CLINICAL MICROBIOLOGY REVIEWS, Apr. 2003, p. 175–188 Vol. 16, No. 2
0893-8512/03/$08.00+0 DOI: 10.1128/CMR.16.2.175–188.2003

Antimicrobial Growth Promoters Used in Animal Feed: Effects of Less Well Known Antibiotics on Gram-Positive Bacteria

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INTRODUCTION

Shortly after the introduction of the therapeutic use of antibiotics, the growth-promoting effect of these products in chickens was discovered by feeding fermentation offal from the chlortetracycline production of *Streptomyces aureofaciens* (122). Several antibiotics have been in use as growth promoters of farm animals ever since. The introduction of these agents coincided with intensive animal rearing. These products improved feed conversion and animal growth and reduced morbidity and mortality due to clinical and subclinical diseases. The average growth improvement was estimated to be between 4 and 8%, and feed utilization was improved by 2 to 5% (90).

The mechanisms of growth promotion are still not exactly known. Experiments with germ-free chickens have seemed to indicate that the action of the growth promoters is mediated by

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TABLE 1. Growth-promoting antibiotics allowed for use in the EC, both past and present

Antibiotic	Banned since:	Antibiotic group	Related therapeutics	Mechanism of action
Bambermycin		Glycolipid		Inhibition of cell wall synthesis
Bacitracin	1999	Cyclic peptide	Bacitracin	Inhibition of cell wall synthesis
Monensin		Ionophore		Disintegration of cell membrane
Salinomycin		Ionophore		Disintegration of cell membrane
Virginiamycin	1999	Streptogramin	Quinupristin/dalfopristin	Inhibition of protein synthesis
Tylosin	1999	Macrolide	Erythromycin and others	Inhibition of protein synthesis
Spiramycin	1999	Macrolide	Erythromycin and others	Inhibition of protein synthesis
Avilamycin		Orthosomycin	Everninomycin	Inhibition of protein synthesis
Avoparcin	1997	Glycopeptide	Vancomycin, teicoplanin	Inhibition of cell wall synthesis
Ardacin	1997	Glycopeptide	Vancomycin, teicoplanin	Inhibition of cell wall synthesis
Efrotomycin		Elfamycin		Inhibition of protein synthesis
Olaquindox	1999	Quinoxaline		Inhibition of DNA synthesis
Carbadox	1999	Quinoxaline		Inhibition of DNA synthesis

their antibacterial effect (91). Four hypotheses have been proposed to explain their action: (i) nutrients may be protected against bacterial destruction; (ii) absorption of nutrients may improve because of a thinning of the small intestinal barrier; (iii) the antibiotics may decrease the production of toxins by intestinal bacteria; and (iv) there may be a reduction in the incidence of subclinical intestinal infections (91).

The use of antibiotics as feed additives has been a hallmark of modern animal husbandry, but this widespread practice is not without criticism. In the early years, all antibiotics were allowed for use, although some did not enhance growth and many were too expensive. The first discussions on the use of antibiotics as growth promoters began in the late 1960s and resulted in the "Swann Report," which was issued in the United Kingdom (20). Concerns were raised that the use of antibiotics as therapeutics and for growth promotion could lead to a problem of increasing resistance in bacteria of human and animal origin, particularly regarding resistance in gram-negative bacteria (*Salmonella* spp. and *Escherichia coli*). In the United Kingdom, the Swann Report proposed that antibiotic use for growth promotion should be restricted to antibiotics that (i) make a significant economic difference in the raising of livestock, (ii) have little or no application as therapeutic agents in humans or animals, and (iii) do not impair the efficacy of a prescribed therapeutic drug through the development of resistant strains. It was suggested that antibiotic residues in meat would not impair human health. Specifically, it was recommended that the use of penicillins, tetracyclines, tylosin, and sulfonamides as growth promoters be discontinued. This report also formed the basis for the European legislation in Directive 70/524, in which a list was published of allowable additives with their maximum and minimum dosages, withdrawal period from slaughter, and animal species in which the product may be used. To be included in the list, additives should meet the following conditions: (i) they must have a favorable effect on livestock production; (ii) they should not endanger animal or human health; (iii) their nature and level must be controllable; (iv) the levels included should not reach those intended for treating or preventing animal disease; and (v) they should not be in use for medical or veterinary purposes. This directive was later implemented in the national legislation of the various European member states. The list of antibacterial feed additives that have been permitted in the European Community (EC) is shown in Table 1. This legislation has been amended on several occasions, and in non-EC member countries other forms of legislation are in force, while in some other countries therapeutically used antibiotics such as tetracyclines and penicillins are still allowed. In 1986, Sweden, now a member of the EC, decided to ban all antibiotics for growth promotion, but ionophore antibiotics are still used as coccidiostats. In 1993, an initial report on the isolation of vancomycin (glycopeptide)-resistant enterococci (GRE) from animals appeared (30). Avoparcin, an antibiotic used only for growth promotion in animals, shows full cross-resistance with the human hospital drug vancomycin and partial cross-resistance with teicoplanin. All these antibiotics are glycopeptides. This is causing great concern because, following the first description of human infections with GRE in 1986 (214), these infections have become a serious problem in the hospital environment, especially in the United States (117). The occurrence of GRE in food animals was associated with the use of the glycopeptide antibiotic avoparcin in Europe (31, 43). Since 1997, this and several other antibiotic feed additives have been forbidden in EC member states (EC directive 97/6/EG and Commission regulation EC 2821/98) (Table 1). The discovery of GRE in animals and the growing resistance problem in gram-positive bacteria have also led to investigations of other antimicrobial growth promoters and related products, some of which are also under investigation or already in use for human therapy.

