Antibiotic Resistance in Production and Companion Animals

About the Reviewer

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Stephen Page is a consultant veterinary pharmacologist and toxicologist based in Australia. He has always been particularly interested in decision making, value of information and appropriate use of veterinary medicines, especially antimicrobial agents. He has worked to develop a framework of antimicrobial stewardship with colleagues at the Ontario Veterinary College in Guelph, has been an invited speaker on antimicrobial resistance at conferences and workshops in Australia, New Zealand, North America, Europe and Asia, and was invited facilitator of the Australian One Health Antimicrobial Resistance Colloquium. He is currently working on antimicrobial stewardship projects with the Australian Veterinary Association and the pig, poultry and cattle industries.

The objective of this narrative review is to raise awareness of the need for the highest quality of antibiotic use in veterinary medicine to help minimise the selection and dissemination of drug resistance. The focus of the review is on food-producing animals, particularly dairy cows, but companion animals and horses are also considered.

Background

In veterinary medicine, antibiotics are used for three main reasons in production animals:[1,2] i) therapeutic treatment of animals with clinical illness; ii) metaphylactic treatment of a group of animals (i.e. illness in a minimum threshold proportion of animals triggers treatment of the entire herd or flock); and iii) prophylactic treatment of a group of healthy animals considered at risk of developing clinical illness. Antibiotics are also an important therapeutic option in the treatment of clinical illness in companion animals.[3]

Antibiotic use in veterinary medicine, as in human medicine, has the potential to select for genetic material that encodes microbial resistance in bacterial pathogens and commensals, i.e. antibiotic use could contribute to drug-resistant bacteria developing in animals.[1,2,4] There is increasing concern that antibiotic use in animals poses a risk to human health,[1] i.e. the possibility that antibiotic resistance may pass from bacteria in animals to bacteria in people or that drug-resistant animal bacteria may infect people. However, few published studies have directly addressed this question.

According to a 2016 comprehensive report on drug-resistant infections, the continued overuse and misuse of antimicrobials (including antibiotics), in both humans and animals, could lead to the global death toll due to drug-resistant bacterial, viral, and protozoal infections increasing from 700,000 per year currently to 10 million per year by 2050.[5] Of particular concern is the development of resistance to antibiotics classified by the World Health Organization as being of greatest importance for human medicine.[4] Classes of these 'critically important' antibiotics that are registered for veterinary use include fluoroquinolones, third- and fourth-generation cephalosporins, and macrolides.

Against this background, the rationale for minimising the development of antibiotic drug resistance in veterinary medicine is two-fold:

1. To maintain the long-term effectiveness of currently available antibiotics, especially as new agents will likely be restricted to human medicine.
2. To minimise the likelihood of transfer of antibiotic drug resistance between the bacteria of animals and humans.

Antibiotic resistance: Development and transmission

The development of antibiotic resistance can occur via mutations in certain genes or via the horizontal transfer of genes that encode resistance mechanisms.[6-8] These resistance genes are often located on mobile genetic elements, including plasmids, that can be transferred between bacteria, allowing resistance genes to be horizontally transmitted between bacteria.

Pathogenic bacteria occur not only in humans and other animal hosts but also in the environment and there are multiple pathways connecting these ecosystems that allow the movement of the bacteria, genetic elements (including antibiotic resistance genes), and antibiotics themselves.[1,9,10] Specific pathways by which antibiotic drug use in production animals can drive the selection of antibiotic-resistant bacterial pathogens that may lead to negative human health outcomes are described in **Figure 1**. For example, the food chain and environment have been identified as likely routes for the spread of antibiotic resistance determinants from food-producing animals to humans.[11]

