Antimicrobial resistance in veterinary medicine: mechanisms and bacterial agents with the greatest impact on human health

Resistência a antimicrobianos em medicina veterinária: mecanismos e agentes bacterianos de maior impacto em saúde humana

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Abstract

Many retrospective and prospective studies have been performed to understand the emergence and dissemination of antibiotic-resistant microorganisms. The rates of antimicrobial drug resistance among bacterial pathogens are high and now represent a worldwide concern, both in human medicine and veterinary practices. The aim of this review is to describe the mechanisms of antibiotic resistance and the risks associated with antimicrobial use in animal production. Pathogens with major impacts on human and animal health are discussed, including multidrug-resistant and extensively drug-resistant Gram-negative and Gram-positive bacteria.

Keywords: Bacterial resistance. Growth promoters. Public health.

Resumo

Vários estudos retrospectivos e prospectivos têm sido realizados para investigar o aumento e a disseminação de microorganismos resistentes a antimicrobianos. As taxas de resistência entre esses agentes são crescentes e representam uma preocupação mundial, tanto em medicina humana como em veterinária. O objetivo da presente revisão é descrever os mecanismos de resistência antimicrobiana e os riscos associados ao uso de antimicrobianos na produção animal. Os patógenos de maior impacto em saúde humana e animal são abordados, incluindo bactérias Gram-negativas e Gram-positivas multirresistentes e extensivamente resistentes.

Palavras-chave: Resistência bacteriana. Promotores de crescimento. Saúde pública.

Antibiotics have been sold like sweets (GILBERT, 2012). Since the discovery of penicillin, which revolutionized the treatment of infectious diseases in the past century, antimicrobial agents have been broadly used worldwide, and many countries do not have legislation to control antibiotic consumption. Currently, the prevalence of antimicrobial-resistant pathogens has increased at a speed inversely proportional to the approval of new drugs. Thus, in regard to infectious diseases, the emergence of resistance is one of the top health challenges in the 21st century, especially in hospital settings. However, when considering veterinary medicine, although the amount of antibiotics consumed in livestock is almost double the amount used by humans, the role of veterinary antimicrobials use in resistance development has only recently been discussed (PHILLIPS et al., 2004; AARESTRUP, 2012). In this context, foodborne pathogens and urinary tract infection-related agents deserve special attention due to the potential of transmission through consumption or

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manipulation of animal-origin food (NORDSTROM; LIU; PRICE, 2013). In this context, the surveillance of resistant strains in Brazilian farms is extremely important because this country is one of the biggest animal food producers in the world.

Mechanisms of resistance

Bacteria can evade the actions of antibiotics using diverse mechanisms. Such antibiotic resistance may be either intrinsic or acquired. Intrinsic resistance is inherent to all specimens of the species. In such cases, in general, the gene that encodes the intrinsic resistance is chromosomal. For example, all Gram-negative bacteria are naturally resistant to vancomycin due to their cell wall structure, which differs from Gram-positive cell walls (MADIGAN et al., 2012). However, acquired resistance involves a change in the organism's genetic composition via either mutation in the chromosomal DNA or the acquisition of exogenous DNA. Mutations occur randomly at a low frequency, and the mutations can sometimes result in advantageous characteristics that can be selected. For example, mutation accumulation in quinolone targets in DNA gyrase is the main mechanism against quinolone binding (JACOBY, 2005). Though bacteria can acquire external DNA by bacteriophage infection and transformation, plasmid mobilization by direct cell-to-cell contact, also termed conjugation, is the most common transfer mechanism of antimicrobial resistance-encoding genes.

The main resistance mechanisms are efflux pumps, permeability reduction, antibiotic target modification and antibiotic inactivation (BARIE, 2012). Efflux pumps decrease cellular drug accumulation because compounds are pumped out of the inner membrane to the periplasmic space or directly to the external medium (HORIYAMA; YAMAGUCHI; NISHINO, 2010). Some efflux pumps are capable of extruding many compounds, including detergents and different antimicrobial classes. In this context, in Gram-negative bacteria, the resistance-nodulation-division (RND) family forms a protein tripartite complex with the inner membrane, periplasmic space and outer membrane, forming an efficient channel to extrude compounds (HORIYAMA; YAMAGUCHI; NISHINO, 2010; ALVAREZ-ORTEGA; OLIVARES; MARTÍNEZ, 2013). In contrast, in Gram-positive bacteria, the main multidrug efflux pumps belong to the multidrug and toxic compound extrusion (MATE) family (ALVAREZ-ORTEGA; OLIVARES; MARTÍNEZ, 2013).

