceptible, intermediate or resistant and are based on:

- MIC distribution in a bacterial population; the MIC90 is the concentration that will inhibit growth of 90% of a particular species of organism (Pharmacodynamic criteria)
- Achievable drug concentration in plasma or tissue; Cmax (Pharmacokinetic criteria)

Clinical breakpoints are set by organisations such as the Clinical Laboratory Standards Institute (CLSI)(USA) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST).
We have recently modified our lab reports to show the BP beside the MIC value, thus facilitating immediate comparison between the MIC of the test organism and the corresponding BP.

How do I select the antimicrobial agent most likely to be effective based on the MIC data provided?

The actual MIC given on the report can be compared to the clinical breakpoint (set by CLSI or EUCAST as explained above) for each agent. If the MIC of the test organism is less than or equal to the clinical susceptibility breakpoint for a particular antimicrobial, the organism is deemed to be clinically susceptible to that agent. If it is greater than the susceptibility breakpoint, it is resistant to that agent.
If there is more than one agent to which the organism is susceptible and the agents are licensed for use and available for the animal you wish to treat, you can use the MIC to help decide which is likely to be most effective antibiotic in the clinical case.

The following example shows how MIC values can be used to select what may be the most effective agent:

Table 3. Example MIC report for a post-surgical wound case in a dog infected with a susceptible *Staphylococcus pseudintermedius*

Agent	Interpretation (R, I, S)	MIC (µg/ml)	Clinical Susceptibility Breakpoints (µg/ml)*
Amoxycillin clavulanate	S	<=2	<=8
Cefalotin	S	<=2	<=2
Gentamicin	S	<=0.5	<=4
Clindamycin	S	0.25	<=0.5
Doxycycline	S	<=0.5	<=4
Trimethoprim-sulphamethoxazole	S	<=10	<=40

*Note: MICs are tested using doubling dilutions of the antimicrobial in question, i.e. 0.5, 1,2,4,8,16, 32, 64 and so on.

Based on our UCDVH prescribing guidelines and the susceptibility pattern above, the following agents could be used to treat this dog
Clindamycin, Cefalexin, Amoxicillin/clavulanate, Trimethoprim/sulphonamide

If all other factors are equal, the most potent drug of the four drugs listed is clindamycin as it has the lowest MIC of all 4 drugs (Potency can be defined in terms of the concentration or amount of the drug required to produce a defined effect)

In general, the clinical breakpoint/ MIC ratio can be used as a useful indicator of potential efficacy of an antimicrobial when used clinically. The BP/MIC ratio for these 4 drugs =
Clindamycin: MIC = 0.25 and BP = 0.5. BP/MIC = 0.5/0.25 = 2
Cefalexin: (use cefalotin as a guide as it is also a 1st generation cephalosporin)
BP/MIC = 2/2 = 1
Amoxicillin/clavulanate BP/MIC = 8/2 = 4
Trimethoprim/sulphonamide BP/MIC = 40/10 = 4

Therefore, based on this parameter, either amoxiclav or trim/sulph are potentially the most effective agents as they have the highest BP/MIC ratios. They are most likely to reach adequate concentration in the tissues.
Cefalexin has a ratio of 1 which means that the tissue concentration is only *just* sufficient to treat the infection. Any variation in dosing, bioavailability, tissue penetration or bacterial susceptibility could lead to lower **actual** tissue concentrations than **predicted** by the in vitro test and possible treatment failure.

Although such comparisons are overly simplistic as they do not account for pharmacokinetics and other factors, they can be useful as a guide to antimicrobial choice. In

this case trimethoprim/sulpha is not active in the presence of pus (this is an infection by a pyogenic organism) and so amoxycillin/clavulanate would be the better choice.

Another factor which may be important in determining antibiotic choice is the route of excretion. For example, if an antibiotic is concentrated in the urine during excretion, it may be effective for treating urinary infections *in vivo* even though the *in vitro* result indicates intermediate susceptibility. This is because the drug accumulates in urine to levels well above those achieved in plasma.

What are time- versus concentration-dependent antimicrobials?

Once an antimicrobial has reached and bound to its site of action in the bacterium, the two major determinants of inactivation of the organism are the *concentration* and the *time* that the antimicrobial remains on the binding sites.

Time-dependent:

For some classes of antimicrobials time is more critical (beta-lactams, macrolides, clindamycin) and these are classified as 'time-dependent antimicrobials. For these antimicrobials efficacy is enhanced if the concentration in the body remains above the MIC for most (at least 50%) of the dosing interval. Increasing the dose may be beneficial but shortening the dose interval is usually more effective, especially if the drug has a short half-life.

Concentration dependent:

Antimicrobials for which concentration is more critical (fluoroquinolones and aminoglycosides) are classified as 'concentration-dependent' antimicrobials. The efficacy of these drugs is best predicted by the ratio of the maximum drug concentration (C_{max}) to the MIC. This ratio should be at least between 8:1 and 10:1. These drugs can usually be administered at longer dosing intervals.

> Some antimicrobial agents, such as the tetracyclines, have features of both time and concentration-dependent killing.