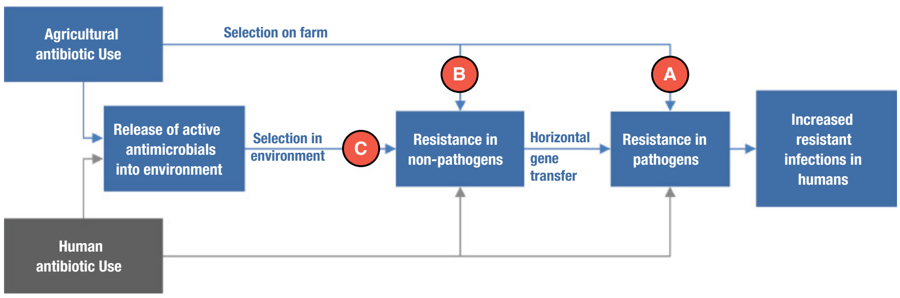

Figure 1. Conceptual model of the potential pathways that antibiotic resistance transmission among farm animals, the environment, wildlife, and humans could lead to an increase in resistant pathogens transmitted to humans.[10] Agricultural antibiotic use selects for resistance in pathogens, which can be transmitted to humans via the food chain or the environment (**A**). Agricultural antibiotic use selects for resistance in non-pathogens (commensals and environmental microbes), which can transfer resistance genes to pathogens with potential for more resistant bacteria causing infections in humans (**B**). Antibiotics are released into the environment where selection occurs predominantly in non-pathogens (soil microbes), and resistance can be transferred horizontally to pathogens with potential for more resistant infections in humans (**C**).

In addition to humans and food-producing animals interacting directly and indirectly (via the food chain and environment), companion animals, horses, and other animal species live in close contact with humans with potential for shared microbiomes.[3,12] The close contact between humans and companion animals creates opportunities for the interspecies transmission of resistant bacteria.[3] An Australian study that demonstrated extensive similarities of fluoroquinolone-resistant *Escherichia coli* isolates from humans and companion animals is suggestive of interspecies transmission in either or both directions.[13] However, current understanding of this phenomena is limited.[3]

Three of nine human antimicrobial-resistant pathogens identified by the WHO as being of international concern have been highlighted as a public health concern in NZ.[14-16] They are methicillin-resistant *Staphylococcus aureus*, Enterobacteriaceae (specifically extended-spectrum beta-lactamase (ESBL)-producing *E. coli* and *Klebsiella pneumoniae*, and carbapenemase-producing *E. coli* and *K. pneumoniae*), and *Neisseria gonorrhoea* (a pathogen of humans, not animals) resistant to third-generation cephalosporins. The concern is primarily due to the ubiquity of these pathogens in both community and hospital settings and their increasing resistance to the major antibiotic classes, penicillins, fluoroquinolones, third-generation cephalosporins, and carbapenems.

The transfer of antibiotic resistance from animals to humans, either directly or indirectly, is difficult to quantify.[10,17] However, there is no doubt that, via selection pressure, antibiotic drug use in animals leads to the emergence of drug-resistant pathogens and that resistance to particular antibiotics has developed in animals.[1,18,19]

In NZ, antibiotic-resistant Enterobacteriaceae have been isolated from food-producing animals, including ampicillin-resistant *E. coli* in pigs, ESBL-producing *K. pneumoniae* in poultry, and cefoxitin-resistant *E. coli* in pig, poultry, calves, and fresh produce.[20-22] Additionally, resistance to certain beta-lactam antibiotics has been identified in *Staphylococcus* isolates and to trimethoprim/sulfamethoxazole in *Streptococcus* isolates from cases of dairy cow mastitis.[23]

In companion animals an increase in resistance to antibiotics commonly used in the treatment of urinary tract infections in dogs, including amoxicillin-clavulanic acid, cephalothin, and enrofloxacin, has been demonstrated in NZ (over the period 2005–12).[24] The emergence of antibiotic resistance among dogs has also been demonstrated in similar studies conducted in North America and Europe.[25-27] Furthermore, multi-drug resistance, including resistance to commonly used antibiotics, has been found in bacterial isolates from NZ foals and young horses (2004–2014).[28,29] The major antibiotic-resistance concerns in companion animals are similar to those highlighted as being a public health concern in NZ, i.e. methicillin-resistant *S. aureus* and ESBL- or carbapenemase-producing Enterobacteriaceae.[14,15]

Antibiotics: Usage patterns

Agricultural antibiotic sales data is used to monitor trends that may indicate changes in antibiotic use in the field, which may inform changes in antibiotic resistance.[30] Inferring antibiotic use from sales data does, however, come with inherent limitations due to variables such as the timing of data collection and antibiotic use, unquantified product loss, and changes in animal population and disease prevalence.

