"Time to change" was the topic of the round table presenting the Pan-European consensus on antimicrobial resistance and use, held at the occasion of the congress of the British Small Animal Veterinary Association in Birmingham, on April 7th 2016. That it’s indeed high time to change became clear after the presentations by certain experts of the European consensus panel – an independent expert panel that has produced a practical guidebook called GRAM ("Guidance for the Rational use of AntiMicrobials") for companion animal veterinarians.

Antibiotic resistance is a very real threat to us now and in the future, and of increasing importance in veterinary practice. Inappropriate use of antibiotics is a contributing factor, often caused by lack of awareness and lack of good practices. Three veterinary experts of the European consensus panel on antimicrobial resistance (see box p.2) provided the audience with a snapshot of the current situation in their respective countries.
Veterinary prescription habits in Italy...

Veterinary practitioners in Italy frequently use so-called last-resort antibiotics as first-line treatment. For example, “over 50% of antibiotics used by Italian veterinarians to treat urinary tract infections in their patients are so-called last-resort antibiotics”, reported Dr Chiara Noli (Italy), a referral veterinary dermatologist. “They also rarely carry out culture and sensitivity testing.” And the consequences are evident. “I am increasingly faced with animals suffering from multidrug-resistant infections, and we’re often struggling to find an antibiotic that is working. This is a huge problem for referral dermatologists, and recently also seen by first-opinion practices”.

... Portugal

Antimicrobial resistance in Portugal is reaching alarming levels – and not just in human medicine. Veterinary prescription habits of antibiotics “could be better” according to Dr Constança Pomba (Portugal). “In Portugal, fluoroquinolones represent some 10% of all antimicrobial tablets for companion animals”, she announced, referring to the 2013 report of the European Surveillance of Veterinary Antimicrobial Consumption. And of all prescribed penicillins for companion animals, in Portugal “just about 100% of these are potentiated penicillins containing ß-lactamase inhibitors such as clavulanic acid”. She applauded the production of the GRAM initiative. “We need to protect our antibiotics”, she stressed.

...and the UK

“Around 40% of companion animal consultations result in antibiotics being prescribed”, announced Dr Tim Nuttall (UK), citing data from the SAVSNET surveillance network in the UK. Studies show that fluoroquinolones and third-generation cephalosporins are used in up to 13% of cases. In 20% of cases the dose was higher than the recommended dose and in 5% of cases it was lower. Another worrying finding was that in 23,5% of cases of acute diarrhoea, antibiotics had been prescribed although they are rarely indicated in this condition.
“The reduction of antibiotic consumption is crucial if we want to preserve them for future use,” stressed Dr Tim Nuttall, adding that rational antibiotic therapy is a “key professional duty.”

First, make sure that there is a bacterial infection. For example, in cases of dermatitis, “use clinical signs and cytology to confirm a bacterial pyoderma; not all itchy animals have an infection” he stressed. He went on to present a long list of conditions where systemic antibiotics are often used but are rarely necessary, including acute diarrhoea, conjunctivitis, feline cystitis, cat bite abscesses, anal sac impaction and juvenile vaginitis.

Secondly, ensure that systemic antibiotics are required – and if not, educate your client. For example, many mild surface or superficial skin infections will respond to topical treatment and management of the underlying problem. Always “select the lowest tier, narrow spectrum” antibiotic, and for treatment duration, “err on the short side: two weeks are not always more effective than five days”.

Empirical antibiotic treatment – without prior culture and sensitivity testing - is acceptable in two situations: first-time mild infections caused by bacteria with predictable susceptibility patterns and where there are no risk factors for resistance, and in cases of life-threatening infections in which a delay of treatment would compromise the outcome.

So when should we do culture and sensitivity testing? “A lot more than we do now!” Dr Nuttall stressed. Indeed, only an estimated 3.4% of European veterinarians systematically carry out sensitivity testing.

Selecting the right antibiotic and the right dosing regimen is another pillar of rational use. Important questions include: what are the most likely causative bacteria and to which antibiotics are they most likely to be susceptible? Which antibiotics penetrate barriers such as the CNS or the prostate? What are the potential side effects?

