A drug interaction is defined as any modification of the effect of a drug when administered with another drug (concurrently or in close sequence). This effect can be a decrease or an increase in the action (therapeutic or toxic) of either of the two drugs. It is important to remember that this interaction can be either beneficial or disadvantageous. It is also important to note that nutraceuticals and herbal supplements can also interact with drugs.

Different outcomes of a drug interaction
If Ea is the effect of drug A, Eb the effect of drug B, and Eab the effect observed when both drugs are given together, there are 4 possible outcomes:

**Neutral effect**
- \( E_{ab} = E_a \) or \( E_b \)
- When 2 drugs have completely unrelated pharmacokinetic profiles, mechanisms of action, or tissue effects and therefore don’t affect each other

**Antagonistic effect**
- \( E_{ab} < E_a \) and \( E_b \)
- When 2 drugs compete for part of their pharmacokinetic profiles; when 2 drugs have action mechanisms that antagonize each other; or when 2 drugs compete for the same receptor

**Additive effect**
- \( E_{ab} = E_a + E_b \)
- When 2 drugs have complementary mechanisms or effects that simply add up

**Synergistic effect (rare despite the term being commonly used instead of additive effect)**
- \( E_{ab} > E_a + E_b \)
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It is important to realize that antagonistic interactions can sometimes have a beneficial outcome for the patient (e.g. antidotal drug decreasing the absorption of a toxic drug) and additive/synergistic interactions can have a negative outcome for the patient (e.g. two nephrotoxic drugs together).

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Drug interactions themselves can be subdivided into categories:

**Pharmacokinetic interactions**
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  - Transporter & mucosal metabolism (e.g. competition for Pg-p or CYP3A4 in GI epithelium)
  - Physiology of absorbing tissue (e.g. prokinetic agent & GI flow & oral absorption; antibiotics & GI flora-dependent entero-hepatic cycle)
  - Availability of transportable form (e.g. activated charcoal & overdose; Al in sucralfate & tetracyclines or fluoroquinolones)
- Distribution interactions
  - Local tissue transporters & drug metabolism (e.g. competition for P-gp transport through blood-brain barrier)
  - Local tissue physiology (e.g. NSAIDs normalizing blood flow to target organ; diuretics & hydrosoluble drug)
  - Plasma protein binding competition; only significant with highly protein bound drugs (>90%) with a narrow therapeutic index and when administered by rapid IV; albumin & acidic drugs or αglycoproteins & alkaline drugs
- Metabolism interactions
  - Enzyme induction (e.g. rifampin; omeprazole; phenobarbital)
  - Enzyme inhibition/competition (e.g. cimetidine; most azoles; many fluoroquinolones; methyxanthines)
  - Liver physiology (e.g. decreased blood flow to liver during anesthesia; acetaminophen-induced GSH depletion & opioid conjugation)
Elimination interactions
- Tissue physiology of the eliminating organ (e.g. decreased renal blood flow during anesthesia; phenobarbital-associated decreased bile flow)
- Local tissue transporters & drug metabolism (e.g. decreased statin elimination by cyclosporine OAT inhibition)
- Urine pH (e.g. acidifying urines to increase the renal elimination of an alkaline drug)

Pharmacodynamic interactions
- At the molecular target level
  - Antagonistic interaction when both drugs target the same molecular target (competition): e.g. using 2 drugs from the same drug class!
  - Additive or synergistic effect when the two drugs have different binding site on their common molecular target: e.g. GABA receptor & benzodiazepine and barbiturates
- At the cellular level
  - Antagonistic interaction when a drug decreases the synthesis of another drug’s target: e.g. azoles decreasing the synthesis of egestrol (amphotericin target)
  - Additive or synergistic effect when two drugs target two different steps in a sequential cellular pathway (e.g. TMP and SMX sequential inhibition of folate pathway in certain bacteria)
  - Positive interaction when a drug promotes the synthesis of a molecule that decreases the toxicity of another drugs (e.g. GSH precursors & acetaminophen toxicity)
- At the clinical outcome level
  - Antagonistic interaction when the clinical effect of two drugs are antagonistic: e.g. immunosuppressive dose of corticosteroids & antibacterial agents; certain diuretics & K supplementation
  - Additive or synergistic effect when two drugs target two different steps in a sequential pathological pathway (e.g. multi-analgesia therapy)