Sales data for antibiotics used in food-producing animals in NZ during the period 2011–14 indicate that the dairy cow, pig, and poultry industries purchased the greatest mass of antibiotics.[30] Antibiotics are used in apparently healthy animals in NZ for prophylaxis and metaphylaxis, e.g. in-feed antibiotics are used in the poultry industry,[31] and on NZ dairy farms antibiotics are prescribed for mastitis prophylaxis and treatment.[30,32] In contrast, antibiotic sales in the other food-producing animals, sheep, beef cattle, and deer, appear to be very low.

In a study that estimated the use of antibiotics for food-producing animals in Australia, NZ, Canada, the US, and twenty-six European countries in 2012, NZ was the third lowest user of antibiotics in production animals.[33] The relatively low usage of antibiotics in production animals in NZ is at least partially attributable to NZ's extensive pastoral, and therefore less intensive, agricultural systems as well as its relatively small pig and poultry industries.[33,34] However, this is no reason for complacency in investigating ways to further reduce antibiotic use.

Regarding the extent of antibiotic use in companion animals, the quantity of antibiotics sold for companion animal use in 2013–2014 was only 1.8% of overall sales of antibiotics for use in all animals.[30] Nevertheless, there is concern that antibiotic use in companion animals also contributes to the development of antibiotic resistance. This concern is primarily based on the conspicuously high proportion of antibiotics considered critically important in human health that are used in companion animals worldwide,[30,35] and the close bonds between pets and their owners increasing the risk of cross-species transmission of resistant bacterial species.[3,36] In a 2008 survey of companion animal veterinarians practicing in NZ, broad-spectrum drugs considered by the WHO to be critically important for human health were among the most frequently prescribed antibiotics in companion animal medicine and they were often prescribed without submitting a sample for culture and susceptibility testing.[37]

Antibiotic therapy: General principles

The overarching aim of antibiotic therapy in veterinary medicine should be to optimise therapeutic efficacy while minimising the potential for the development of antibiotic resistance.[38]

All veterinary medicines, including antibiotics, used in NZ must be authorised under the [Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997]. To guide appropriate use of antibiotics, the NZVA has developed policy guidelines on the [judicious use of antimicrobials].

The NZVA policy guidelines recommend that there must be evidence of bacterial infection, or a risk of imminent infection, to justify antibiotic use and that alternative methods of disease control or adjuncts to antibiotics have been considered to reduce antibiotic use.[38] The policy guidelines also state that antibiotic use should not be a replacement for disease control programmes, which typically involve a number of infection prevention measures, including hygiene and disinfection procedures, biosecurity, management alterations, stocking rate changes, and vaccination, in addition to antibiotic use.

According to the NZVA policy guidelines for prudent use of antimicrobials, antibiotic selection should be based on:[38]

1. Accurate diagnosis.
2. Sensitivity testing.
3. Pharmacokinetic/tissue distribution.
4. Immunocompetence status.
5. Dosing compliance.

In reality, antibiotic therapy may need to be commenced before culture and sensitivity test results are known; therefore, therapy will need to be reassessed once test results have been received. In the initial absence of test results, empirical antibiotic prescribing will likely be required. This should be based on:[38]

1. What has previously been effective in similar types of problems.
2. Knowledge of previous antibiotic efficacy or sensitivity testing on the premises.
3. Relevant controlled clinical trial data, where available.

In terms of drug selection, the NZVA antimicrobial use policy guidelines also recommend that:[38]

1. Narrow-spectrum antibiotics should be selected in preference to broad-spectrum drugs
2. Antibiotics considered of high importance in human medicine should be avoided.

Certainly, particular care should be taken when prescribing antibiotics that could give rise to cross-resistance with drugs used for the treatment of serious infections in humans, i.e. third- and fourth-generation cephalosporins, fluoroquinolones, and macrolides.[38] Use of these antibiotics should be avoided, unless routinely-used agents are not likely to be effective. Antibiotics used most commonly for antimicrobial therapy in animals should be limited to those that are of least importance to human health.