“Although most antibiotics prescribed by companion animal veterinarians are broad-spectrum, probably based on a ‘just in case’ scenario, we should move to a narrow spectrum whenever possible.” Although amoxicillin + clavulanate may seem a “safe bet” choice, it increases the risk of selection for ESBL-producing bacteria. “So de-escalate and opt for a narrower spectrum whenever possible.”

Finally client education and compliance are essential. “A drug will only work if the owner can and will give it,” and palatable antibiotics or treats to hide medication will help the medicine go down. In its recommendations, the GRAM book provides “Top ten tips” on getting the pill into the pet, thus helping clients (and pets) comply with the therapy, for an improved response and a reduced resistance pressure.

Clear communication is important. “Write it down!” Dr Nuttall advised, “and be clear: say ‘every twelve hours’ rather than ‘twice daily’.”

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**THE FOUR PILLARS OF RATIONAL USE**

**How can you help limit the development of resistance when using antibiotics?**

1. **Accurate diagnosis is essential to limit the use of systemic antibiotics.** Always ensure that there is an infection, and avoid systemic antibiotics whenever possible (e.g. superficial pyoderma, abscesses).

2. **Diagnose and treat underlying disease, as bacterial infections are almost always secondary.**

3. **Select the appropriate antibiotic,** guided by cytology and/or sensitivity testing as well as pharmacokinetic and pharmacodynamic properties and host factors. Prefer narrow over broad-spectrum antibiotics and avoid the use of critically important antibiotics.

4. **Administer at the correct dosing regimen (dose, administration intervals, duration) until clinical cure.**
To help companion animal practitioners make the right choice when prescribing antibiotics, an independent European expert panel has produced a practical guidebook, the so-called GRAM, short for Guidance for the Rational use of AntiMicrobials.

GRAM book
Practical guidance for appropriate use

- **37** disease fact sheets, covering the most common infectious diseases in dogs and cats, with treatment diagrams and colour-coded antibiotic guidance.
- **29** recommendations in response to frequently asked questions on a wide range of topics including sampling, interpretation, antibiotic classification, causes of failure and dealing with multidrug-resistant infections.
- **6** synopsis chapters, with facts and figures on hygiene, antisepsis, the pharmacological basis of antibiotic therapy, prevalence and relevance of antibiotic resistance.
- **Appendices** (glossary, tables and references).
Panel member Dr Chiara Noli showed how the GRAM book can be used, with a practical example.

Disease fact sheet: diagnostic approach

“Let’s say a 2-year-old male Golden Retriever comes into your consultation, with a 1-year history of pruritic dermatitis and recurrent otitis. He has already been treated with several antibiotics, with variable results. How should such a case be approached?”

She showed how the practical decision diagram in the Pyoderma fact sheet of the GRAM book highlights the first step: cytology, an “essential” tool. “We should first make sure this is really a case of pyoderma. If we can avoid the use of antibiotics, we should.” The guidebook also explains how cytology samples should be taken for the different types of lesion, how to stain and how to interpret the results. “Cytology is easy and inexpensive, and provides a lot of information.” For example, if cytology shows it is simply a case of bacterial overgrowth (i.e. surface pyoderma), a 2-week treatment with topical antiseptics (shampoos, sprays or wipes) is sufficient. The guidebook lists the antiseptics in order of preference. “Also in case of superficial pyoderma (presence of neutrophils with bacteria inside), topical antiseptics usually suffice. Only if there is no response, should systemic antibiotics be added”, she explained.

Recommendations: FAQs

“This brings us to the next step: culture and sensitivity testing.” When should this be done – and when not? Besides disease fact sheets, the GRAM book also contains a chapter of recommendations that answer frequently asked questions, such as: when is culture and sensitivity testing of little use, recommended and indispensable?

- In surface pyoderma, there is no need for antibiotics – nor for culture. And in first-occurrence superficial pyoderma, although recommended, an empirical, probabilistic choice of antibiotics usually does the trick if topical therapy is insufficient.” In all other cases, culture and sensitivity testing is indispensable.

- Once you’ve got your sensitivity results, then what? “Always use first-line antibiotics first, and only choose second-line substances if susceptibility test shows bacterial resistance towards first-line antibiotics.” The disease fact sheet of the GRAM book provides a clear overview of antibiotics that can be used, with green, orange and red colour-coding showing the order of preference (see box next page). “A systematic approach and downscaling is essential.”