In addition to efflux pumps, porin loss can confer resistance to a range of antimicrobials. Porins are nonspecific diffusion channels in the outer membrane that permit the influx of small hydrophilic agents, including antibiotic molecules. Thus, non-functional porin production or gene repression that results in porin loss decreases the membrane permeability, resulting in antimicrobial resistance (NIKAIDO; PAGÉS, 2012).

Regarding antibiotic target modification, accumulations of mutations in DNA gyrase and DNA topoisomerase IV have been reported as the main mechanisms of resistance to quinolones, as these mutations can result in enzymes being unable to bind to quinolones due to structural modification. Penicillin-binding proteins (PBPs) are cell wall-synthesizing enzyme targets for beta-lactams. Alterations in PBP confer penicillin resistance. For example, methicillin-resistant *Staphylococcus aureus* produces PBP 2a, which is incapable of binding methicillin (GEORGOPAPADAKOU, 1993).

Although all resistance mechanisms deserve attention, antibiotic inactivation has been described as a main global problem in health care units and communities. Bacteria may produce enzymes that modify or destroy antimicrobial chemical structures, which results in ineffectiveness. Phosphotransferases, acetyltransferases and adenyltransferases chemically modify aminoglycosides, which interferes with either drug transport or the binding of the drug at the site of antibacterial action, the 30S ribosomal subunit

(WRIGHT, 1999). Recently, an aac6Ib variant, aac6Ib-cr, was identified that encodes an acetyltransferase that inactivates quinolones (ROBICSEK et al., 2005). Many commercialized antimicrobials belong to the beta-lactam class; due to rapid spread, beta lactamases became the most important inactivating antimicrobial enzymes.

Some bacteria, mostly *Enterobacteriaceae, Staphylococcus* spp., *Enterococcus* spp. and *Pseudomonas aeruginosa,* become more readily resistant to certain antibiotic categories than others, such as Clostridium spp. and Streptococcus spp., which are still fully susceptible to penicillin G (BOGAARD; STOBBERINGH, 2000; MAGIORKAS et al., 2012).

Recently, a group of international experts from the Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control (ECDC) created a standardized international terminology with which to describe acquired resistance profiles in healthcare-associated microorganisms and published lists of antibiotics for susceptibility tests. According to the standard definitions, multidrug-resistant was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories, whereas extensively drug-resistant was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e., the bacterial isolates remain susceptible to only one or two categories). Strains non-susceptible to all agents in all antimicrobial categories are classified as pandrug-resistant bacteria (MAGIORAKOS et al., 2011).

Antimicrobial use in animal production

Following penicillin use as a human therapeutic agent, the advantages of antibiotics were soon thereafter applied in veterinary medicine and agriculture, including food animal production, pets and aquaculture (TEUBER, 1999, 2001). The extensive use and misuse in all settings has created strong selection pressure, which has resulted in the survival and persistence of resistant strains.

In veterinary medicine, substances exhibiting antimicrobial activity are extensively used in animals for therapy, prophylaxis, metaphylaxis and growth promotion (MARSHALL; LEVY, 2011). Therapeutic use is the administration of an antimicrobial to an animal or group of animals that exhibit frank clinical disease. In farms, individual treatment is often impractical, particularly in food-producing animals, which are kept in larger groups.

Usually, antimicrobials in such large animal groups are administered when single animals of the group present with symptoms of the disease, as it is expected that most of the group will become affected. Prevention/prophylaxis is the administration of an antimicrobial to exposed healthy animals considered to be at risk before expected onset of disease and for which no etiological agent has yet been cultured. Metaphylaxis is a term sometimes used when there is clinical disease in some animals, but all are treated with the aim of reducing the numbers of sick and/or dead animals (PHILLIPS et al., 2004).

Growth promotion is the administration of an antimicrobial, usually as a feed additive, over a period of time to growing animals that results in improved physiological performance. At least four mechanisms have been proposed as explanations of antibiotic-mediated growth enhancement: the inhibition of sub-clinical infections, the reduction of growth-depressing microbial metabolites, the reduction of microbial use of nutrients and the enhanced uptake and use of nutrients through the thinner (PHILLIPS et al., 2004).

In this context, the amount of antibiotics consumed in livestock is almost double that used by humans. This is an important reason for the emergence of intestinal resistant bacteria and, due to the similarities between veterinary and human antimicrobials, has led to cross-resistance (MARSHALL; LEVY, 2011). In other words, the same resistance mechanism confers resistance to veterinary and human antibiotics. For example, CTX-M beta-lactamase production leads to resistance to both ceftiofur (veterinary use) and

cefotaxime (human use) cephalosporins. Thus, the food animal gut may become a reservoir of resistance genetic determinants.