According to a recent study in which NZ cattle veterinarians were surveyed about factors influencing their prescribing of antibiotics, prescribing was predominantly based on diagnosis and response to previous therapy and antibiotic culture and sensitivity testing was not widely used.[39] Non-technical factors also influenced prescribing, including farmer feedback about perceived efficacy and perceptions of cost versus benefit. The finding that personal experience was a key factor in the selection of antibiotics, and the lack of use of antibiotic susceptibility testing, suggest that guidelines and stewardship programmes, although widely available, may be underutilised by veterinarians and that better tests to identify pathogens and determine susceptibility are needed.[5]

In the same study, focus groups of dairy farmers suggested that, although farmers trusted veterinarians and their advice, they considered personal experience on their farm to be important as well.[39] Also, the farmers did not appreciate the importance of assessing efficacy using bacteriological cure and considered bacterial culture to be of limited value. These findings appear to indicate a need for veterinarians to improve their communication with farmers regarding antibiotic selection and requirement for assessment of efficacy. Similar conclusions have been made in studies in Europe.[40,41]

Antibiotic use in dairy cows

The greatest use of antibiotics in the dairy industry is for dairy cow mastitis and in particular dry cow therapy,[30,32] with entire herds being treated prophylactically in many cases.[32] However, increasingly there have been calls for use of antibiotics in dairy cows only as a treatment where there is clear evidence of infection.[42,43] Consistent with this trend, and recognising that there are now effective alternatives to dry cow antibiotic therapy (e.g. internal teat sealants and better herd management practices), the NZVA has proposed that, by 2020, dry cow therapy will only be used in the treatment of existing intramammary infections.[44]

There are three ways to reduce the use of antibiotics:

1. Reduce the number of animals needing treatment with antibiotics via improved integrated herd management, disease prevention, and use of non-antibiotic alternative treatments.[32]
2. More prudent use of antibiotics, i.e. treating known disease only and not treating the herd prophylactically.[32]
3. Reducing the duration of antibiotic therapy, since total mass of antibiotic used = dose x duration of treatment x mass of animals treated x number of animals treated.

The NZVA's guidelines for the judicious use of antimicrobials in dairy cows advocate that, in general, antibiotic treatment is only indicated when both of the following conditions are satisfied:[45]

- There is a bacterial infection or there is sufficient reason to suspect that an actual bacterial infection is present.
- The infection is unlikely to resolve without antibiotic therapy.

In addition, the occurrence of infections should be countered by preventive measures where possible, and non-antibiotic treatments should be used in preference to antibiotics.

The NZVA's guidelines for the judicious use of antimicrobials in dairy cows are summarised in **Table 1**.[45]

Antibiotic use in companion animals and horses

Antibiotic resistance in companion animals and horses is a concern because of the close contact between humans and their pets and the potential for cross-species transmission and the frequent prescribing of human-critical antibiotics for companion animals.

Similar to the NZVA guidelines on the use of antimicrobial agents in dairy cows,[45] the basis of the NZVA antimicrobial use guidelines for cats and dogs and horses is also antibiotic resistance risk reduction.[46,47]

The core principles of judicious antibiotic use in cats and dogs and horses advocated by the NZVA are summarised in **Table 1**.[46,47]

Antibiotic use: core principles
Dairy animals
1. All dairy farmers and their vets must be committed to producing safe food. 2. Dairy farms should be managed to reduce the risk of disease challenge and, therefore, the need to use antibiotics. 3. Dairy farmers and their vets should draw up, implement, and regularly review an appropriate herd health plan that outlines routine preventive treatments (e.g. biosecurity, vaccination programmes, etc.) and disease control policy. 4. Antibiotics should only be prescribed by a vet when there is evidence of a susceptible bacterial infection, treatment is necessary to maintain animal health and welfare, and no other treatment such as drainage or antisepsis is likely to be effective. Treatment should be restricted to individual animals where possible. 5. Choice of antibiotic should be based on knowledge of common pathogens and local laboratory data. 6. Antibiotics and dose regimens should be chosen to minimise the development of clinically significant resistance in people or animals. 7. An appropriate withholding time must be applied before the slaughter of treated animals or inclusion of milk from treated cows to the bulk milk tank. 8. Accurate information must be kept on the identity of the treated cattle, the nature of the condition being treated, drugs used, and withholding period.
Companion animals and horses
1. Prevention of conditions that could require antibiotic therapy is a key focus of veterinary practice. 2. Consider the impact of antibiotic use on the animal, its owner and other people, and the environment. 3. Animals should receive antibiotics only when there is a susceptible bacterial infection, antibiotics are required to maintain their health and welfare, and when no other treatment will work. 4. When antibiotics are used, dose rates and regimens should be designed for maximal efficacy and to limit re-treatment. 5. There are antibiotics considered so important in human medicine that they should not be used as first-line therapy, and only used where no other therapy will work. 6. There will be a reduction in selection pressure for antibiotic resistance if a smaller total amount of antibiotics is used in veterinary and human medicine. 7. Strategies reducing the number of animals given antibiotic agents are employed where this will not compromise animal health or welfare.