Drug interaction risk factors
When considering unwanted drug-drug interactions, several risk factors need to be taken into account by the clinician very carefully:
- Drugs that interfere with PK
- Polypharmacy (e.g. hospitalization, especially in ICU; chronic diseases)
- Conditions that already affect important PK factors (e.g. decreased plasma protein levels in advanced liver disease)
- New drugs for which the profession has little toxicity background
- Compounding, which can modify the drug PK profile

Predicting, preventing, identifying drug interactions
Numerous softwares have been developed for human medicine that can help clinicians prevent and/or identify potential drug interactions. They are commonly used by human pharmacies, but they have not yet been evaluated and/or adjusted for veterinary species.

Therapeutic drug monitoring (TDM) can also be very helpful in cases of drug interactions, and should be considered as common practice in high-risk patients whenever possible.

References
Over the past few decades, we have seen a significant increase in the incidence of allergic immune disorders, such as asthma, contact dermatitis or food allergy, in industrialized countries. This has happened too fast to be explained by genetic changes. At the same time, the amount of man-made chemicals with immunotoxic properties has drastically increased in these same countries. Researchers and clinicians are therefore hypothesizing that there could be a connection between the two phenomena.

What is immunotoxicology?

General immunotoxicology
Immunotoxicology is the field of toxicology that studies the effects of chemicals on the immune system. Environmental immunotoxicology focuses on xenobiotics present in our environment (e.g. diet).

Developmental immunotoxicology
This research field focuses more specifically on the effect of chemical exposure during key periods of the immune system development: in utero, neonatal, childhood, and adolescence. Immunotoxicants might have some effects on the developing immune system at lower doses than what would be toxic in the adult immune system. In addition, the nature of the effect might also be different. Some consequences of a disrupted immune development might not be noticeable until later in life, but others might happen early but only be transient.

Mechanisms of immunotoxicity
The immune system can be affected at any level: immune cell differentiation, proliferation, maturation, activation, and end function (e.g. antibody production by B lymphocytes; antigen presentation by macrophages). For any immune cell target, the cell can be affected at different locations as well: primary and secondary immune organs, circulatory system, or even in non-immune tissues where immune cells reside. Importantly, the immunotoxic effect of a chemical can vary with age, but also between species, gender. The molecular mechanisms behind such immunotoxic effects remain uncertain, but likely involve complex networks of cell signaling pathways.

Examples of environmental immunotoxicants
This proceeding will focus on a specific category of environmental toxicants called endocrine disruptor chemicals. The US Environmental Protection Agency (2012) defines them as “exogenous agents that interfere with the production, release, transport, metabolism, binding, action, or elimination of the natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes”. However, there is increasing evidence that these chemicals are also significantly immunotoxic.

Bisphenols
Bisphenols, such as bisphenol A (BPA), are monomers found in epoxy resins used for lining to separate content from metal and in plastic objects to ensure shape and durability. They are found in food cans, plastic bottles, cosmetic containers, dental and medical material and in cashier receipts.

Phthalates
Phthalates, such as di-ethylhexyl-phthalate (DEHP), are polymers used to soften plastics in food or drink containers, medical tubing, medication coating, or toys; they have also been used in cosmetic care products and they are also found in various building and furniture materials.

PCBs
Polychlorinated biphenyls were widely used in dielectric or cooling fluids. Their production was banned in the US in 1979 and more broadly in 2001. However, they are very stable compounds and accumulated in the environment.

PBDEs
Polybrominated diphenyl ethers are flame-retardants that are widely used to decrease flammability (e.g. textiles, furniture, building materials, plastics.) The 2001 Stockholm Convention only restricted their production without fully banning it.

Exposure to immunotoxicants
Sources
Several millions of tons of endocrine disruptors are produced every year throughout the world. A central issue is that these chemicals are usually not covalently bound to the product matrix they were added to, and they can leach out. The second problem is that these chemicals are often very stable and can accumulate in the environment and in the body.
Routes
The most common route of exposure is usually thought to be the oral route. Food & drinks usually represent the most significant portion of the exposure. However, oral exposure also includes ingestion of house dust, chewing on plastic objects, or medications. In addition, inhalation (e.g. house dust; fragrances) and cutaneous exposure (e.g. cosmetics; house cleaning products) sometimes provide significant additional exposure.