Many of the products reviewed here are not well known since they are not clinically available or not important in human therapy. Clinicians may be anxious that the use of antibacterials for animal growth promotion, largely unknown to them, is compromising their therapeutic means. The aim of this review is to summarize the data available on the lesser known antibiotics, giving special attention to their spectrum of antibacterial activity and their effects on the intestinal flora, resistance mechanisms, and prevalence of resistance. When available, data on pharmacokinetics and toxicity are presented. Since no resistance breakpoints are available for most of these antibiotics, the definition of susceptibility and resistance of bacteria to growth-promoting antibiotics is discussed first.

DIFFERENTIATING SUSCEPTIBILITY AND RESISTANCE TO GROWTH-PROMOTING ANTIBIOTICS

Differentiation between susceptibility and resistance of bacteria to antibiotics is commonly based on microbiological, pharmacological, and clinical criteria. The second criterion

implies that bacteria are susceptible to a given antibiotic when its attainable levels in blood can be expected to be higher than the MIC of the antibiotic for the bacterium. Since pharmacological data are lacking for most growth promoters and many of these drugs are not absorbed from the intestines and thus have no systemic effects, this criterion is not applicable. Clinical criteria cannot be applied either, since these antibiotics are generally not used therapeutically. Therefore, only the microbiological criterion is described and discussed here.

To determine susceptibility to a given antibiotic in this way, the distribution of MICs for strains belonging to a given species is analyzed, and when a monomodal distribution is evident, no acquired resistance is present. MICs in this monomodal Gaussian distribution can be more or less broadly distributed, in both lower and higher concentration ranges. Acquired resistance by this criterion is detected by loss of the normal monomodal distribution and is evident by tailing of the distribution, or by the appearance of a second group of MICs (bimodal distribution) or more extra distributions toward the higher concentration range. This criterion is used for bacterial species, since all strains of a given species react in a uniform way to an antibiotic, except when they have acquired resistance. The distribution ranges of susceptible and resistant strains may not always be easy to analyze since they may overlap. In these cases, the only way to determine susceptibility is to search for acquired resistance mechanisms or resistance-determining genes in these strains. A prerequisite for this is that resistance mechanisms and the genes encoding them should be known, which is not always the case. The difficulties encountered with respect to the differentiation between resistance and susceptibility as defined here are discussed in relation to each antibiotic reviewed.

There is no doubt that describing resistance to drugs other than those in clinical use is problematic. There are currently no standardized method and universally accepted interpretative criteria being applied to describe the antibiotic susceptibilities of isolates from the greater environment. The procedure to solve this problem described here is a proposal, not a consensus opinion. This is a significant question in need of a solution.

Bambermycin

The product. Bambermycin (synonyms: moenomycin, flavophospholipol, and flavomycin) is a glycolipid antibiotic produced by *Streptomyces* species including *S. bambergiensis*, *S. ghanaensis*, *S. geysirensis*, and *S. ederensis* (114, 115, 229). The product is manufactured as a complex of very similar components, of which moenomycin A, a phosphorus-containing glycolipid, is the main component (114, 209). Bambermycin is used only as a growth-promoting antibacterial in animal feeds.

Mechanism of action. Bambermycin inhibits peptidoglycan synthesis by inhibiting peptidoglycan polymerases through impairment of the transglycolase activities of penicillin-binding proteins (PBPs) (115, 220, 221, 225). This inhibition results in a specific block of the formation of the murein polysaccharide strands (127). The formation of the linear glycan strands of peptidoglycan is inhibited when the membrane intermediate *N*-acetylglucosaminyl-*N*-acetylmuramyl-(pentapeptide)-pyrophosphoryl-undecaprenol is used as a substrate (221). These PBPs are classified and designated by their differences in molecular masses. PBP 1b, which is the polymerase responsible for this reaction in *Escherichia coli*, is inhibited by bambermycin. PBP 1a and PBP 3 of *E. coli* are also sensitive to the action of bambermycin (222). Recently, PBP 1c, which possesses transglycolase activity (190), was shown to be inhibited by bambermycin (225). In *Streptococcus pneumoniae*, PBP 2a is the target of bambermycin (167). The PBPs inhibited by bambermycin in other bacteria have not yet been determined. Differences in PBPs between *Enterococcus* species (244) might explain their differing susceptibility to bambermycin (40). PBPs are of cardinal importance in the action and in the resistance to β-lactam antibiotics, but since these drugs act on different PBPs, there is no cross-resistance between β-lactams and bambermycin (167).

Spectrum of activity. Bambermycin is active primarily against gram-positive organisms; to some extent, it also inhibits certain gram-negative bacteria, such as *Pasteurella* and *Brucella* (115). Its spectrum of activity covering staphylococci and streptococci is similar to that of penicillin G and in some respects to that of the macrolide antibiotics (139). Members of the *Enterobacteriaceae* are only slightly susceptible. MICs obtained for different bacteria are strongly medium dependent (39). The addition of blood, proteins, and fatty substances and variations in pH and inoculum size affect the in vitro susceptibility of gram-positive bacteria (39, 40, 230), thereby complicating the interpretation of susceptibility test results (40). *Clostridium perfringens* and many other clostridial species, bacteria of the *Enterococcus gallinarum* group (*E. gallinarum* and *E. casseliflavus*), and most species from the *E. faecium* group (*E. faecium*, *E. mundtii*, and *E. hirae*) show natural resistance to bambermycin (39, 40, 42, 46, 72, 79, 80, 81).