Farm and slaughterhouse workers, including veterinarians, have a high risk of being colonized or infected with resistant bacteria via direct contact with infected or colonized food animals and derived products (GARCIA-ALVAREZ et al., 2012). Moreover, occupational workers and their families provide a conduit for the entry of resistance determinants into community, hospital and environmental settings. These genes may potentially be transmitted to pathogens, as bacteria are capable of acquiring exogenous DNA (PHILLIPS et al., 2004; MARSHALL; LEVY, 2011). Indirect transmission via the animal production chain can occur through food consumption and manipulation. Moreover, the resistance genes may be horizontally transferred to indigenous intestinal microflora and pathogens, resulting in therapeutic failure in potential endogenous infections. Figure 1, adapted from Phillips et al. (2004), describes the possible pathways and routes of transmission of gastrointestinal pathogens and bacteria from microbiota between animals (wild animals, pets and food animals) and humans. Considering these routes, antimicrobial-resistant bacteria can be transmitted between animals and humans and vice versa.

As a precaution, European Union member states banned some growth promoters after the emergence of vancomycin-resistant enterococci (VRE), based on the hypothesis of selection of VRE in the intestinal flora of poultry and pigs and due to the use of avoparcin as a feed additive (BOGAARD; STOBBERINGH, 2000). In Europe, colonization with VRE occurs in the community, whereas in the United States, such colonization has been demonstrated only in hospital settings. As a result of some epidemiological studies, the use of avoparcin at subtherapeutic levels was banned by Denmark in 1995, followed by Germany in 1996 and, subsequently, the entire European Union. Bans on using bacitracin zinc, spiramycin, tylosin and virginiamycin in animal feed became effective for the 15 member states of the European Union on July 1, 1999 (TOLLEFSON; MILLER, 2000). The group of antimicrobials that can be used as growth promoters in animal production in Brazil is presented in Table 1.

The literature on cross-resistance induced by growth promoters is very controversial, and the impact of the ban in Europe remains under discussion because it might even have adverse effects on human health. There is epidemiological evidence that the growth-promoters ban had a marked effect, with decreased VRE rates in the fecal flora of man and animals. Although there was an overall 50% decrease in the total

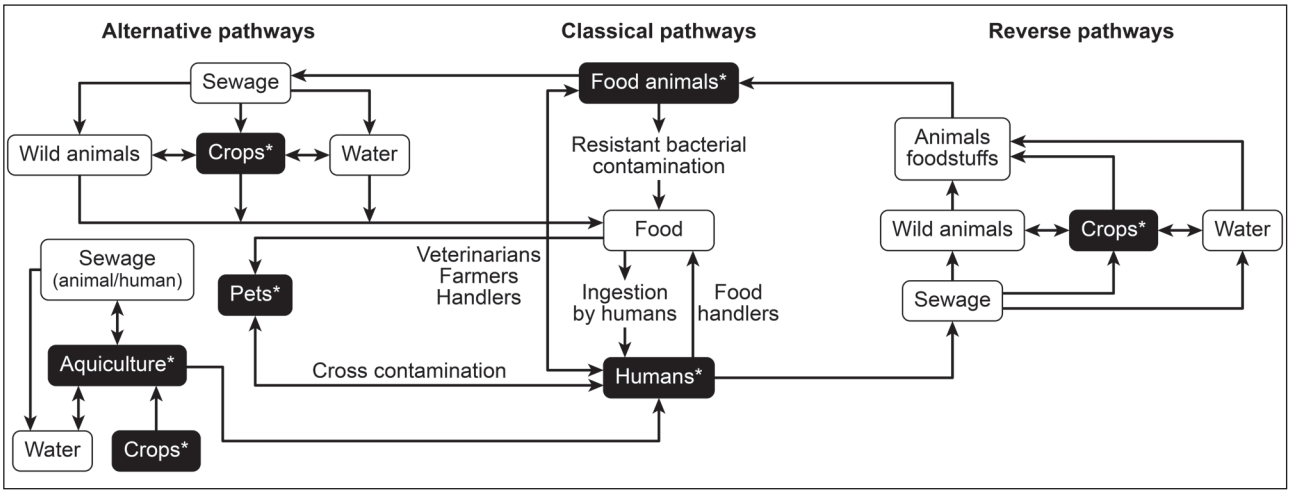

Figure 1 - Possible pathways and routes of transmission of gastrointestinal pathogens and bacteria from microbiota between animals (wild animals, pets and food animals) and humans
Fonte: Adapted from Phillips et al. (2004).

