Review

Novel agents for resistant Gram-positive infections—a review

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Gram-positive infections have increased in recent years, particularly those that are of nosocomial origin, leading to a broad use of agents with activity against these pathogens. Concomitantly, antimicrobial resistance of these pathogens also became widespread. Among the most common Gram-positive resistant pathogens are: *Streptococcus pneumoniae,* resistant to penicillin and macrolides, methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide-intermediately-resistant *S. aureus* (GISA), methicillin-resistant *S. epidermidis*, glycopeptide-resistant enterococci and vancomycin-resistant enterococci (VRE). The response of the pharmaceutical industry to this challenge was the development of new antibiotics active against these pathogens. Among these antibiotics, this review will focus on: linezolid, an oxazolidinone; GAR-936, a tetracycline derivative; daptomycin, a lipopeptide; and ortivancin (LY-333328), a glycopeptide related to vancomycin. Except for linezolid, which has been recently launched in many countries, all other agents referred to in this review are still at various developmental stages. It is hoped that in the near future most of these agents will be approved and thus the grim outlook of patients infected with resistant Gram-positive bacteria may improve.

Emerging bacterial resistance to many available antimicrobial agents has led to a recent surge of pharmaceutical development, which has resulted in production of several new antibiotics. Whereas resistant Gram-negative bacteria were a major problem in previous years, the past decade has seen a crescendo of problems with Gram-positive bacteria, including multidrug-resistant staphylococci, penicillin-resistant *Streptococcus pneumoniae*, and vancomycin-resistant enterococci (VRE). Novel agents, almost all derivatives of old compounds, have recently been introduced into clinical practice.

In this review we focus on leading anti-Gram-positive compounds. We discuss their mode of action, antimicrobial properties and the clinical experience available from data derived from the best-designed clinical trials. As a result of space limitations we will not review all new agents, such as: the new fluoroquinolones, ramoplanin, beta-lactams, and the quinupristin/dalfopristin, which is already on the market. The reader is advised to refer to specific reviews on each drug.

LINEZOLID

The oxazolidinones are a unique family of antimicrobial agents, first developed in the late 1970s for agricultural use.[1] The agents are effective against a wide range of Gram positive bacteria, anaerobes and *Mycobacterium tuberculosis*. Linezolid was the first derivative with acceptable tolerability in man to advance to clinical trials, and is the first Federal Drug Administration approved oxazolidinone for the treatment of pneumonia and skin and soft tissue infections caused by susceptible organisms, and infections caused by VRE. It has not yet been approved for the treatment of penicillin-resistant *Streptococcus pneumoniae*.[2]

Eperezolid is an additional oxazolidinone agent that is presently undergoing clinical trials.

Mechanism of action

Oxazolidinones exert their antibacterial activity via inhibition of the initiation phase of bacterial protein synthesis.[3] The compounds bind to the 50S ribosome where chloramphenicol and lincomycin competitively inhibit their binding. However, unlike these drugs, the oxazolidinones have no effect on the peptidyl transferase.[4] Therefore, similar to chloramphenicol and lincosamides, the oxazolidinone are usually bacteriostatic,[5,6] however there is no cross-resistance between the oxazolidinones and chloramphenicol or the lincosamides.

Antimicrobial activity

Linezolid possesses activity against staphylococci, including *Staphylococcus aureus,* irrespective of its oxacillin susceptibility,[7,8] and against the recently isolated glycopeptide-intermediately-resistant *S. aureus* (GISA).[9,10] Linezolid is active against glycopeptide-resistant coagulase-negative staphylococci.[7] In addition, activity against other major multidrug-resistant Gram-positive pathogens, including VRE and penicillin-resistant *Streptococcus pneumoniae* has also been

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demonstrated, independent of their resistance profile to other antibacterials.[8,11,12] Linezolid is also active against anaerobic streptococci, *Clostridia* spp. and Gram-negative anaerobes. However, it has limited activity against Gram-negative bacteria. The Enterobacteriaceae and Pseudomonas spp. are usually not susceptible.