Prevalence of resistance. Few publications have dealt with the susceptibility testing of bacteria to bambermycin. The only data available are the MICs for enterococci, lactobacilli, *Staphylococcus* species, and clostridia (2, 42, 46, 71, 72, 80, 81, 112, 154). Acquired resistance has not yet been reported with certainty. Although most *E. faecium* strains were scored resistant in Danish and Dutch studies (2, 154), this resistance was probably natural or intrinsic. The few susceptible strains detected in these studies might have been wrongly identified, since phenotypic identification errors are relatively frequent with species other than *E. faecalis* (29). The application of arbitrary breakpoints (resistant when MIC is $\geq$16 μg/ml) and the fact that MICs of bambermycin are extremely dependent on the composition of the medium might also influence the resistance percentages reported. Few human bacterial strains have been tested against bambermycin. Methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* strains isolated from humans were both uniformly susceptible to bambermycin (128). In a large collection of *S. aureus* strains isolated from chickens and abattoir workers, no resistance to bambermycin was detected (112). Cross-resistance to other antimicrobials has not been reported.

Pharmacokinetics and toxicity. Bambermycin is absorbed poorly after oral administration in several animal species. A slight absorption was detected only when high doses were administered (32, 187, 230). When administered parenterally, bambermycin remains unchanged, being slowly excreted in the urine (187). In chickens, oral doses of 20 ppm did not produce residues in tissues or organs (160). Residues of bambermycin

could not be detected when high doses of the feed additive were administered (32, 187). No data are available on the active concentrations of the antibiotic in the intestines of animals.

Effects on intestinal flora. Bambermycin reduces the number of *C. perfringens* organisms in the intestines, a fact which contrasts with the relative insensitivity of this species to this agent in vitro (35, 38, 207). No influence was noted on the counts of enterococci, coliforms, and lactobacilli in the feces of broilers (38). In one study, the number of *E. coli* organisms in swine feces was decreased while the total numbers of enterococci remained the same. The number of *E. faecalis* strains, however, was dramatically decreased (219). Bambermycin in the feed did not affect intestinal *Salmonella* colonization in experimentally infected chickens (97, 116). This was in contrast to a recent study that reported reduced shedding of *Salmonella* in chickens (35) and other studies of calves and swine (67, 199). No effect has been seen on the incidence or degree of *Campylobacter* shedding (35).

Using germ-free mice inoculated with pig flora, it was demonstrated that bambermycin administered at 5 ppm diminished the numbers of antibiotic-resistant coliforms (65). Two in vivo studies, one with pigs receiving a feed containing bambermycin and the other with calves, demonstrated a decrease in the number of resistant *E. coli* organisms in the intestines (69, 219). Similar findings were noted with *Salmonella*-infected calves and swine (67, 199), while a decrease in the number of resistant *Salmonella enterica* serotype Typhimurium organisms in broilers could not be demonstrated (97).

In vitro, bambermycin inhibits the transfer of a wide variety of plasmids of different incompatibility groups containing a variety of different resistance determinants. An inhibitory effect was seen on the growth of *E. coli* containing these plasmids, although an increase of plasmid transfer occurred in a minority of strains (99, 139). A recent study described a significant inhibition by bambermycin of the transfer of the vancomycin resistance gene cluster- containing plasmid in *E. faecium* (182).

Streptogramins

The products. The streptogramins always consist of an A component and a B component which act synergistically. They belong to the MLS (macrolide-lincosamide-streptogramin) group of antibiotics. Both the streptogramin A and streptogramin B components are macrocyclic lactone peptolides, as are the macrolides. The lincosamides are devoid of a lactone ring (61, 204). The group A components are polyunsaturated cyclic peptolides, and the group B compounds are cyclic hexadepsipeptides (61). Until now, only three streptogramins have been marketed either as therapeutics or for growth promotion: virginiamycin, pristinamycin, and quinupristin/dalfopristin. Virginiamycin has been used both in topical preparations for human and veterinary medicine and as a growth promoter in animal feed. It is produced by *Streptomyces virginiae* as a natural mixture of two chemically different components, virginiamycin M (a streptogramin A component) and virginiamycin S (a streptogramin B component), that work synergistically. Pristinamycin, produced by *S. pristinaspiralis* (63), has been used orally and topically in human medicine in a limited number of countries (143), most often in France (76). Quinupristin (streptogramin B component)/dalfopristin (streptogramin A component) was introduced into human medicine only very recently and is derived from the original pristinamycins (92). This compound is useful in treating infections due to vancomycin-resistant *E. faecium* and methicillin-resistant *S. aureus* (50, 145, 158, 159, 169, 185, 186, 211). It was approved in the United States in 1999 for the treatment of vancomycin-resistant *E. faecium* bacteremias, as well as of *S. aureus* and *Streptococcus pyogenes* skin and soft tissue infections.

Activity. The combination of the streptogramin A and B components acts by binding to the bacterial 23S rRNA of the 50S ribosomal subunit to form a stable dalfopristin (virginiamycin M) (A component)-ribosome-quinupristin (virginiamycin S) (B component) complex, which irreversibly inhibits protein synthesis, resulting in bacterial cell death (62). Individually, the components cause only bacteriostasis (62). The streptogramin A component inhibits the elongation phase in the ribosomal assemblage of the proteins (60). It interferes with the function of peptidyltransferase and also triggers a conformational change in the ribosome, which increases the affinity for the streptogramin B components (36). The streptogramin B component prevents the extension of polypeptides (peptide chain elongation) and induces the detachment of incomplete protein chains (57). The binding site of the B component overlaps with the binding site of the macrolide and lincosamide antibiotics (63, 235). The streptogramin antibiotics have a narrow spectrum of activity, including gram-positive bacteria (mainly staphylococci, streptococci, and enterococci) and some gram-negative cocci (101, 142). Not all enterococci have a similar susceptibility to streptogramins: *E. faecalis* is less susceptible than *E. faecium* (37, 64). Most gram-negative bacteria are naturally resistant, due to the impermeability of their cell wall (63). Quinupristin/dalfopristin is also active against *Toxoplasma gondii* (125).