Table 1 - Antimicrobials with authorized use in feed as animals grow promoters in Brazil

Antimicrobial	Animal specie
Avilamycin	Broiler, turkey, swine
Bacitracin methylene disalicilato	Broiler, laying hen, turkey, swine
Bacitracin Zinc	Broiler, laying hen, turkey, quail, swine, bovine
Colistin sulphate	Broiler, laying hen, swine, bovine
Chlorhexidine hydrochloride	Broiler, laying hen, swine
Enramycin	Broiler, laying hen, swine, bovine
Erythromycin	Swine
Spiramycin	Broiler, swine, calf
Flavomycin	Broiler, swine, rabbit, bovine
Halquinol	Broiler, laying hen, swine,
Lasalocid	Bovine
Lincomycin	Broiler, swine
Monensin	Bovine, ovine
Salinomycin sodium	Swine, bovine
Tiamulin	Swine
Tilosina	Broiler, laying hen, swine
Virginiamycin	Broiler, turkey, swine, bovine

number of kilograms of antibiotic used as feed animal additive, the therapeutic use of some drugs increased extensively. The emergence of some gastrointestinal problems, as clostridial necrotic enteritis in poultry and *Lawsonia intracellularis* infections in pigs, has been associated with bacitracin withdrawal. The increase in the incidence of food-borne pathogens, as *Campylobacter* and *Salmonella*, after antibiotic bans is now a human health concern (PHILLIPS et al., 2004).

Bacteria and mechanisms of major impact in human health

Gram-negative bacteria

For Gram-negative bacteria, beta-lactamase production has been identified as the most important problem in bacterial infection management (HAWKEY; JONES, 2013).

Beta-lactamase production is the most common mechanism associated with beta-lactam resistance, including resistance to penicillins, cephamycins, monobactams, cephalosporins and carbapenems, which is clinically significant for treating Gram-negative bacterial infections (BUSH, 2013). There are two classification schemes for the multiplicity and diversity of beta-lactamases. The Ambler's scheme groups beta-lactamases into the A, B, C and D classes according to conserved and distinguishing amino acid motifs (AMBLER, 1980). Originally, Ambler subdivided beta-lactamases that were active-site serine beta-lactamases and metallo-beta-lactamases, which require a bivalent metal ion for activity, into the A and B classes, respectively. AmpC beta-lactamases were later grouped into the C class, and OXA-type enzymes, in general, were included in the D class (BUSH; JACOBY; 2010). In contrast, the Bush-Jacoby-Medeiros system classifies beta-lactamases according to their functional characteristics (substrates and inhibitors) (Table 2). The Lahey Clinic maintains a website with beta-lactamase classifications and amino acid sequences for TEM, SHV and OXA extended-spectrum and inhibitor-resistant enzymes and other enzymes with clinical significance (BUSH; JACOBY, 2013). At present, there are a large number of described enzymes. In most cases, plasmids harboring beta lactamase-encoding genes are responsible for the

Table 2 - Beta-lactamases classification according to Bush-Jacoby-Medeiros

Bush-Jacoby group	Molecular class (Ambler's scheme)	Distinctive substrate(s)	Inhibited by:		Representative Enzyme(s)
			Clavulanic acid	EDTA	
1	C	Cephalosporins	-	-	*E. coli* AmpC, P99, ACT-1, CMY-2, FOX-1, MIR-1
1e	C	Cephalosporins	-	-	GC1, CMY-37
2a	A	Penicillins	+	-	PC-1
2b	A	Penicillins, early cephalosporins	+	-	TEM-1, TEM-2, SHV-1
2be	A	Extended-spectrum cephalosporins, monobactams	+	-	TEM-3, SHV-2, CTX-M-15, PER-1, VEB-1
2br	A	Penicillins	-	-	TEM-30, SHV-10
2ber	A	Extended-spectrum cephalosporins, monobactams	-	-	TEM-50
2c	A	Carbenicillin	+	-	PSE-1, CARB-3
2ce	A	Carbenicillin, cefepime	+	-	RTG-4
2d	D	Cloxacillin	Variable	-	OXA-1, OXA-10
2de	D	Extended-spectrum cephalosporins	Variable	-	OXA-11, OXA-15
2df	D	Carbapenems	Variable	-	OXA-23, OXA-48
2e	A	Extended-spectrum cephalosporins	+	-	CepA
2f	A	Carbapenems	Variable	-	KPC-2, IMI-1, SME-1
3a	B(B1)	Carbapenems	-	+	IMP-1, VIM-1, CerA, IND-1
3b	B(B2)	Carbapenems	-	+	CphA, Sfh-1

Source: Bush et al. (2010).

rapid spread of these enzymes and the high emergence rates of resistant phenotypes.