Resistance

Enterococci and staphylococci resistant to linezolid can be selected in vitro, with difficulty, in association with mutations in genes encoding the central loop domain V of 23S rRNA.[13] Thus far, in the clinical setting, resistance to linezolid has predominantly been reported in enterococci, especially when subtherapeutic drug concentration was used, and for the treatment of non-removable foci of infection.[14-17] Recently, a clinical isolate of *Staphylococcus aureus* resistant to linezolid has also been described. Interestingly, this resistant isolate was recovered from a patient treated with linezolid for peritonitis caused by a different *S. aureus* strain that was sensitive to linezolid. Pulsed-field gel electrophoresis revealed that the two strains were unrelated.[18]

Thus, linezolid is active against a wide range of Gram-positive pathogens through a unique mode of antibacterial action, without a cross-resistance with other agents. Therefore, it has a potential role in the treatment of nosocomial infections with a low risk of emerging resistance. This review reports on three randomized, double-blind equivalence trials evaluating linezolid in the treatment of nosocomial pneumonia and skin and soft tissue infection (SSTI).

Clinical trials

Nosocomial pneumonia
In a randomized, double-blind, multicentre study, linezolid (600 mg twice daily) was compared to vancomycin (1 g twice daily), both antibiotics were administered concomitantly with aztreonam for the treatment of nosocomial pneumonia.[19] A group of 396 patients were included in the intention-to-treat (ITT) analysis. Groups were well matched with regard to patient characteristics. Over 52% of patients were at least

65 years old. In addition, more than 50% were on mechanical ventilation at study entry, and more than 50% had multiple lobe involvement. Mean APACHE II scores were similar, and above 20 in approximately 33% of the patients. The clinical cure-rate was defined as resolution or improvement of baseline symptoms and radiographs with no requirement for additional antimicrobial therapy. Clinical cure rate was achieved in 71 (66.4%) out of 107 and 62 (68.1%) out of 91 clinically evaluable patients in the linezolid and vancomycin groups, respectively (Table 1). Microbiological eradication rates were 25 of 41 (61%) versus 15 of 23 patients (65.2%) for *Staphylococcus aureus*, 15 of 23 (65.2%) versus 7 of 9 (77.8%) for methicillin-resistant *S. aureus* isolates (MRSA), and 9 of 9 (100%) versus 9 of 9 (100%) for *Streptococcus pneumoniae* in the linezolid versus vancomycin groups, respectively. Therapeutic failures were similar in the two treatment groups. No patient who had a microbiological failure developed a resistant organism to either linezolid or vancomycin. There were no deaths as a result of therapeutic failure in the linezolid group, and four deaths (8.2%) in the vancomycin group.

Skin and soft tissue infection
In a randomized, double blind study, linezolid (400 mg twice daily) was compared with clarithromycin (250 mg twice daily) as treatment for uncomplicated SSTI.[20] The ITT groups comprised 332 patients, divided equally between the two treatment arms. The most frequent SSTI types were cellulitis, skin abscesses and furuncles. Clinical cure rates were similar between the two treatment groups. Clinical cure rate was achieved in 113 (91%) out of 124 and 114 (93%) out of 123 clinically evaluable patients in the linezolid and clarithromycin groups, respectively (Table 1). For microbiologically evaluable patients, the microbiological success was 98% and 97%, respectively. The rate of eradication of *Staphylococcus aureus* was 97% (38 of 39) for the linezolid arm and 96% (51 of 53) for the clarithromycin treatment group (Pharmacia, unpublished data).

The efficacy of linezolid in complicated SSTI has also been assessed in a randomized, double-blind, multicentre study.[21] Linezolid (600 mg twice daily) was compared to oxacillin (2 g every 6 h). The excellent bio-

Table 1. Clinical and microbiological efficacy of linezolid versus comparator drugs

Infection site	Treated(n)	Drug	Clinical cure rate (%)	Microbiological success (%)
Nosocomial pneumonia	203	Linezolid	66	68
	193	Vancomycin	68	72
Uncomplicated SSTI	166	Linezolid	91	98
	166	Clarithromycin	93	97
Complicated SSTI	400	Linezolid	89	88
	419	Oxa/Dicloxacillin	86	86

availability of linezolid meant that, upon improvement of the patient's condition, it could be switched, in the same dosage, to oral treatment. Oxacillin was switched to dicloxacillin. Concomitant aztreonam was added when deemed necessary. The ITT groups comprised 400 linezolid-treated and 419 penicillinase-resistant penicillin-treated patients. The most frequent types of SSTI were cellulitis, skin abscesses and erysipelas. Clinical cure rates were similar, achieved in 264 (88.6%) out of 298 and 259 (85.8%) out of 302 clinically evaluable patients in the linezolid and penicillinase-resistant penicillin groups, respectively (Table 1). Microbiological eradication in was 88.1% and 86.1%, respectively, in *Staphyloccocus aureus* cases: 85 (91.4%) out of 93 in the linezolid group versus 87 (54.5%) of 103 in the oxacillin group. However, patients infected by oxacillin-resistant strains were removed from the study. In the *Streptococcus pyogenes*-infected patients eradication rates were 23 (79.3%) of 29 and 27 (84.4%) of 32, for linezolid and oxacillin, respectively. In the group B streptococci the rates were 7 (100%) out of 7 and 4 (77.7%) of 6, respectively.