Resistance genes and mechanisms. Resistance to streptogramins can be mediated by target site alteration, inactivation of the antibiotic, or active efflux of the antibiotic (183). The nomenclature of the resistance genes has recently been adapted (183). Target site alteration is mediated by the *erm* genes, affecting the binding of the B component of the streptogramins to the bacterial ribosome (140). The methylase encoded by these genes N^6-demethylates a specific adenine residue at position 2058 (*E. coli* numbering) in 23S RNA (135). The combination of the A and B components, however, remains active, although this activity may be reduced in certain strains (53, 142). Cross-resistance with the macrolides and lincosamides (MLS_b phenotype of resistance expressed constitutively or inducibly) due to the overlapping binding sites of these antibiotics (157) is one characteristic of such combinations. Constitutively expressed MLS_b resistance is often due to deletions or insertions in the regulatory region of the *erm* genes (223, 236, 239).

A second resistance mechanism is mediated by inactivation of the antibiotic. In enterococci, this resistance mechanism can be mediated by an acetyltransferase that inactivates the A component of the streptogramin complex and is encoded by the *vat(D)* (formerly *satA*) gene (180). Recently, a new gene, *vat(E)* (formerly *satG*), that also encodes an acetyltransferase has been reported (240). Different *vat(E)* alleles have been

TABLE 2. Streptogramin resistance in enterococci of human origin

Species	Yr	Source	Resistance (%)	Reference
Not specified	1997	Human	30[a]	217
E. faecium	1999	Human	3	19
E. faecium	1999	Human	8	189
E. faecium	1999	Human	0	188
E. faecalis	1999	Human	75	189
E. faecalis	1999	Human	26–43	19

[a] Selective isolation procedure with MLS antibiotics in the media.

described and have been numbered from E-1 to E-3 (198). In staphylococci, resistance by inactivation of the A component can be mediated by an acetyltransferase: the VatA (formerly Vat), VatB, or VatC protein, encoded by the *vat(A)* (formerly *vat*) (11), *vat(B)* (12), or *vat(C)* (13) gene, respectively. The *vgb(A)* (formerly *vgb*) gene (16), encoding a hydrolase (lactonase) inactivating the B compound, is found in staphylococci and enterococci (119, 211). Inactivation of streptogramin antibiotics has also been described in lactobacilli (77), recently, the *vgb(B)* gene has been demonstrated in staphylococci (13).

A third mechanism of resistance involves the active efflux of streptogramins and is encoded by the *vga(A)* (formerly *vga*) gene (15) or the *vga(B)* gene (14) in staphylococci. The *vga(A)* gene encodes a putative ATP binding protein (11). A variant of this gene has been described recently (111). Another gene, *mrs(A)* [referring to both *mrs(A)* and *mrs(B)*], is found solely in staphylococci and encodes active transport of the streptogramin B component. The latter is inducible by erythromycin and also confers resistance to 14- and 15-membered macrolides (184). This gene is a putative member of the ATP binding cassette transporter superfamily (141, 183, 184, 247). Only recently, an *msr(A)*-like gene, designated *mrs(C)*, has been described and was shown to encode an efflux pump in enterococci (173).

Prevalence of resistance. Because there are not yet any clearly established interpretative virginiamycin susceptibility breakpoints for enterococcal strains, acquired resistance is difficult to assess by phenotypic means (41). In a study (197) in which a trimodal distribution of MICs for *E. faecium* strains was found, resistance genes were present only in the strains for which the MICs were highest. Strains with intermediate resistance to quinupristin/dalfopristin had drug MICs of 4 to 16 μg/ml. It is uncertain whether this is to be regarded as acquired resistance. Care should been taken in the interpretation of results obtained by different investigators (Tables 2 and 3), since different breakpoints might have been used. The search for resistance genes is a more reliable method for detecting streptogramin resistance (41).

In 1962, streptogramin resistance was described for the first time in staphylococci (181). No human streptogramin-resistant staphylococci were found in any countries except France and Algeria until 1983 (161). In these countries, resistance rates among human isolates of staphylococci remained low at ≤ 5% (84, 85, 143). Similar results were obtained with human isolates of *E. faecium* (19, 188, 189) (Table 2). However, the high resistance percentages published for *E. faecalis* (19, 188) should be interpreted cautiously since this species is only marginally susceptible to streptogramins. In addition, selective isolation procedures with MLS antibiotics incorporated in the media were used in some studies (217, 218), which explains in part the discrepancies seen between resistance percentages reported by different investigators (44). Among animal enterococci, resistance rates were especially high in strains isolated from poultry and pigs (Table 3). This high prevalence, however, was not reflected in strains isolated from pork. In staphylococci and lactobacilli, rates of resistance to streptogramins were generally low except among strains infecting pigs (2, 41, 42, 72, 73, 78, 79, 112). Resistance in *Clostridium perfringens* was low (72, 79, 231). Selection for streptogramin resistance

TABLE 3. Streptogramin resistance in enterococci of animal origin

Species	Yr	Source	Country	Resistance (%)	Reference
E. faecium	1982	Poultry	Belgium	0	80
Not specified	1997	Pigs	The Netherlands	75[a]	217
Not specified	1998	Beef and pork	Germany	3	126
E. faecium	1998	Pigs	Denmark	47	2
E. faecium	1998	Poultry	Denmark	43	2
E. faecium	1998	Cattle	Denmark	8	2
E. faecium	1999	Animals and meat	Belgium	26	41
E. faecium	1998	Pigs	Denmark	99	2
E. faecium	1997	Pigs	Sweden	45[a]	218
E. faecium	1995–1996	Pigs	The Netherlands	72[a]	218
E. faecium	1998	Pigs	The Netherlands	42/64[b]	154
E. faecium	1998	Poultry	The Netherlands	64/72[b]	154
E. faecium	1998	Calves	The Netherlands	46/54[b]	154
E. faecium	1998	Chicken meat	Belgium	58/58[b]	41
E. faecium	1998	Pork	Belgium	0/0[b]	42
E. faecium	1998	Cheese	Belgium	0/0[b]	42
E. faecium	1998–1999	Broilers	Belgium	74	46
E. faecium	1998–1999	Pigs	Belgium	9	46
E. faecium	1998–1999	Ruminants	Belgium	0	46
E. faecium	1998–1999	Avian pets	Belgium	0	46
E. faecium	1998–1999	Mammalian pets	Belgium	3	46

[a] Selective isolation with MLS antibiotics in the media.
[b] Left percentage, virginiamycin; right percentage, quinupristin/dalfopristin

was found in the *E. faecalis* and *E. faecium* intestinal flora of chickens when they were fed a diet supplemented with virginiamycin (123). In turkeys, virginiamycin-resistant *E. faecium* strains were isolated increasingly during the administration of subtherapeutical levels of the antibiotic, with 100% of isolates becoming resistant by the end of the rearing period (238).