The extended-spectrum beta-lactamases (ESBLs), which hydrolyze the third- and fourth- generation cephalosporins, are included in Ambler's class A. These enzymes are sensitive to competitive inhibitors such as clavulanic acid, tazobactam and sulbactam. AmpC beta-lactamases hydrolyze cephamycins, such as cefoxitin, and belong to class C according to Ambler's scheme (BARIE, 2012).

Carbapenems (imipenem, ertapenem and meropenem) are the more effective beta-lactams available against Gram-negative bacilli. The carbapenemases are widely described among *Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Acinetobacter baumannii* strains, mainly in health care units. Some studies have described high mortality due to infections with resistant strains. Carbapenem-resistant phenotypes among non-fermentative bacteria have been reported globally due to KPC (*Klebsiella pneumoniae* carbapenemase), metallo-beta-lactamase and OXA-type enzyme production. In Brazil, outbreaks caused by carbapenemase producers are frequently reported in hospital intensive care units (ICUs) (ROSSI, 2011).

In Brazil, the most commonly beta-lactamases identified in the food animal production chain belongs to class A according Ambler's scheme, which groups the SHV, TEM and CTX-M ESBLs. It is speculated that wide use of ceftiofur on animal farms have contributed to the emergence of ESBL producers in livestock. In Brazil, extended-spectrum cephalosporin-resistant strains on animal farms have been described for many years (CORTEZ et al., 2006).

Salmonella enterica

Salmonella enterica have assumed epidemiological importance due the large number of outbreaks and

infections caused by contaminated water and food consumption. Although most salmonellosis cases result in self-limited gastroenteritis and do not require antimicrobial therapy, severe infections can occur in patients of extreme ages, both neonates and elderly, and the immunocompromised. In Brazil, *Salmonella enterica* has been reported as the main bacterial agent associated with foodborne diseases. According to the *Secretaria de Vigilância em Saúde,* from 1999 to 2008, 1275 *Salmonella enterica* outbreaks occurred in Brazil, corresponding to 42.9% of total foodborne outbreaks (BRASIL, 2009). In Rio Grande do Sul state, 74 of the 99 total foodborne outbreaks reported in the year 2000 were caused by *Salmonella enterica* (NADVORNY; FIGUEIREIDO; SHIMIDT, 2004).

Resistances to tetracyclines, aminoglycosides and sulfonamides have been frequently described (FONSECA et al., 2006; PEIRANO et al., 2006; MICHAEL; CARDOSO; SCHWARZ, 2008; VAZ et al., 2010; RIBEIRO et al., 2011); however, in contrast to other *Enterobacteriaceae*, such as *Escherichia coli* and *Klebsiella pneumoniae*, ESBL-producing Salmonella enterica reports are still rare in Brazil. In 2004, Mulvey et al. reported a *Salmonella* Agona OXA-type beta-lactamase producer isolated in 1996 from a hospitalized patient. Peirano et al. (2006) conducted a study including *Salmonella* strains isolated from humans, animal feed, food-producing animals, foodstuffs and other sources regarding antimicrobial resistance, and they identified CTX-M-8 and CTX-M-9 type ESBL-producers without specifying the origin (human or animal). Recently, clonally unrelated *Salmonella* Typhimurium carrying CTX-M-2-encoding genes has been reported in isolates from the poultry production chains in Sao Paulo and Porto Alegre (FERNANDES et al., 2009), and Silva et al. (2013) confirmed that the $bla_{\text{CTX-M-2}}$ gene spread among the *S.* Schwarzengrund and *S.* Agona serotypes on poultry farms from the Southern region of Brazil. Thus, the dissemination of multiresistant phenotypes in animal production has been increasing among *Salmonella* strains.