Table 1. Core principles of responsible antibiotic use in dairy, companion animal, and equine veterinary practice.[45-47]

Antibiotic selection

In terms of drug selection for dairy cattle, companion animals, and horses (**Table 2**), the presence of antibiotic resistance and the risks associated with antibiotic resistance selection should always be considered when choosing an antibiotic. Hence, whenever possible:[45-47]

1. Microbiological culture and sensitivity testing should be used to guide selection.
2. Pharmacokinetics and pharmacodynamics should be used to ensure therapeutic concentrations at the site of infection.
3. Selection should be based on knowledge of common pathogens and local laboratory data.
4. Human-critical antibiotics should be restricted to agents of last resort.
5. Narrow-spectrum antibiotics are preferred to broad-spectrum agents.
6. Topical therapy is preferred to systemic therapy.
7. Duration of treatment should be kept as short as possible.

First-line agents	Second-line agents or agents restricted to specific indications	Third-line agents†
For use under therapeutic guidelines	For use under therapeutic guidelines	For use only following a specific veterinary diagnosis on a case-by-case basis with sufficient evidence to indicate need
Dairy cattle		
• Procaine penicillin • Penethemate hydroiodide • Oxytetracycline	• Aminoglycosides • Semi-synthetic penicillins: ampicillin, amoxicillin/clavulanic acid • First- and second-generation cephalosporins • Cloxacillin • Potentiated sulphonamides	• Third- and fourth-generation cephalosporins • Fluoroquinolones • Macrolides
Cats and dogs		
• Procaine penicillin • Tetracyclines	• Aminoglycosides • Semi-synthetic penicillins: ampicillin, amoxicillin/clavulanic acid • First and second generation cephalosporins • Potentiated sulphonamides	• Macrolides and lincosamides • Third- and fourth-generation cephalosporins • Fluoroquinolones
Horses		
• Sodium penicillin, procaine penicillin • Oxytetracycline • Trimethoprim/ sulphadiazine • Aminoglycosides: gentamicin, neomycin • Rifampicin (off label) • Azithromycin (off label)	• Doxycycline (off label) • Metronidazole (off label) • Streptomycin	• Third- and fourth-generation cephalosporins: ceftiofur (off label), cefquinome (off label) • Fluoroquinolones: enrofloxacin, marbofloxacin

† Antibiotics considered important in treating refractory conditions in human and veterinary medicine.

Table 2. Common antibiotic drug selection for first-, second-, and third-line therapy of infection in animals.[45-47]

Antibiotic stewardship

In the absence of new classes of antibiotic drugs to treat microbial disease in animals (and indeed humans), stewardship is an important intervention to moderate the development of antibiotic resistance.[1,31]

Antibiotic stewardship is the concept of multifaceted approaches to sustaining the clinical efficacy of antibiotics, including monitoring of their use, surveillance of resistant bacteria, improved infection control and prevention, and improved knowledge and understanding of veterinary prescribing.[31,43]

With its aspirational goal that antibiotics will not be needed in NZ for the maintenance of animal health and wellbeing by 2030, the NZVA established its leadership role in antibiotic stewardship. The NZVA recommends that the "5 R's" should form the basis of any stewardship programme:[45,46]