An investigation of Dutch streptogramin-resistant *E. faecium* strains revealed a high prevalence of the *vat(D)* (formerly *satA*) gene among isolates from humans (51%), while in animal strains only 19% of these strains were *vat(D)* positive. In many resistant strains, no known resistance genes could be detected (119). In a Danish study, 25% of the strains from pigs and poultry contained the *vat(D)* gene (107). Further investigations of the Dutch animal and human strains demonstrated the presence of *vat(E)* in *vat(D)*-negative strains (110). The *vat(A)* (formerly *vat*) and *vgb(A)* (formerly *vgb*) genes were found combined with the *vat(E)* gene in only one human strain (110, 119). Another study demonstrated only the *vat(E)* gene among human *E. faecium* strains, while *vat(D)* and *vat(E)* were equally distributed in animal strains. In this investigation, no resistance genes could be detected in many resistant strains (197).

While the *vat(D)* gene was detected in about 10% of the Danish virginiamycin-resistant *E. faecium* strains from broilers and pigs, this gene was not detected in Finnish strains. Seventy-two percent of the Danish virginiamycin-resistant *E. faecium* strains from broilers carried the *vat(E)* gene, while all Finnish strains carried the *vat(E)* gene. In about 20% of the broiler strains and in the majority of the pig strains, no known resistance gene could be detected (6).

In *E. faecium* isolates of poultry origin, the *vat(E)* gene was frequently linked (in 74% of the strains) to the *erm(B)* gene (120). Only 2 strains were found to carry the *vat(B)* and *vat(B)* genes among 118 staphylococci of poultry origin (4). A large portion of human streptogramin-resistant staphylococcal strains contained multiple resistance genes: *vga(A), vat(A)*, and *vgb(A)*. Some strains had only the *vat(B)* gene, while in others no resistance gene could be detected (17, 143). The combination of several resistance genes has also been described by Lina et al. (144).

Pharmacokinetics. Orally administered virginiamycin is not absorbed from the guts of animals (175). Likewise, no residues of virginiamycin could be found in kidneys, livers, or muscles of chickens fed virginiamycin (160). Pristinamycin is not water soluble and therefore not applicable parenterally (36). Quinupristin/dalfopristin, a water-soluble derivative of pristinamycin, is administered only by injection (36, 175). A new streptogramin under development (RPR 106972) showed good oral absorption (36).

Effects on intestinal flora. The number of *C. perfringens* organisms in the intestines of chickens was reduced by the addition of 55 ppm of virginiamycin to feed (217). Virginiamycin reduces the mortality and severity of necrotic enteritis caused by *C. perfringens* (98). No effects on the shedding of *Salmonella* in chickens or swine were noted (7, 8, 195). However, in combination with a competitive exclusion flora (a preparation based on whole cecal contents of healthy chickens), virginiamycin was shown to protect chickens against an *S. enterica* serotype Typhimurium infection (116).

Avilamycin

The product. Avilamycin belongs to the oligosaccharide (orthosomycin) group of antibiotics and is used only for growth promotion (130). Until recently, another antibiotic of this group, everninomycin, was investigated for use in human medicine (163, 233, 245). However, the development of this antibiotic has been stopped. Avilamycin is produced by *Streptomyces viridochromogenes* (47, 153). It is a mixture of several major and minor components (153).

Activity. Avilamycin acts through binding with the 30S subunit of the ribosome and interferes with the polypeptide-synthesizing function by affecting the attachment of aminoacyl-tRNA to the ribosomes (245). Recent findings, however, suggest that the antibiotic also binds, or solely binds, to the 50S subunit (56, 152).

Avilamycin and everninomycin are active mainly against gram-positive bacteria (95, 121, 128, 163). However, few reports have dealt with the in vitro activity of these antibiotics. Recently, the effective action of everninomycin against *Borrelia* species and *Legionella* species was demonstrated (70, 83).

Resistance. Resistance is associated with mutations in the L16 50S subunit ribosomal protein in *S. pneumoniae* (9), *E. faecalis*, and *E. faecium* (5). Spontaneous mutants of susceptible *S. pneumoniae* isolates also showed mutations in their 23S ribosomal DNA; these mutations were located at two different stems of the peptidyltransferase region of domain V (10). In the antibiotic-producing bacterium *S. viridochromogenes*, resistance is mediated by different mechanisms: a putative ATP-binding cassette transporter system, which confers a low level of resistance, and two rRNA methyltransferases, one of which confers a low level of resistance and one of which confers a high level of resistance (237). Another resistance mechanism, mediated by a methyltransferase (EmtA), has been described recently in an *E. faecium* strain from an animal. The gene encoding this resistance (*emtA*) was located on a plasmid-borne transposable element (149).