Klebsiella pneumoniae

Klebsiella pneumoniae isolates carrying ESBL genes are endemic in Brazil. According to Rossi (2011), approximately 40-50% of K. *pneumoniae* isolates produce ESBL-type beta-lactamases. The constant isolation of ESBL-producing strains and the risk of treatment failure with cephalosporins have led to increased use of carbapenems; consequently, carbapenem-resistant phenotypes have been disseminated. The carbapenem resistance in *K. pneumoniae* strains can arise by the loss or modification of porins, which is associated with the production of metallo-beta-lactamases (MBLs) and non-metallo-carbapenemases (KPC, GES or OXA types); this type of resistance is associated with high mortality rates (GARCÍA-FERNÁNDEZ et al., 2012). *Klebsiella pneumoniae* carbapenemase (KPC) is an active-site serine enzyme that hydrolyzes carbapenems and extended-spectrum cephalosporins and is disseminated worldwide. The first KPC-producing *K. pneumoniae* strain was isolated in 2006 in Recife (Northeastern of Brazil) and was found to harbor $bla_{\text{CTX-M-2,}}$ $bla_{\text{TEM-1}}$ and $bla_{\text{SHV-11}}$ additional beta lactamase-encoding genes (ROSSI, 2011). KPC enzymes enable resistance to cephalosporins and carbapenems, are endemic in Brazilian ICUs and represent a serious challenge regarding bacterial infections (ANDRADE, 2011). Infections due to KPC producers are usually treated with colistin and/or tigecycline. However, tigecycline use is not recommended for bloodstream infections.

Escherichia coli

TEM- and SHV-type beta-lactamases are endemic in developed countries, but in South America, including Brazil, CTX-M-type is the prevalent ESBL. The first report of the CTX-M group occurred a *Proteus mirabilis* strain with a cephalosporin-resistant phenotype isolated from a patient in 2000 (BONNET et al., 2000). Later, in 2007, the first community-origin *Escherichia*

coli isolate that produced CTX-M-2 was reported (MINARINI et al., 2007). In the same year, a European study identified the blaCTX-M-2 gene in E. coli isolated from poultry imported from Brazilian farms (WARREN et al., 2008). According to literature reports, CTX-M-2 group bacteria are endemic in Brazil among *Enterobacteriaceae* isolates and have been described in many states (São Paulo, Rio de Janeiro, Minas Gerais, Santa Catarina, Rio Grande do Sul) (SILVA; LINCOPAN, 2012). Thus, CTX-M-2-producing *E. coli* have been intensively reported in Brazil, in hospital settings and from community and animal origins, including the poultry and swine production cycles (WARREN et al., 2008; SILVA et al., 2011) Recently, the CTX-M-15 enzyme has gained importance as an ESBL of major epidemiological importance worldwide, particularly due to its acquisition by a virulent strain belonging to the Multilocus Sequence Typing (MLST) group ST131 (COQUE et al., 2008; COELHO et al., 2011; HAWKEY; JONES, 2013). The CTX-M-15 enzyme was recently described in Brazilian hospitals in *E. coli* and *K. pneumoniae* strains (CERGOLE-NOVELLA et al., 2010; TOLLENTINO et al., 2011). Carbapenem resistance in Escherichia coli isolates is rare, but KPC-2-producing isolates have been described in hospital settings in Brazil (D'ALINCOURT CARVALHO-ASSEF et al., 2010; ALMEIDA et al., 2012).

Some ESBL strains also present resistance to fluoroquinolones and trimethoprim-sulfamethoxazole. The emergence of fluoroquinolone-resistant extraintestinal pathogenic *E. coli* (ExPEC) has been limiting the utility of fluoroquinolones for treating human patients with urinary tract infections (UTIs), and delays in appropriate UTI therapy increase morbidity and mortality from ExPEC. In veterinary medicine, enrofloxacin use can select resistant phenotypes (PITOUT, 2012; NORDSTROM; LIU; PRICE, 2013).

Non-fermentative bacteria

Among the non-fermentative Gram-negative bacteria, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are frequently associated with nosocomial infections. According to a Sentry study, almost 30% of all lower respiratory tract infections are caused by *Pseudomonas aeruginosa* (SADER et al., 2003). Moreover, this bacterium is capable of causing sepsis and is common in burn and diabetic patients. The most prevalent beta-lactamase produced by *Pseudomonas aeruginosa* in Brazil is SPM-1, which was first described in Sao Paulo and is disseminated in many Brazilian regions. Other metallo-lactamases have been reported, such as VIM and IMP-type MBL (ROSSI, 2011).

Similarly, *Acinetobacter baumannii* complex isolates have emerged as important nosocomial pathogens and cause ventilator-associated pneumonia, bacteremia and UTIs (ROSSI, 2011). The bacterial complex has been associated with diverse outbreaks in ICUs. Most carbapenem-resistant phenotype outbreaks are caused by OXA-23 producers. More recently, OXA-143, a novel beta-lactamase capable of hydrolyzing carbapenems, has been identified in Brazilian hospitals (ANTONIO et al., 2011).