- More detailed background information on the classification of antibiotics, resistance mechanisms and owner and patient compliance can also be found in the GRAM book.
Dr Constança Pomba presented another common clinical case: feline cystitis, and showed how the GRAM book can assist.

**Bacteria involved**

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>25-59%</td>
</tr>
<tr>
<td><em>Enterococcus spp.</em></td>
<td>10-43%</td>
</tr>
<tr>
<td>(E. faecalis most common)</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus spp.</em></td>
<td>8-20%</td>
</tr>
</tbody>
</table>

**Systemic antibiotics that can be used (for topical therapy, see Surface and superficial pyoderma, p.132)**

**Pathogen 1:**
Meticillin sensitive *Staphylococcus spp.*

<table>
<thead>
<tr>
<th>Antibiotics that can be used</th>
<th>In vitro sensitivity</th>
<th>Tissue distribution</th>
<th>Treatment choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin +/- clavulanate</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Cefalexin / Cefadroxil</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Cefovecin</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

**Pathogen 2:**
Meticillin (multidrug) resistant *Staphylococcus spp.*

Antibiotics to be used only if sensitivity tests show resistance to the antibiotics mentioned for meticillin-sensitive antibiotics.

<table>
<thead>
<tr>
<th>Antibiotics that can be used</th>
<th>In vitro sensitivity</th>
<th>Tissue distribution</th>
<th>Treatment choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim sulfonamides</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Doxycycline / Minocycline</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Marbofloxacin / Enrofloxacin</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Pradofloxacin</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol / Florfenicol</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

**“The disease fact sheet starts by stressing that bacteria are rarely the primary cause of FLUTD”, she pointed out. It then provides a table with the most commonly occurring urinary pathogens, as well as a practical diagram for the therapeutic approach. Here too, cytology is a useful tool, allowing first to confirm the presence of a bacterial infection and then (if confirmed) to perform an empirical choice of antibiotics while awaiting results of culture.**

**Again, the GRAM provides information on best sampling practices and gives guidance on antibiotic prescription, according to the pathogen identified. For example, it reminds readers that cephalosporins, trimethoprim sulfonamides and clindamycin are not useful in case of infection due to *Enterococcus spp.*, as this pathogen does not respond in vivo to these antibiotics.**

**GRAM book provides a clear overview of antibiotics that can be used.**

**Urine cytology is essential to confirm the presence of bacterial infection.**
“Critically important antibiotics or CIAs are what they say they are: substances that are essential against specific human infections, where there is a lack of sufficient therapeutic alternatives,” Dr Tim Nuttall quoted.

The GRAM book provides a detailed overview of classes of antibiotics and ranks them in order of preference. So when can third and fourth-generation cephalosporins and fluoroquinolones be used? “Never as a first-line empirical treatment,” he stressed, “and only if supported by culture and sensitivity test results.” The only exception would probably be life-threatening situations – and even then, therapy should be de-escalated whenever possible. “In most cases, first-line antibiotics are every bit as effective as third and fourth-generation cephalosporins and fluoroquinolones.” There are no “strong” or “weak” drugs, he added, and “you do not necessarily need to reach for the big guns”, as shown by a study done in teaching hospitals. “Despite a caseload skewed toward critically ill referral cases, drugs designated as first-line accounted for over 90% of 21,152 prescriptions.”

In the appendices of the GRAM book, detailed guidance and examples of antibiotic classes are provided. “First-line antibiotics licensed for pets are those that are well established with good evidence of high efficacy and safety. They should be used whenever appropriate and possible.” Examples include penicillins, first-generation cephalosporins, amoxicillin and trimethoprim sulfonamides.

“I’m passionate about responsible antibiotic use. I do not want our children to grow up in a post-antibiotic era. That’s why so many hours of collaborative effort went into the GRAM project, which combines all essential basic theoretical and practical knowledge about appropriate antibiotic use.”

Dr Tim Nuttall
GUIDANCE FOR THE RATIONAL USE OF ANTIMICROBIALS

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For good medical practices in antibiotherapy.

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A guide based on efficacy and prevention of resistances as well as feasibility for the vets and owners

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EASY TO USE

Made to find the information you need in a blink

ETHICAL

For a better use of antibiotics to protect Human and Animal health

As little as possible and only as much as necessary.