In vivo levels
There is mounting evidence confirming the reality of human exposure to endocrine disruptors (CDC report 2009). All endocrine disruptors that have been investigated to date have been detected in one body fluid or another, sometimes with higher levels in children. For instance, over 95% of the US population, including newborns, shows detectable levels of phthalates in multiple body fluids (CDC report 2009).

Exposure of pets to endocrine disruptors has been investigated to a much lesser extent than for humans. However, BPA and PCBs have been detected in canned foods for dogs and cats. In addition, BPA and phthalates were found in dog toys and training devices. PCBs, PBDEs, BPA, and phthalates have been detected in the blood of the cats and dogs that have been tested so far.

Evidence of environmental immunotoxicity
Numerous studies (human epidemiology, laboratory animals, in vitro cell assays) have suggested or demonstrated the immunotoxic effects of various endocrine disruptors. For instance, higher levels of certain phthalates have been measured in the house dusts of adults and children with allergic disorders (e.g. asthma, contact dermatitis). BPA and certain phthalates have been shown to increase immune markers in animal models of these allergic disorders. Numerous endocrine disruptors have been found to affect various immune cells in vitro, by killing them or by activating them.

There is little literature available about pets and environmental toxicity. No study has been published so far about the immunotoxicity of endocrine disruptors in pets. However, a few recent investigations found some supporting evidence towards a relationship between PBDEs & hyperthyroidism, acromegaly, or diabetes in cats. A few relatively old studies looked at BPA and phthalate toxicity in laboratory dogs, which appeared more sensitive to phthalate toxicity than rats. BPA was also recently shown to kill certain canine cells in vitro (coronary smooth muscle and kidney cells).

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Immunomodulatory Therapy: Can Clinicians Play the Immune System to their Advantage?

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What is “immunomodulation”?
Immunomodulation can be defined as the adjustment of the immune function, an increase in case of immunostimulation or a decrease for immunosuppression.

Immunotoxicology is a relatively new science. Some limited research was conducted between the end of the 19th century and the beginning of the 20th century, and immunossuppressive agents only started being used for therapeutic purposes in the 1960s. Modern immunotoxicology as we know it, started in France in the 1970s, but the field itself was only officially created in 1983.

Immunosuppressants

Corticosteroids
- Mechanism of action: through intracellular glucocorticoid receptors (genomic effects; delayed) & membrane receptors (non genomic, rapid)
- Immunosuppressive effects: neutrophils (decrease adhesion and migration); antigen presenting cells (decrease cytokines; decrease antigen processing; decrease phagocytosis); lymphocytes (especially T; decrease activation, proliferation and cytokines)
- Side effects: multiple and potentially significant (PUPD; polyphagia; hypothalamic-pituitary-adrenal axis suppression; healing delay; infection & tumor risks...)

Antimetabolite agents
- Azathioprine
  - Mechanism of action: bioactivated to a toxic metabolite (6-TGN) responsible for both the wanted immunosuppressive effect but also the numerous and significant side effects; also inactivated to 6-MMP by thiopeptide methyltransferase (TPMT) and 6-TA by xanthine oxidase; delayed effect
  - Immunosuppressive effects: all immune cells
  - Side effects: potentially severe bone marrow toxicity and hepatotoxicity (GI toxicity can usually be controlled); cats are especially sensitive
  - Variability in efficacy and side effects, probably due to drug metabolism polymorphism (e.g. TPMT)
- Methotrexate
  - Mechanism of action: folate analog that inhibits folic acid pathway
  - Immunosuppressive effects: all immune cells
  - Side effects: bone marrow and GI toxicity
- Mycophenolate
  - Prodrug: bioactivated to mycophenolic acid by hydrolysis
  - Mechanism of action: inhibition of Inosine Monophosphaste Dehydrogenase, key enzyme in the guanine synthesis
  - Immunosuppressive effects: mainly lymphocytes
  - Side effects: relatively mild compared to other agents (GI and bone marrow toxicity)
- Leflunomide
  - Mechanism of action: prodrug bioactivated in the GI tract or plasma; dihydrorotate dehydrogenase inhibitor therefore inhibiting pyrimidine synthesis; might also interfere with tyrosine kinases necessary for cytokine synthesis
  - Immunosuppressive effects: mainly lymphocytes
  - Side effects: mild GI toxicity; (some idiosyncratic immune-mediated hepatotoxicity reported in humans)