Therapeutic options

Polymyxins (colistin)

Discovered in the 1940's, polymyxins are cationic polypeptides with a high affinity for the outer membrane, which destabilizes LPS and results in outer membrane disruption. Moreover, Gram-negative bacteria may become more susceptible to hydrophobic antibiotics followed by polymyxin exposure (ZAVASKI; GOLDANI; NATION, 2007; YAHAV et al., 2012). The clinical use of the only polymyxins (polymyxin B and colistin) available for this treatment was discarded due to reports on nephrotoxicity and neurotoxicity in the 1970s, and polymyxins were replaced by other antibiotics (BERGEN et al., 2012). Polymyxins are not active against Gram-positive bacteria, but they are effective against a variety of Gram-negative bacilli,

including most relevant *Enterobacteriaceae* and non-fermentative species. Recently, due to the emergence of multiresistant pathogens, the optimal treatment remaining undefined and high treatment failure rates, polymyxins have been reintroduced into clinical use with the aim of treating severe "superbug" infections, particularly carbapenemases-producing *Pseudomonas aeruginosa, Acinetobacter baumannii* and KPC-producing *Klebsiella pneumoniae* (ZAVASKI, GOLDANI, NATION, 2007; LANDMAN et al., 2008; YAHAV et al., 2012). Polymyxin administration combined with imipenem, tigecycline or fluoroquinolone results in lower rates of treatment failure than monotherapy (ZAVASKI, GOLDANI, NATION, 2007; LEE; BURGESS, 2012), though resistant pathogens have emerged (CAI et al., 2012).

There are two commercial forms of colistin available, which differ in their fatty acid residues: the colistin methanesulfonate, which is less toxic and recommended for parenteral use; and colistin sulfate, which is used only for topical therapy (MORALES et al., 2012). In veterinary medicine, colistin sulfate is often used in oral preparations because it displays good activity against *Escherichia coli* and *Salmonella* spp. and presents poor absorption after oral administration and low rates of resistance. Considering these pathogens, acquired resistance to polymyxins has been attributed to the substitution of phosphate groups in membrane lipopolysaccharides. In Brazil, *Escherichia coli* and *Salmonella* spp. exhibiting high minimal inhibitory concentrations (MICs) (32 and 8 μg/ml, respectively) to colistin have been reported among strains isolated from swine (MORALES et al., 2012).

Gram-positive bacteria

Enterococcus

Enterococci are natural inhabitants of the gastrointestinal microbiota of animals and may be released into the environment by fecal material. They have been detected in soil, water, plants and wild animals (HAMMERUM, 2012). In humans, *Enterococcus faecalis* and *E. faecium* can cause urinary tract infections, sepsis, wound infections and endocarditis (KWON et al., 2012). More recently, Enterococci have emerged as important nosocomial pathogens. The isolation from vulnerable patients in ICUs, renal and oncology units, often associated with intravascular catheters, has increased (BARIE, 2012). Enterococci infection treatment may be difficult because these bacteria are intrinsically resistant to a number of first-line antimicrobials, such as beta-lactams and aminoglycosides (HOLLENBECK; RICE, 2012; KWON et al., 2012). Moreover, Enterococci can acquire genetic determinants of resistance to other antimicrobials, such as quinolones, macrolides, tetracyclines, streptogramins and glycopeptides (CHA et al., 2012; BRAGA; POMBA; LOPES, 2013). In this context, the emergence of vancomycin-resistant enterococci (VRE) is a challenge during nosocomial infections because newer antibiotics such as linezolid, daptomycin and tigecycline have good in vitro activity against enterococcal isolates; however, their clinical use is limited, and resistant phenotypes have emerged (BARIE, 2012; BRAGA; POMBA; LOPES, 2013).

The intensive use of avoparcin has been associated with high vancomycin resistance rates among enterococcal strains (PHILLIPS et al., 2004; MARSHALL; LEVY, 2012). Several studies from countries around the world have shown that vancomycin-resistant *E. faecium* persisted in animals for an extended time after avoparcin was banned. The most frequent determinants of resistance to vancomycin are the *vanA* and *vanB* genes. In Brazil, VRE were first reported in 1996. The resistance alleles are located at transposon Tn1546 and have been currently identified in VRE strains (PALAZZO et al., 2011).