Acquired resistance to avilamycin in *E. faecium* and *E. faecalis* strains from animal sources has been reported only recently (2, 41, 46). Resistance rates were generally low, with the exception of broiler strains in Denmark (1, 2). Only one human strain, a clinical isolate of *S. pneumoniae* isolated in South Africa during a clinical trial, was found to be resistant to everninomycin (9). Full cross-resistance of avilamycin with everninomycin has been demonstrated (1). Searches for acquired resistance have been performed on only a limited number of bacterial species (2, 41, 72, 231). Among human enterococcal strains, no resistance has been reported (189), and no resistance has been found in *C. perfringens* strains from various food-producing animal species (72, 231).

Pharmacokinetics. Avilamycin administered orally at 60 ppm is excreted almost exclusively in the feces, and only very small residues are found in the tissues of swine and rats (148). Everninomycin can be administered only by intravenous injection (163).

Effects on intestinal flora. Few authors have investigated the influence of avilamycin on the gut flora. The number of *C. perfringens* organisms in chicken intestines was reduced by adding 10 ppm of avilamycin to the feed (87). Avilamycin also prevents necrotic enteritis caused by *C. perfringens* in broilers

(224). In a semiquantitative PCR study, the amount of PCR product was reduced in ileal and colon DNA extracts when the feed was supplemented with 40 ppm of avilamycin; these results indicate a reduction in the number of *C. perfringens* in the ileum and colon (215). The addition of avilamycin to the feed did not favor the colonization of *Salmonella* serotype Kedougou in young chickens (113). At relatively high doses, avilamycin reduced stress-induced postweaning diarrhea in piglets (130).

Bacitracin

The product. Bacitracin, a polypeptide antibiotic produced by *Bacillus licheniformis*, is a mixture of several major components—the most important of which are A, B and C—and at least 13 other minor components. Bacitracin is more stable as a zinc salt (166) and is used both as a growth promoter and in some topical preparations in human and veterinary medicine. It has also been tested, with limited success, for its applicability in the elimination of vancomycin-resistant enterococci (21, 55, 102, 165, 234).

Activity. Bacitracin forms a complex with C_{55}-isoprenyl pyrophosphate, a carrier for the *N*-acetylmuramyl peptapeptide intermediates for the synthesis of the peptidoglycan. Dephosphorylation by the C_{55}-isoprenyl pyrophosphatase is inhibited, thereby not allowing for the recycling of the carrier and inhibiting the bacterial cell wall formation. Bacitracin may also interfere with additional cellular processes (172, 193, 202, 203).

Bacitracin is active mainly against gram-positive bacteria, although many differences exist among the bacterial species (166). Its antibacterial spectrum is similar to that of the antibiotics of the penicillin group (226).

Resistance mechanisms. Resistance mechanisms have been described among gram-negative bacteria, in the bacitracin-producing organism *B. licheniformis*, and only very recently in other gram-positive bacteria (49, 54, 171, 172). The *bacA* gene in *E. coli* was found to encode a protein that increases isoprenol kinase activity. It was suggested that the *bacA* gene, which resides on the bacterial chromosome, confers resistance by phosphorylation of undecaprenol, thereby increasing the level of the carrier C_{55}-isoprenyl phosphate (49). Genes homologous to the *bacA* gene have been found in *S. aureus* and *S. pneumoniae*. Allelic replacement mutants of these strains showed an increased susceptibility to bacitracin, indicating that the *bacA* gene product is involved in C_{55}-isoprenyl phosphate recycling (54). It is unclear whether these genes play a role in acquired bacitracin resistance since they seem to be naturally present in a wide variety of bacterial species, including bacitracin susceptible ones. These genes might be related to the natural susceptibility level of these bacteria to bacitracin. In *B. licheniformis*, resistance was encoded in the *bcr* region (171). The Bcr proteins are components of an ATP binding transporter system which exports unidirectional bacitracin (171). Recently, a new bacitracin resistance gene, $bcrC_{ec}$, encoding a homologue to the resistance gene in *B. licheniformis*, was described in *E. coli* (109).

Prevalence of resistance. Problems with breakpoints between susceptibility and resistance have been encountered (41) and cause difficulties in interpreting resistance percentages. Rates of resistance to bacitracin as high as 60% were reported in 1984 in *E. faecium* and *E. faecalis* from poultry (80, 81). More recently, only 3% of pig *E. faecalis* strains were found to be bacitracin resistant in Denmark (2), while in Belgium 16% of the strains from different animals and foods were resistant (41). In *E. faecium* isolates from pigs and poultry in Denmark (2), resistance rates were much higher (31 and 41%, respectively), but in Belgium they were similar to those of *E. faecalis* (41). Resistance rates among animal staphylococcal species are below 1% (2, 71, 112). While no resistance was found in *Lactobacillus* species from pigs, 10 and 24% of cattle and poultry strains, respectively, were resistant (78). In *Streptococcus suis*, bacitracin resistance was absent from 1968 to 1992. In 1992, 5.2% of the strains were resistant (3). In group L streptococci (*Streptococcus dysgalactiae*) from different animal species and in *Streptococcus porcinus* from pigs, no resistance to bacitracin could be detected (136, 194). Few animal *Clostridium* strains have been shown to be resistant (79, 79, 82). Bacitracin resistance in streptococci, enterococci, and staphylococci of human origin has been detected occasionally (89, 205) The resistance mechanisms in these gram-positive bacteria remain unknown to date.

Pharmacokinetics and toxicity. All bacitracins are nephrotoxic when administered parenterally. They are absorbed very little or not at all from the intestines, as demonstrated for rats, swine, and chickens (74, 94, 160). Because of this, no residues can be found in meat when the product is administered orally. Allergic reactions after absorption through skin lesions have been described occasionally in humans (166).