Alkalynating agents
Mechanism of action: covalent binding to DNA, stopping cell cycle
- Cyclophosphamide
  - Prodrug: biaactivated to acrolein & phosphoramid acid
  - Immunosuppressive effects: mainly lymphocytes (especially B)
  - Side effects: bone marrow toxicity; GI toxicity; sterile hemorrhagic cystitis
- Chlorambucil
  - Immunosuppressive effects: mainly lymphocytes (B≈T); slow acting
  - Side effects: much less than cyclophosphamide

**Calcineurin inhibitors (cyclosporine, tacrolimus)**
- Mechanism of action: bind to an intracellular receptor that then bind to calcineurin, preventing it from stimulating IL-2 synthesis, further preventing lymphocyte proliferation and differentiation
- Immunosuppressive effects: lymphocytes (mainly T)
- Side effects: relatively mild compared to other agents (GI disturbances; nephrotoxicity; neurotoxicity; hypertension; metabolic abnormalities such as diabetes or dyslipidemia)
- Therapeutic Drug Monitoring available; be careful with PK drug interactions for cyclosporine

**Others**

**Human IVIG** (highly purified active immunoglobulins isolated from a large pool of healthy human plasma)
- Mechanism of action: unclear (Fc receptor binding? Cytokine profile modifications? Complement pathway inhibition? Fas apoptosis inhibition?)
- Immunosuppressive effects: all levels of immunity
- Side effects: appear limited; mainly acute hypersensitivity (even in humans); but also reports of thromboembolism, renal failure, hypotension, aseptic meningitis, and fluid overload
- Danazol
  - Mechanism of action: androgenic agent, but mechanism of its immunosuppressive activity unknown
  - Immunosuppressive effects: decrease B lymphocyte-mediated immunity (decreases antibody production; decreases complement & antibody interactions with platelets and red blood cells)
  - Side effects: related to its androgenic activity
- Pentoxifylline
  - Mechanism of action: immunosuppressive mechanism unknown
  - Immunosuppressive effects: decreases cytokines production, inhibits lymphocyte activation, decreases neutrophil and NK cell activity
  - Side effects: limited (no cardiac or respiratory effects)
- Anti-cytokine agents (mainly anti-TNFα agents)
  - Mechanism of action: inhibit a cytokine central to immune function (e.g. TNFα)
  - Immunosuppressive effects: non specific
  - Side effects: secondary infections and tumors
- Gold derivatives (aurothioglucose, auranofin)
  - Mechanism of action: unknown
  - Immunosuppressive effects: delayed; seem to affect T lymphocytes, macrophages and neutrophils
  - Side effects: nephrotoxicity, blood dyscrasia, skin reactions

**Immunostimulants**

We know much less agents that stimulate the immune system than immunosuppressive drugs. It is important for clinicians to realize that there is a striking lack of EBM information to support the therapeutic use of these agents, especially in veterinary medicine.

**Cytokines & immune derived proteins**
- **Lymphocyte T-Cell Immunomodulator** (LTCI, IMULAN from BioTherapeutics) is a protein isolated from the supernatant of bovine thymic epithelial cells. It is thought to stimulate immature T helper cells and has been approved as adjunctive therapy in FeLV and FIV cats.
- **IFNγ**: To date, there is only EBM available to support its use in certain viral infections in several species.
- **GM-CSF** stimulates myeloid hematopoiesis of granulocytes/monocytes precursors and their differentiation into granulocytes and monocytes. It also stimulates the early differentiation of myeloid precursors into reticulocyte precursors.