The efficacy of linezolid in the treatment of MRSA was evaluated in a randomized, open-label comparison with vancomycin.[22] The predominant infections were SSTI and pneumonia and the response rate between the two groups was similar.

Safety

Oxazolidinones are monoamine oxidase inhibitors and linezolid is a mild inhibitor. Patients should be counselled to avoid adrenergic agents, including food or beverages with a high tyramine content.[16] However, thus far no related adverse events have been noted.[19,21] Linezolid is a relatively safe drug; the most common adverse events are headache, diarrhoea and nausea.[16] If therapy exceeds the recommended course of 28 days, bone marrow suppressive effects may appear. These effects (anaemia, thrombocytopenia and leucopenia) disappear when the drug is discontinued.

In conclusion, linezolid proved effective in the treatment of nosocomial pneumonia and SSTI in randomized controlled studies, and also in community-acquired pneumonia, in randomized, single-blind and open-label studies (data not shown), all caused by Gram-positive organisms. Until now, penicillinase-resistant penicillin was the drug of choice for treating community-acquired SSTI. However, in view of the recent increase in oxacillin resistance among community-originating *Staphylococcus aureus* (MRSA),[23] this practice needs a re-evaluation. Linezolid, effective against both oxacillin-sensitive and oxacillin-resistant strains of *S. aureus* becomes therefore an attractive alternative for empiric therapy for these infections.

However, excessive use of this unique drug, might foster the emergence of drug-resistant pathogens, as has already been reported. Even though linezolid is

approved for the treatment of nosocomial pneumonia, community-acquired pneumonia and SSTI, it would be prudent to administer it only in selected conditions, such as in vancomycin-intolerant patients with life-threatening MRSA infections.

DAPTOMYCIN

Daptomycin is the first in a new class of cyclic lipopeptide drugs derived from the fermentation of *Streptomyces roseosporus*. It was first discovered in the 1980s and was shown to be effective in the treatment of SSTI. However, because of muscle toxicity, which appeared at higher doses as used in the treatment of endovascular infections and endocarditis, and because of clinical failures,[24] clinical trials were suspended. The emergence of infections caused by resistant Gram-positive bacteria led in 1997 to renewed interest in daptomycin, with new data obtained in the laboratory and in animal and human studies.

Mechanism of action

Daptomycin is bactericidal against a wide range of Gram-positive bacteria. It appears not to enter the cytoplasm of either bacterial or mammalian cells, but rather, in the presence of calcium ions, to disrupt bacterial membrane function.[25,26] Calcium ions modulate the hydrophobicity of daptomycin, facilitating its interaction with the target bilayer.[27] Thereafter the daptomycin molecule dissipates, in a dose-dependent manner, the membrane action potential, with parallel loss of viability.[28]

Antimicrobial activity

Daptomycin is active solely against Gram-positive bacteria. In recent surveys from the United States and Europe, including over 3,300 isolates, daptomycin was active against all *Staphylococcus aureus* and coagulase-negative staphylococci, independently of their oxacillin susceptibility. Daptomycin was also active against beta-haemolytic streptococci, viridans streptococci, as well as against Gram-positive rods such as *Leuconostoc*, which are characteristically resistant to glycopeptides.[29-31] The effect of calcium in the medium was especially evident when enterococcal susceptibility was evaluated. Daptomycin was active against most strains, including VRE. However, added calcium increased the activity of daptomycin two- to fourfold.[30,32] Unlike most other antibiotics, which are only bacteriostatic against enterococci, daptomycin exhibits rapid, concentration-dependent bactericidal activity against these pathogens, as well as against other bacteria.[32]

Resistance

Resistance to daptomycin among clinical isolates is rare.[30] As expected, exposure of organisms to incre-

mental concentrations of daptomycin resulted in MICs 8–32 times higher than those of the original isolates. Moreover, this resistance became stable and persisted even after passages in antibiotic-free medium.[33,34]