Effects on intestinal flora. Studies have demonstrated a decrease in the number of enterococci when bacitracin was included in the animal feed (27, 212). This decrease was due mainly to a decrease in the number of *E. faecalis* organisms (123). However, the number of *E. faecium* organisms increased compared to that in the control group during prolonged administration of the antibiotic (123). Necrotic enteritis caused by *C. perfringens* in chickens was prevented by the addition of bacitracin at doses of 55 to 110 ppm to the feed (174, 243). In addition, the number of *C. perfringens* organisms was decreased by the use of bacitracin (206). In a field trial, bacitracin appeared to reduce lesions of intestinal adenomatosis caused by *Lawsionia intracellularis* porcine in pigs (134). Bacitracin increases the colonization of *S. enterica* serotype Enteriditis in the ceca of chickens (150). Surprisingly, in combination with a competitive exclusion flora (cecal contents of healthy adult chickens or mixtures of bacteria cultured from ceca, sprayed over 1-day-old chickens to establish a stable intestinal flora), protection against *S. enterica* serotype Typhimurium infection was observed (116). On the other hand, colonization of serotype Infantis seemed to be inhibited by the administration of zinc bacitracin (164).

Ionophore Antibiotics

The products. Most ionophore antibiotics are produced by *Streptomyces* spp., although *Streptoverticillium*, *Nocardiopsis*, *Nocardia*, and *Actinomadura* spp. are also known to produce them (33). Along with the natural products of microorganisms, several chemically modified ionophores exist. They belong to a vast group of ionophores, only a subset of which are used as growth promoters or in the prevention of infections in animals.

This subset can be divided into three major classes on the basis of their transport modes: the neutral ionophores, the carboxylic ionophores, and the channel-forming quasi-ionophores. Neutral ionophores, of which valinomycin is an example, do not have strong antibacterial activity and are not used as antibacterials. Carboxylic ionophores (also called polyether antibiotics) are subdivided into monovalent and divalent polyether antibiotics, depending on their preferential transport of monovalent or divalent cations (241). The ionophores incorporated into animal feed all belong to the carboxylic group. Examples of channel-forming quasi-ionophores include gramicidin and the polyene antibiotics, the best-known representatives of which are the antimycotic agents nystatin and amphotericin B. These antibiotics have a different mechanism of transmembrane transport: they open up ion conduction channels (177, 228). The ionophore antibiotics are active against parasites, including coccidia (*Eimeria*) and *Plasmodium* (25, 103, 104, 191), as well as against gram-positive organisms and mycoplasmas. They are not used therapeutically in humans. In animals the ionophores are used mainly for growth promotion and as "coccidiostats," in the prevention of coccidiosis (39, 51, 72, 81, 201, 228).

Monensin, lasalocid, salinomycin, narasin, and maduramycin are used in Europe. Only monensin (in bovines) and salinomycin (in pigs) are effectively registered as growth promoters. The other registered ionophores can be used in poultry feed as coccidiostats. Monensin is a monovalent carboxylic ionophorous polyether antibiotic produced by *Streptomyces cinnamonensis* that was previously referred to as monensic acid. It transports Na^+ more efficiently than K^+ (48, 108). Lasalocid is a divalent ionophore antibiotic (228). Although it transports bivalent ions such as Ca^{2+} and Mg^{2+} very well (176), it is also an efficient K^+ carrier (48). Salinomycin is a monovalent carboxylic ionophorous polyether antibiotic which is produced by the fermentation of a *Streptomyces albus* strain isolated from soil in Japan (146). It transports K^+ more efficiently than Na^+. Narasin, also a monovalent ionophore, is produced by a strain of *Streptomyces aureofaciens* (75) and carries K^+ more efficiently than Na^+ (48, 52).

Monensin controls or prevents swine dysentery caused by *Brachyspira* (formerly *Serpulina*) *hyodysenteriae* (131) and has been proven active against an *Enterococcus*-like pathogen in rainbow trout (51). Lasalocid can be used in the treatment of *Mycoplasma* infections in chickens (200). Salinomycin is effective in controlling swine dysentery (S. C. Kyriakis, K. Sarris, A. C. Tsinas, and J. C. Papatsas, Proc. 12th Int. Vet. Soc. Cong., p. 289, 1992) and porcine intestinal adenomatosis (131), and it can be helpful in controlling *C. perfringens* type A infections in growing pigs (133). Care should be taken with the dosage of these products. With elevated levels, growth performance is impaired (124).

Mechanism of action. Polyether antibiotics interfere with the natural ion transport systems of both prokaryotic and eukaryotic cells. Ionophores lower the energy barrier necessary for the transmembrane transport of ions and catalyze an electroneutral cation-proton exchange across the barrier. Consequently, they abolish the gradients of Ca^{2+}, Mg^{2+}, K^+, and Na^+, causing cell death (242). The cell walls of most gram-negative bacteria do not permit the penetration of hydrophobic molecules with molecular weights of 600 and above and thus are not susceptible to the action of ionophores (242).

Resistance. A resistance mechanism has been described on only one occasion. *Streptomyces longisporoflavus*, which produces tetronasin, a polyether antibiotic not used in animal feed, contains genes encoding an ATP-dependent efflux system which defends the bacterium against the action of tetronasin (147). The slight increases of MICs for resistant strains (45) indicate that an efflux mechanism might be responsible in these strains. This needs further investigation. MICs of ionophores for several bacteria should be interpreted cautiously. One medium that imitates a more natural environment (a medium containing feed particles) demonstrated a relative insensitivity of several bacteria to ionophores (151). The pH of the medium can also influence the activity of ionophores (58). The addition of blood and incubation in a CO_2-enriched atmosphere alter MIC results (39). Serum proteins inhibit the ion transport capacities of ionophores in erythrocytes and the antimalaria activities of ionophores (100). It has been postulated, based on the fact that medium composition has a large influence on MICs, that MICs do not provide accurate assessment of microbial growth inhibition by ionophores in vivo (58). Resistance to ionophores has been described in *Staphylococcus hyicus* isolated from pigs and *S. aureus* and coagulase-negative staphylococci isolated from cattle (2). Decreased susceptibility both in *E. faecium* and in *E. faecalis* has been reported in Belgium (45): resistance or decreased susceptibility of *E. faecium* was as high as 75% in poultry strains and 33% in strains from swine feces. The rates were much lower in *E. faecalis*, with 33% of the poultry strains and 8% of the porcine strains showing decreased susceptibility. Resistance rates in The Netherlands were similar (154). There was no complete cross-resistance between the ionophores tested. While certain strains showed decreased susceptibility to salinomycin and narasin, this was not the case for monensin and lasalocid (45). The reason for this incomplete cross- resistance remains unclear. Acquired resistance to ionophores has not yet been reported either for clostridia (33, 34, 72, 79, 82, 129, 228) or for other anaerobic bacteria (228).