The global spread of a genetic lineage of *E. faecium* inserted in clonal complex 17 (CC17) has contributed to change the epidemiology of enterococcal infections. This lineage is characterized by resistance to ampicillin and quinolone and harbors some virulence genes. In Brazil, outbreaks caused by strains belonging to CC17

are sporadic, and the MLST type ST114, which not is part of this clonal complex, is prevalent among all STs described. However, VREs belonging to ST50, ST115, ST97, ST281 and, more recently, ST412, ST448 and ST478, all of which belong to CC17, have been reported in Brazilian hospitals, displaying high MICs to vancomycin (>256 μg/ml) (PALAZZO et al., 2011; SILVA et al., 2012).

As for animal origin isolates, *Enterococcus faecalis* isolated from chicken meat has shown resistance to tetracycline, erythromycin and streptomycin (FRACALANZZA et al., 2007). The reported prevalence of VRE in pigs and pig environments is highly variable around the world; thus far, resistance to vancomycin, teicoplanin or linezolid among *Enterococcus faecium* and *Enterococcus faecalis* isolated from animal sources in Brazil has not been reported. It is important to note that the Brazilian government has not permitted avoparcin use as a growth promoter in animal production since 1998.

Staphylococcus

Staphylococcus spp. are ubiquitous environmental organisms that colonize the skin of humans and animals. These organisms cause both local and systemic invasive infection. Common infections involve skin, soft tissue, mammary glands or lymph nodes, whereas systemic infections cause dissemination to joints, bones, kidneys, liver, muscles, lungs and heart valves (JACKSON; NEWLAND, 2011).

The emergence of resistant *Staphylococcus* occurred quickly after the introduction of the therapeutic use of penicillin G, with rates of 30% in the early 1950s, exceeding 80% resistance in US hospitals in the late 1950s. The production of plasmid-encoded penicillinases has spread the resistance, which has become common mainly among isolates of *S. aureus*. Currently, the global resistance rate of community-acquired coagulase-positive and coagulase-negative *Staphylococcus* spp. exceeds 70% for penicillin G (benzylpenicillin). Resistance rates are also high for penicillin V, ampicillin, amoxicillin and carbenicillin. Infections are currently being combated using anti-staphylococcal penicillins, such as methicillin and oxacillin, and first- and second-generation cephalosporins (JACKSON; NEWLAND, 2011).

In Brazil, more than 70% of the *S. aureus* and *S. epidermidis* strains isolated from the community or the hospital environment are resistant to penicillin, ampicillin and amoxicillin. The frequencies of strains resistant to methicillin (MRSA) and oxacillin (ORSA) are quite variable but can vary between 30 and 100% in nosocomial infections. However, the strains in the extra-hospital environment often have sensitivity to oxacillin (above 80%), allowing for the possible use of this antibiotic in community-acquired infections. Methicillin resistance in the extra-hospital environment is usually related to the patient's hospitalization history and previous use of this drug in a hospital setting (TAVARES et al., 2000).

Generally, staphylococci are susceptible to glycopeptides, but the emergence of MRSA and/or ORSA strains resistant to vancomycin and teicoplanin must be closely monitored, especially in Japan and the United States, where encountering these strains has become frequent due to selection pressure exerted by the use of antibiotics to combat hospital infections (TAVARES et al., 2000; GARCIA-ALVAREZ et al., 2012).

Perspectives

The dissemination of resistant phenotypes is a great concern in human and veterinary medicine because it restricts therapeutic options when treating multiresistant strains, the so-called "superbugs." Given the nature of the Brazilian economy, the ban of antimicrobial use in food-animal production is unreasonable. Rather, multidisciplinary studies aimed at finding the most adequate strategies for antibiotics use in animal and human medicine are necessary. Specifically in animal production, the controlled use of antimicrobials may lead to export advantages for demanding consumer markets, such European

countries, which ban the use of growth promoters. Broad-spectrum antimicrobials favor resistance development because they disrupt competing susceptible microflora, and narrow-spectrum drugs are more appropriate. In hospital settings, antimicrobial rotation, guided by resistance surveillance systems, has yielded good results (BROWN; NATHWANI, 2005). Moreover, combined therapy with synergic drugs may be an alternative when dealing with multiresistant isolates. Sanitary measures to avoid bacterial dissemination and to prevent infection are also required, as is the education of veterinarians, farmers, food producers and consumers about the rationale for the prudent use of antimicrobials, disease prevention and prevention of zoonotic infections in humans and animals (LANDERS et al., 2012).

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