Clinical trials

Daptomycin has proven effective in various animal models of Gram-positive infections.[35–37] To balance between the activity of daptomycin, which is concentration dependent, and the cytoskeletal toxicity, which is dose and time interval dependent, a once daily regimen was selected.[38]

Consequently several global randomized, prospective, double-blind phase III trials investigating the efficacy of daptomycin in the treatment of complicated SSTI and community-acquired pneumonia were initiated. One of the SSTI studies has recently been completed. In this study, 562 patients with major abscesses, wound infections and infected skin ulcers requiring hospitalization and parenteral antimicrobial therapy were enrolled. Patients received either daptomycin (4 mg/kg once daily i.v.) or vancomycin (1 g twice daily) or a penicillinase-resistant penicillin (4–12 g/day divided into four daily doses). Clinical success rates were equivalent in the daptomycin and the comparator arms. Clinical success in the ITT populations was 81% among the two arms, and in those clinically evaluable with Gram-positive pathogen(s), it was 91%. Clinically successful patients receiving daptomycin required fewer days of intravenous therapy than patients receiving the comparator agents. In addition, the incidence of total adverse events, particularly the feared muscle toxicity, was similar in both arms of the trial.[39]

Two multicentre, international, randomized, prospective, double-blind studies evaluating daptomycin 4 mg/kg once daily i.v., versus ceftriaxone once daily i.v. in the treatment of community-acquired pneumonia are currently in progress.[39]

The antibacterial spectrum of daptomycin, and its rapid bactericidal activity make this drug an attractive agent to be tested in the treatment of infective endocarditis. Review of initial phase II studies, performed before clinical trials with the drug were halted for several years, indicate that daptomycin (3 mg/kg twice daily) was as efficacious as the comparator drug in the treatment of infective endocarditis.[40,41] In a rat model of experimental *Staphylococcus aureus* endocarditis, daptomycin administered at a dose equivalent to 6 mg/kg in humans, was more effective than vancomycin. Even at a dose equivalent to 4 mg/kg in humans, daptomycin trended towards greater efficacy than vancomycin.[42]

Safety

Early development of daptomycin was suspended as a result of mild, reversible skeletal muscle damage, which manifested as myalgia and muscle weakness associated with elevated serum creatinine phosphokinase.[43] In phase I and phase II trials daptomycin proved safe, and no serious adverse events were considered to be drug related.[39,43]

GAR-936

Tetracyclines have been important broad spectrum antimicrobial agents for the last 40 years. In order to overcome resistance to these drugs, modification of their structures was undertaken. Glycylcyclines are obtained by modification of the 9-position of chlortertracycline, minocycline, or doxycycline. GAR-936 is a novel derivative of minocycline, active against tetracycline-resistant organisms.[44]

Mechanism of action

The tetracyclines act by inhibiting protein translation by reversibly interacting with the bacterial 30S ribosomal subunit, blocking the binding of aminoacyl tRNA to the mRNA–ribosome complex. Thus, preventing incorporation of amino acid residues into the elongating peptide chains. Resistance is most commonly mediated through either efflux pump in both Gram-positive and Gram-negative bacteria, or by ribosomal alterations ('changed target') that diminish binding of the antibiotic in Gram-positive bacteria.[45] GAR-936 does not exhibit cross-resistance with many other tetracyclines.[46] The difference in the activity of tetracycline and GAR-936 is probably caused by a difference in the mechanism of action or a different mechanism of resistance. Glycylcyclines bind to the 70S ribosomal targets with five times greater affinity compared with the tetracyclines.[47] Experiments studying the mechanism by which glycylcyclines overcome efflux-based tetracycline resistance indicate that these substances are not recognized as substrates by the efflux pump.[48]

Unlike tetracyclines that are generally considered bacteriostatic, GAR-936 possesses bactericidal activity against *Streptococcus pneumoniae* and bacteriostatic activity against most other Gram-positive cocci.[49]

Antimicrobial activity

GAR-936 is generally less active than its parent compound against minocycline sensitive, oxacillin-susceptible and -resistant staphylococci, but it does show in vitro activity against minocycline-resistant strains of *Staphylococcus aureus* and CoNS. However, mean MIC against these isolates is higher than the MIC against the susceptible strains.[50,51] In addition, GAR-936 inhibited two strains of GISA that were also resistant to tetracycline and minocycline, at MIC of 1 and 2 μg/ml.[50] Recently, GAR-936 was also shown to be active against six GISA strains, with a MIC of 0.06–1.0 mg/L.[52]