**Antimicrobials**
- Levamisole
  - Mechanism of action: uncertain (phosphodiesterase inhibition)
  - Immunosuppressive effects: restores T lymphocyte and antigen presenting cell functions, and promotes differentiation of lymphocyte precursors into T lymphocytes
  - Side effects: GI and neurotoxicity
  - EBM: limited info in cats, dogs, pigs
Antioxidants
Antioxidants are often considered to be immune stimulants, however there is very little evidence (especially direct evidence) supporting this belief. Indeed, confounding factors and biases contaminate many of the few studies available. The other issue associated with antioxidant therapy is the fact that the content (of the active ingredient and of potential contaminants) is not guaranteed in nutraceuticals as it is with FDA-controlled drugs.

See the CVC San Diego 2015 Proceeding “Antioxidant therapy” for more information. -

“Biotics”
Prebiotics are indigestible food ingredients (including dietary fiber) that have a beneficial effect on commensal bacteria. The World Health Organization defines probiotics as “live microorganisms which when administered in adequate amounts confer a health benefit on the host”. Finally, synbiotics are a mixture of pre- and pro-biotics with the underlining assumption that the combination will have a synergistic effect.

Like for antioxidants, there is no reliable evidence that “biotics” improve immunity itself. However, there is increasing evidence that local and overall immunity is affected by the microbiome (commensal microbes), and that “biotics” affect that microbiome. So future research on the interactions between immunity and “biotics” will hopefully support some interesting therapeutic applications.

Others
- Lactoferrin
- Herbs

References
Drug Interactions in the Life of a Clinician
Sidonie Lavergne, DVM, PhD
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If $E_a$ is the effect of drug A, $E_b$ the effect of drug B, and $E_{ab}$ the effect observed when both drugs are given together, there are 4 possible outcomes:

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References
What is oxidative stress?
It is an imbalance between the effects of oxidants (such as reactive oxygen species, ROS) and the ability of antioxidant biological systems to detoxify the oxidant or to repair the damage it induced.

It is important to realize that an oxidant usually is an oxidizing agent as well. Indeed, it can oxidize another molecule by acquiring one or several of its electrons. An electron donor molecule (usually in the form of an hydrogen atom) would be a reducing agent that gets oxidized in the process.

Free radicals are molecules with an unpaired electron on their outer orbit. They therefore seek to acquire electrons from other molecules to stabilize their structure. Reactive oxygen species (ROS) are small molecules that contain oxygen atoms with missing electrons (e.g. superoxide radical $\cdot O_2$ or hydroxyl radical $\cdot HO$). $H_2O_2$ (hydrogen peroxide) is not an ROS per se, but it can form ROS when reacting with transition metals such as iron. These molecules are very instable and highly reactive as they seek electrons from other molecules, oxidizing them in the process.

Where do ROS come from?
ROS can be endogenous or exogenous. Most cellular ROS are byproducts of the mitochondrial respiration. Their leakage into the cytosol increases when the integrity of the mitochondrial membrane is compromised. This is the case during hypoxia or ischemia for instance. Normal cellular enzymatic reactions, especially those involving oxidation, also generate some ROS.

Exogenous ROS can come from the ingestion of certain toxins (e.g. certain mycotoxins) or exposure to ionizing radiations (e.g. UV).

What are the beneficial aspects of oxidative stress?
ROS have beneficial effects that are part of normal body functions. For instance, they are a key component of innate immunity against microbes (e.g. neutrophil burst). In addition, ROS play an important role in regulating gene expression; more specifically, the expression of genes with an Antioxidant Response Element (ARE) in their promoter, is regulated by the intracellular redox status. ROS are also important in controlling apoptosis. Interestingly, ROS are part of the therapeutic function of radiotherapy.

What damages ROS and oxidants in general can do?
ROS are highly reactive molecules that can react with cellular macromolecules (proteins; lipid membranes; DNA). The oxidation process can either affect the macromolecule structure or its activity. This can eventually lead to cell death and if this becomes to extensive, serious tissue damage can occur. Thus oxidative stress has been shown to play an important role in the pathogenesis of numerous diseases: e.g. ischemia-reperfusion injury; degenerative diseases; immune disorders; burn; cardiovascular diseases…

What are the natural cellular defenses against oxidative stress?