1. **Reduction in antibiotic use.**
   Measures to directly reduce the amount of antibiotic used include disease prevention (via husbandry, vaccination, monitoring, and staff training), eliminating use of antibiotics where there is no infection (e.g. an uncomplicated viral infection), using topical or local rather than systemic formulations, and avoiding prophylactic use unless justified.
2. **Refinement of prescribing practices and therapeutic plans.**
   Ongoing evaluation of prescribing practices and therapeutic plans based on treatment response, previous similar cases, controlled clinical trials, and local resistance data.
3. **Replacement of antibiotics by using non-antibiotic alternatives, where there is peer-reviewed evidence of efficacy.**
   In dairying, examples of alternatives to antibiotics are use of teat sealants (without adjunctive use of antibiotics) to reduce the risk of intramammary infection, and use of prostaglandin F2α in the treatment of cows with a corpus luteum (CL+ cows) exhibiting signs of endometritis.
4. **Responsibility being taken for prescribing, treatment, and management of animals.**
   The success of a stewardship plan requires engagement, understanding, and personal accountability being assumed by all parties involved.
5. **Review of the plan periodically (at least annually) to ensure objectives are being met.**
   Review can involve auditing of compliance, monitoring of reduction and replacement strategies, susceptibility surveillance, and ongoing investigation of strategies to improve antibiotic stewardship within a veterinary practice.

Education is a pillar of antibiotic stewardship and veterinarians require access to continuing professional development and the impetus to educate farmers and clients.[31] In a study of the attitudes of NZ farmers to the use of antibiotics and risk of antibiotic resistance, farmers had limited knowledge or concern about the risk of drug resistance and less than half agreed or strongly agreed that use of antibiotics on their farm would increase the risk of resistance in their herd or in humans.[39] The need to improve the acceptance of stewardship practices has also been reported for dairy farmers in the US.[48]

These findings emphasise the importance of educating farmers and farm workers about prudent antibiotic use. It has been suggested that farmers may be more motivated towards effective use of antibiotics in farm animals if doing so generated tangible benefits in terms of reduced costs or improved productivity.[1]

Another pillar of successful antibiotic stewardship is collaboration. Recent research from the UK demonstrated how a participatory policy development process enabled dairy farmers, veterinarians, industry partners, and researchers to work together to develop and implement an antibiotic stewardship policy that included measures to change on-farm use of antibiotics at the same time as maintaining or improving herd health and welfare.[49] The key principles around which the policy was developed were: disease reduction, correct use of antibiotics, avoidance of prophylactic use, and quality data recording and use.

Stewardship is also part of the collaborative multidisciplinary 'One Health' approach for controlling antibiotic resistance, which recognises the interconnectedness of humans, animals, and the envrionment.[31,50]

TAKE-HOME MESSAGES

- Resistance genes can contribute to the spread of antibiotic resistance between bacterial species and from non-pathogens to pathogens.
- Pathways exist by which antibiotic-resistant bacterial pathogens can move in either direction between animals and humans.
- Antibiotic use in veterinary medicine has the potential to drive the development of antibiotic drug resistance.
- Loss of efficacy of antibiotic drugs will compromise both human and animal health.
- Prudent use of antibiotics in production and companion animals is imperative to limit the development of drug resistance.
- Antibiotic use in production animals can be reduced by:
  - Improving herd management and disease prevention practices.
  - Avoiding prophylactic and metaphylactic treatments.
  - Treating only known bacterial disease.
- Antibiotic stewardship has a fundamental role to play in preventing the development and spread of antibiotic resistance.

EXPERT'S CONCLUDING COMMENTS

The NZ veterinary profession has shown significant global leadership with the antimicrobial stewardship initiatives that the NZVA has developed and is implementing. As identified in this review the quantity of antimicrobial use compares extremely favourably with the rest of the world as does the evidence on antimicrobial resistance (AMR) occurrence in bacterial isolates from farm and companion animals. Despite the differences in production practices between countries this is an enviable position and clearly one that the NZ veterinary profession wishes to further enhance. The introduction of antimicrobial stewardship plans will allow the quality of antibiotic use to be assessed – harder to measure but potentially of greater importance to AMR selection than antibiotic quantity alone. The more targeted approach to antibiotic use outlined in the judicious use guidelines will significantly enhance the quality of use. As improved methods of infection detection and diagnosis become available the NZ approach to optimal use can be even more finely honed. It is salutary to compare the NZVA objectives and aspirations with the AMR action plans of FAO (2016), OIE (2016), and WHO (2015).[1-3] It can only be concluded that the NZ veterinary profession recognises the enormity of the global AMR crisis and although already exhibiting many global best practices remains dedicated to introspection, learning, and continuous improvement. Collaboration with medical and other stakeholders will allow an advanced One Health AMR strategy to evolve with great benefits to health and welfare.

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