Macrolide and tetracycline resistance occurs mainly in penicillin non-susceptible strains of *Streptococcus*

pneumoniae. On evaluation of isolates of penicillin-susceptible and penicillin-resistant *S. pneumoniae*, GAR-936 had lower MICs than tetracycline, minocycline and doxycycline. Its activity was independent of their penicillin susceptibility.[49,51]

Enterococcus spp. were sensitive to GAR-936, irrespective of their tetracycline susceptibility. This effect was predominantly evident against VRE, which are usually resistant to tetracycline and its derivatives.[50,51]

GAR-936 possesses activity against *Listeria monocytogenes*, similar to its parent compound.[50] In addition, it was highly active against Gram-positive rods, including *Lactobacillus* spp., *Leuconostoc* spp. and *Pediococcus* spp.[50]

The activity against aerobic Gram-negative rods is fair. Many *enterobacteriaceae*, including *Escherichia coli* were inhibited by GAR-936 (*Proteus* spp. excluded). However, other strains were resistant, with the potency of other antibiotics, including ciprofloxacin, ceftazidime and imipenem, being significantly better.[51,53] In addition, GAR-936 retains its activity against some nonfermentative bacteria such as *Stenotrophomonas maltophilia*, although it is not active against *Pseudomonas aeruginosa*.[51,54]

GAR-936 also proved effective against a wide variety of aerobic and anaerobic animal and human bite wound pathogens.[55]

Most strains of *Neisseria gonorrhoeae* are susceptible to GAR-936, including penicillin- or tetracycline-resistant strains.[46,56] In addition, GAR-936 is highly active against other sexually transmitted diseases pathogens, including *Chlamydia trachomatis*,[57] as well as against *Mycoplasma* spp. and *Ureaplasma urealyticum*.[58]

Resistance

The glycylcyclines manifest the broad range of antibacterial activity that tetracycline had some years ago. However, particularly regarding staphylococci, GAR-936 potency is already lower than that of its parent compounds.[50]

The most frequently occurring tetracycline-resistance determinant in Gram-negative bacteria encodes the membrane residing antiporter protein TetA, which catalyses active tetracycline efflux. Recently, two veterinary *Salmonella* isolates that carry a novel tetA(A) variant were found to have reduced susceptibility to glycylcyclines, although GAR-936, was the least affected.[59]

Clinical trials

Gar-936 is currently in phase II clinical trials.

LY-333328 (ORITAVANCIN)

Vancomycin was introduced in 1956 because of its effectiveness against penicillin-resistant staphylococci.

Approximately 30-years later, acquired glycopeptide resistance in *Enterococcus* spp. was reported, followed by clinical isolates of GISA in 1997.[60] However, to overcome resistance, vancomycin derivatives that have hydrophobic substituents on the vancosamine nitrogen have been developed. LY-264826 is a naturally occurring glycopeptide with the same core structure as vancomycin but with differences in associated sugars present.[61] Alkyl modification of the disaccharide amino led to several compounds, the most active of which is LY-333328.[61]

Mechanism of action

The antibacterial activity of the glycopeptides results from their ability to bind intermediates involved in the biosynthesis of the cell wall peptidoglycan. The glycopeptide antibiotic binds to the terminal D-alanyl-D-alanine residues of the peptidoglycan precursor [lipid-linked disaccharide (N-acetyl-glucosamine-N-acetyl-muramic acid)-pentapeptide (L-Ala-D-Glu-L-Lys-D-Ala-D-Ala)] and inhibits the transglycosylase reaction, thereby an intermediate product is accumulating and polymerization of the peptidoglycan is prevented.[60] Resistance of enterococci to vancomycin results from replacing the terminal D-Ala-D-Ala with D-Ala-D-Lactic acid, which significantly reduces its affinity to vancomycin, sufficient to confer resistance (in a VanA-type). The inhibitory activities of glycopeptides that contain a hydrophobic side-chain (e.g. teicoplanin) is enhanced further, by virtue of the side-chain anchoring the agent at the membrane-associated target site, facilitating an intramolecular interaction.[62] In addition, dimerization of glycopeptide molecules can also enhance their affinity to the cell wall.[62]