Protein antioxidant systems
- Superoxide dismutase & Catalase: SOD reduces $O_2^-$ to $H_2O_2$. CAT then reduces $H_2O_2$ to water.
- GSH pathway enzymes: $\gamma$-glutamyl cysteine synthase and GSH synthase form GSH from glutamate, cysteine and glycine. This reduced form of GSH can be oxidized while reducing $H_2O_2$ to $H_2O$ by GSH peroxidase. GSH reductase reduces GSH back to its reduced form using NADPH.
- Misc proteins: Certain proteins chelate transition metals that could entertain a ROS chain formation: e.g. transferrin; lactoferrin; albumin…

Non-protein antioxidants
- Vitamin E & Vitamin C: Tocopherols and ascorbic acid can both reduce oxidants. Vitamin C is present in the water compartments of the cell while vitamin E is present in the lipid membrane structures. Vitamin C can reduce back the oxidized form of vitamin E. The DHA reductase reduces back the oxidized form of ascorbic acid (DHA) using GSH.
- Glutathione (GSH) & cysteine: GSH is a tripeptide with one functional thiol group on its cysteine. GSH is the main intracellular small antioxidant while cysteine is very important in extracellular fluids. – See GSH pathway below. -

Evaluating oxidative stress in vivo
It is presently very difficult to accurately assess oxidative stress in patients. Indeed, of all the markers known to be associated with oxidative stress or antioxidant systems, we do not know which combination accurately reflects the redox status of an individual. In
addition, some of the assays presently available to measure some of these biomarkers are difficult to conduct routinely in clinics. Finally, collection and processing can affect redox markers in biological samples.

**Examples of oxidative stress measurements:**

- Levels or activity of antioxidant proteins
- Levels of ROS themselves: NMR; Electron Paramagnetic Resonance; Electron Spin Resonance and Radical Trapping
- Lipid peroxidation markers: Thiobarbituric Acid; Reacting Substances; malondialdehyde lipid hydroperoxides; conjugated dienes; F2-isoprostanes
- Protein oxidation markers: glutathionylation; carbonation; nitration; halogenation
- DNA oxidation markers: DNA adducts; DNA breaks

**Pharmacological antioxidants**

It is important to distinguish pharmaceuticals from nutraceuticals when it comes to antioxidants. In the first case, the agent has gone through a thorough regulatory process to prove its safety and efficacy for certain indications in certain patients. The production of these approved antioxidants is then controlled and inspected by the FDA. Nutraceuticals are not regulated by the FDA; there is therefore no guaranty that they are effective, safe, or that the formulation contains the claimed amount of active ingredient and no contaminants.

It is also important to realize that most antioxidants undergo oxidation when reducing their target oxidant. Although usually much less reactive than the oxidant it reduced, an oxidized antioxidant will have to be removed or reduced back by the cell. This means that in excess, such such antioxidants can also be toxic.

**Vitamins**

- Vit C (ascorbate)
- Vit E (tocopherol)
- B vitamins (thiamine; riboflavin; niacin…)
- Carotinoids (βcarotene; lycopene…)
- Flavonoids

**Minerals**

- Selenium
- Zinc

**GSH precursors**

- N-acetylcysteine (NAC)
- S-adenosylmethionine (SAMe)

**Others**

- Melatonin
- Lactoferrin

**Nutritional antioxidants**

A balanced diet normally contains numerous antioxidants. It is well known that anorexia, but also unbalanced diets, are associated with oxidative stress. Importantly, a well-balanced diet might not provide enough antioxidants if those are not properly absorbed. For instance, vitamin E absorption is chylomycron-dependent, and the absorption of selenium depends on the presence of methionine and cysteine.

**References**


Antibiotic Stewardship: Antibiotic Resistance Crises and Veterinary Medicine
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What is antibiotic stewardship?
Antimicrobial stewardship, in general, can be defined as an activity that promotes the appropriate selection of antimicrobials and the appropriate dosing regimen during antimicrobial therapy (IDSA guidelines, Infectious Diseases Society of America).

Why do we need antibiotic stewardship?
We have to use antibiotics judiciously: to eradicate (or prevent) the infection more effectively; to reduce toxic side effects; to prevent the emergence or selection of antibacterial resistance; and to save time and limit cost.