Pharmacokinetics and toxicity. The ion transport capacity of ionophores does not discriminate between bacterial and mammalian membranes. Since they have good oral absorption (24, 191), these products are quite toxic for mammalians and birds. Several accidents have been reported with overdoses of ionophores in mammalians, mostly involving acute intoxications, although reports of chronic intoxications have also appeared (156, 162, 170). Horses and rabbits seem to be particularly susceptible to ionophore intoxications (22). Both acute and chronic intoxication have been described, especially with maduramycin in cattle fed poultry litter (192). Ionophore intoxication is also well known in birds (18, 26, 28, 179). Not all bird species are equally sensitive to the toxicity of ionophores. Turkeys, guinea fowl, and Japanese quail seem to be more susceptible to monensin intoxication than other birds are (106, 179).

Ionophores are incompatible with several therapeutic antibiotics. Incompatibilities between ionophores and tiamulin, chloramphenicol, erythromycin, oleandomycin, and certain sulfonamides have been demonstrated (213, 227). Some antioxidants (XAX-M, duokvin, TD) are also incompatible with some ionophores (178). Embryo toxicity has been described for

salinomycin in chicken eggs (23). This ionophore can be transported from the laying hen to the egg.

Effects on intestinal flora. Few studies have been performed on the antibacterial effects of ionophores in the intestines. No effect of monensin was observed on the cecal colonization ability of *Salmonella* (150), and no resistance selection in coliforms and streptococci could be demonstrated in chickens (96). This product inhibits *C. perfringens* (types A and C) in chickens and turkeys, suggesting that it could be used to prevent necrotic enteritis (86, 207). Narasin has is also effective in the treatment and prevention of *C. perfringens* infections in chickens (86, 224). In pigs, salinomycin reduces the lesions and the presence of *Lawsonia intracellularis*, causing proliferative entheropathy in the intestines in fattening pigs (Kyriakis et al., Proc. 12th Int. Vet. Soc. Congr., 1992).

Other Growth-Promoting Antibacterials

Quinoxalines. Carbadox and olaquidox are synthetic antibacterials that act by inhibiting DNA synthesis. They are active mainly against gram-negative bacteria (88, 210). Although these quinoxalines sometimes are regarded as growth promotors, they are used mainly in the prevention of swine dysentery caused by *Brachyspira hyodysenteriae* and thus are not discussed here.

Efrotomycin. Efrotomycin, an elfamycin antibiotic, is used solely as a growth promoter. However, its usage has been very limited to date. For reasons unknown to the authors, this product has not been marketed by the manufacturer to any extent in Europe. Efrotomycin belongs to the kirromycin-like class of antibiotics and is produced by *Nocardia lactamdurans*. It is an *N*-methylhydroxypridone glycoside (59, 66, 138, 232). The molecular structure consists of a central dihydrooxytetrahydrofurane ring, a pyridone ring system, and a goldimioc acid (168) Efrotomycin inhibits bacterial growth by the formation of a nondissociable ribosome elongation factor Tu (EF-Tu) complex (137, 246). The product is inactive against gram-negative bacteria because it cannot penetrate the cell, although EF-Tu of gram-negative bacteria is inhibited by efrotomycin in cell-free systems (105). Some activity against *Neisseria gonorrhoeae* and *Haemophilus influenzae* has been demonstrated (138). Streptococcal species are relatively insensitive (138). Efrotomycin is inactive against staphylococci (105, 138), some *Lactobacillus* species (138), certain enterococcal species (155), and some *Bacillus* species (138) due to the insensitivity of their EF-Tu to this antibiotic. The susceptibility patterns of the various enterococcal species seem to be the inverse of those of bambermycin, with the species of the *E. faecium* group (*E. faecium*, *E. durans*, *E. hirae*, and *E. mundtii*) being susceptible and the other species being resistant (155). Efrotomycin has good in vitro activity against *C. difficile* and *C. perfringens* (59, 208). The finding in laboratory experiments of mutant *E. coli* and *B. subtilis* strains resistant to elfamycin antibiotics has been described previously (196, 216). Efrotomycin is rapidly absorbed orally (93). It had no influence on *S. enterica* serotype Typhimurium prevalence, shedding, and resistance profile in swine (118). It diminished the numbers of *C. perfringens* organisms in the ileal contents of chicks (208).

CONCLUDING REMARKS

Only some of the antibiotics that are used today or that have been used in the past for growth promotion in animal husbandry have been well investigated. These include the antibiotics of therapeutic importance to humans. For others, a large body of knowledge is available indirectly because related products are used in human medicine. The spectrum of the growth-promoting antibiotics, with the exception of the quinoxalines, is limited to gram-positive bacteria. Nowadays, much research is being done on products active on these organisms since major problems exist in the therapy of infections caused by multiresistant gram-positive bacteria in humans. New chemical adaptations to products now used solely for growth promotion might be useful in therapy dealing with multiresistant gram-positive bacterial infections. The fact that some antibiotics treated in this review are used solely in animals offers opportunities to study transfers of resistance-determining genes between different ecosystems. Only fragmentary information is available on the possible spread of resistance genes from animals to humans.

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