LY-333328 and related compounds act at the same site in peptidoglycan synthesis as vancomycin in both vancomycin-sensitive and vancomycin-resistant enterococci.[63] The property of the new glycopeptides that possibly contributes to their enhanced antibacterial activity, is their propensity to form dimers and anchor to the cell membrane in a manner similar to teicoplanin.[63] They do not, however, bind in a higher affinity to either D-Ala-D-Ala or D-Ala-D-Lactic acid termini.[62]

Antimicrobial activity

In vitro susceptibility assays of LY-333328 are method-dependent (broth microdilution vs. agar dilution, type of broth). In a study evaluating LY-333328 against VRE strains, the discrepancy in the MICs in different methods used was more than 16-fold, while with other agents the inter-assay variability was less pronounced.[61,64]

In several global surveys, testing altogether over 2000 strains, using the usual NCCLS recommended Mueller-Hinton broth microdilution assay, LY-333328 proved effective against the major multi-drug-resistant Gram-positive bacteria.[65–67]

LY-333328 was equally effective against oxacillin-susceptible and methicillin-resistant *Staphylococcus aureus* (MRSA). However, its activity for most strains was either identical or less efficient than other glycopeptides (vancomycin and teicoplanin).[65,67] In addition, LY-333328 was highly active against methicillin-susceptible and methicillin-resistant CoNS, including those resistant to teicoplanin.[65-67] In a recent report evaluating the activity against three different GISA strains, LY-333328 was consistently, in a concentration-dependent manner, the most active glycopeptide, and showed synergism with gentamicin.[68]

LY-333328 possesses good *in vitro* activity against enterococcal spp., including glycopeptide-resistant strains of the three major phenotypes (VanA, VanB, and VanC), with MICs significantly lower than the other glycopeptides.[65-67,69] In another survey evaluating the antimicrobial susceptibility of 4,208 clinical isolates of enterococci, LY-333328 was highly effective, showing no cross-resistance with vancomycin.[70] In addition, unlike the bacteriostatic effect of vancomycin and teicoplanin, LY-333328 manifested bactericidal activity against some of the strains tested.[64,71]

Pneumococci, and other viridans streptococci, were highly susceptible to LY-333328, irrespective of their penicillin susceptibility, with current MICs lower than that of the other glycopeptides.[65-67] LY-333328 was uniformly bactericidal against *Streptococcus pneumoniae*.[72]

Resistance

In a series of experiments using laboratory-constructed enterococcal strains that acquired LY-333328 resistance. Resistance was mainly a result of mutations leading to production of precursors ending in D-Lac with complete elimination of precursors terminating in D-Ala.[73] These observations indicate that emergence of LY-333328 resistance should be anticipated.

Clinical trials

A phase II, open-label, controlled, multicentre study in patients with *Staphylococcus aureus* bacteraemia is ongoing. An additional phase II, double-blind, multicentre study, for the treatment of patients with complicated SSTI, has finished enrolling patients.

CONCLUSIONS

Drug-resistant Gram-positive bacteria are a serious emerging problem in clinical practice. In particular, nosocomial strains resistant to all the antimicrobials are becoming increasingly common. Several new agents to combat these strains have been developed in recent years, linezolid (and quinupristin/dalfopristin) have already been approved by the United States Federal Drug Administration for several indications, whereas the other agents are still undergoing clinical trials. Thus

far there have been only scant reports comparing head to head the above-reviewed new agents against the major pathogens, and in the majority no significant differences were found.[74-76] One report indicated better activity of daptomycin versus linezolid against staphylococci and enterococci.[9] Therefore, other parameters, including the susceptibility profile of the isolated bacterium, should lead us in selecting the appropriate drug. At the present time it is impossible to forecast which agent would be clinically the most useful. In addition, the clinical safety profiles of these agents remain unknown.

Many new antimicrobial agents are being evaluated yearly.[77] However, only few enter clinical studies and less are eventually approved. It is somewhat discouraging that among the more advanced agents targeted against Gram-positive pathogens, no true novel product exists, but rather they are derivatives of old molecules. Consequently the duration for which we should expect them to be clinically efficient before resistance emerges is limited. Therefore, in addition to dusting off old agents in the search for new drugs, we should be more judicious in using the current antibiotics in order not to induce resistance. It is hoped that with the unfolding of the genomic structure of many pathogens, newer targets allowing for new agent development will enrich the clinical arena with effective new agents.

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