Antimicrobial resistance is a growing concern worldwide that is significantly associated with misuse of antimicrobial drugs. The incidence of antibacterial resistance is increasing, especially with antibiotics used very (too) commonly, such as cephalosporins and fluoroquinolones. Even relatively newer drugs, like carbapenems (imipenem), are now associated with alarming rates of resistance. The other side of this worrying situation is that the pharmaceutical industry is not developing new antibiotics. Governments have therefore started taking action, and veterinary medicine is one of their main targets.

Guidelines and recommendations on judicious antibiotic use have been published to address this issue in human medicine. In 2011, the American Veterinary Medical Association (AVMA) created a five-member steering committee to work with the FDA on a policy overseeing veterinary use of antimicrobials. The committee has been focusing on food animals so far to provide input to the FDA about policies and regulations that will dictate the use of antimicrobials in these animals. Unless the antibiotic resistance crisis gets under control, it is unlikely that restrictions will continue to only target food animals in the future. The World Organization for Animal Health has also included objectives for veterinary drugs, especially antimicrobials, in its Strategic Plan.

Factors entering the decisions around antibiotic therapies

Inadequate reasons to use an antibiotic when considered on their own
- Fever
- High white blood cell count
- Emergency status
- Clinical sign severity
- Patient already receiving an antibiotic, prescribed by ourselves, a colleague, or a referring veterinarian

Decision factors based on the bacteria
1. Is it really a microbial infection? Or is there a real risk for a microbial infection to develop?
2. If yes, is it a bacterial infection rather than another type of microbe?
3. If yes, which bacteria might be involved (based on empirical deduction or culture)?
4. What antibiotics is this bacteria sensitive to? (based on empirical choice or sensitivity test)

Decision factors based on the antibacterial agent
- Effective drugs available against the suspected bacteria
- Pharmacokinetic profile: absorption; tissue distribution; elimination mechanisms; half-life…
- Toxicity profile; side effects and potential drug interactions
- Resistance profile

Decision factors based on the patient
- Species; age; gender…
- Infection location
- Health status

Decision factors based on practicality
- Dosing regimen & duration
- Cost
- On- and off-label options
- Bans (in food and athlete animals)
- Withdrawal times for food animals or athlete animals.

Decision factors based on the environment & the community
- Likelihood for resistance emergence or selection (especially with cephalosporins and fluoroquinolones)
- Drug residues in the environment (not just for food animals!)
Drug residues in the food supply (for food animals)

Judicious use of an antibiotic

Examples

- Restrict prophylactic antimicrobial therapy unless there is a very strong rationale for an infection risk (especially with surgery) (#)
- Favor narrow spectrum antibiotic therapy whenever possible (avoid “umbrella antimicrobial therapy” at all cost despite its reassuring appeal)
- Favor local administration when possible (BUT make sure EBM is available for efficacy, but also safety)
- Clearly communicate the importance of compliance with the owner to avoid relapse or resistance emergence/selection
- Do not use antibiotics for longer than necessary (*)
- Rotate antibiotics in long-term therapy

(#) When using antibiotic prophylaxis in surgical patients, protocols (timing, dose, route) should not be directly transferred from one species to another or from one drug to another without verifying that pharmacokinetic parameters are similar between situations.

(*) One of the main efforts in antibiotic stewardship started in human medicine is also to reduce the duration of antibiotic therapy as much as possible. For instance, antibiotic courses have been reduced to 3 days for uncomplicated UTIs in women or 7 days for pneumonia in otherwise healthy patients. A few studies in veterinary medicine have tried to investigate shorter antibiotic courses as well.

Infection prevention & alternatives to antibiotics

One of the key aspects of antibiotic stewardship is to not use antibiotics whenever possible. Several other strategies can be used to prevent an infection:

- Vaccination
- Disinfection of facility, cages, and material
- Hand washes before and after each patient
- Decrease surgery duration as much as possible
- Decrease hospitalization duration as much as possible
- Test employees for multi-resistant carriage when repeated multi-resistant bacteria are isolated
- Isolate the patient when a resistant strain is suspected or has been isolated

Other strategies can be considered instead of, or in addition to, antibiotics when a bacterial infection occurs:

- Remove infected sites and/or infected tissue debris whenever possible
- Alternative therapy: e.g. probiotics or immunostimulants

References

http://www.cdc.gov/getsmart/healthcare/learn-from-others/CME/antimicrobial-stewardship.html