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# Newer Antibacterial Drugs for a New Century

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## Abstract

Antibacterial drug discovery and development has slowed considerably in recent years with novel classes discovered decades ago and regulatory approvals tougher to get. This article describes newer classes of antibacterial drugs introduced or approved after year 2000, their mechanisms of action/resistance, improved analogs, spectrum of activity and clinical trials. It also discusses new compounds in development with novel mechanisms of action as well as novel unexploited bacterial targets and strategies which may pave the way for combating drug resistance and emerging pathogens in the 21st century.

### Keywords

antibacterial; drug discovery; drug resistance

Infectious diseases are one of the leading causes of death worldwide, especially in low and middle income (LMIC) countries where second line antibacterial drugs against resistant bacteria are generally unavailable or unaffordable. In upper income countries (UIC), the emergence of multi-drug resistance in both community and hospital acquired infections has outpaced development and delivery of new drugs to the clinic. Most recently, the emergence of carbapenem resistance among *Klebsiella* sp. and related Gram negative bacteria illustrates the magnitude of the problem, as these multi-drug resistant infections are associated with high mortality rates and few treatment options 1. While the market potential for new antibacterial drugs is estimated in the many billions of dollars [2], the discovery pipelines of most major pharmaceutical companies run near empty. The paucity of new antibacterial drugs has led the Infectious Disease Society of America (IDSA) and others to call for action in rebuilding infrastructure and efforts to develop next generation drugs.

Despite the many grim predictions of failure in combating infectious diseases in the future [3, 4], all is not lost, as several classes of new antibacterial compounds as well as derivatives of older therapeutics have emerged. In this review we examine some of these new antibacterial drugs that have recently been approved by the FDA (and EMEA) or are in late stages (phase II development or beyond) of the pipeline. These new drugs belong to the following classes of compounds that include: oxazolidinones, glycopeptides, ketolides, glycylcyclines, carbapenems and fluoroquinolones (Table 1). This article will describe in detail the mechanism of action (novelty), spectrum of activity, selected *in vivo* efficacy and mechanisms of resistance to these antibacterial drugs and also discusses briefly more new drugs in development (Table 2). We also have included unpublished information reported at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the Infectious Disease

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Society of America (IDSA) 46th Annual Meeting in 2008 and here after noted as ICAAC/IDSA. In addition, we also explore novel strategies such as targeting host infection response pathways, anti-infective antibodies or the vitamin cofactors of selective microbial targets and offer a glimpse into the anti-infective drug discovery pipeline of the future.

# 1. ANTIBACTERIAL DRUGS

## 1.1 Oxazolidinones

**Mechanism of Action—**Oxazolidinones are considered to be the first truly new class of antibacterial drugs introduced in the past 3 decades. **Linezolid** was approved by the FDA in 2000 for adults and for pediatric use in 2005 5. The oxazolidinone linezolid inhibits bacterial protein synthesis at the initiation/elongation step. In vivo drug-ribosome crosslinking studies reveal that oxazolidinones bind to the peptidyl transferase center (PTC) of the 50S ribosomal subunit 6› 7. Oxazolidinones also bind to LepA, a universal bacterial elongation factor which back translocates ribosomes from a “POST” translocation state to a pre-translocation state 8. Linezolid has been shown to bind to the A site of PTC (site of entry of the aminoacyl tRNA) , indicating that the drug interferes with the positioning of the aminoacylated-CCA end of the A-tRNA, not the P-site tRNA (site where the peptidyl tRNA forms) 9. Thus, oxazolidinones compete with PTC binding drugs chloramphenicol and lincomycin 7. Binding of oxazolidinones to PTC is conformation dependent and requires a P-site ligand (P-tRNA). However, it is unclear whether oxazolidinones are initiation or elongation inhibitors 10 as they inhibit binding of the aa-tRNA to the A-site of the 70S initiation complexes, and also the POST ribosomes which have P and E-sites filled. It is interesting to note that oxazolidinones bind only to the mitochondrial 70S ribosomes and not the cytoplasmic 80S ribosomes, explaining the myelosuppression and toxic optic neuropathy observed in patients treated with linezolid for as little as 14 days 11› 12.

**Spectrum of Activity/ Improved Analogs—**Oxazolidinones have activity against Gram positive bacteria, such as methicillin-resistant *Staphylococcus. aureus* (MRSA), vancomycin resistant enterococci (VRE) and *Streptococcus pneumoniae* and *Mycobacterium tuberculosis* [13–16]. Oxazolidinones also have activity against all *Nocardia* species [17, 18]. In an attempt to find newer oxazolidinones with improved potency, aqueous solubility and reduced toxicity, modifications of the A, B and C rings of linezolid have been reported [19]. **Radezolid (RX-1741)** is a new oxazolidinone, discovered using the crystal structure of 50S ribosome subunit and in a Phase II clinical trial with 150 patients for uncomplicated skin and skin structure infections (uSSSI) a 97.4% clinical cure rate was achieved (450mg once a day) compared to 97.4% with linezolid (600mg twice a day) [20]. **Torezolid (TR-700)**, a new oral oxazolidinone is 4–8 fold more active than linezolid in linezolid-susceptible and resistant strains of staphylococci and enterococci and upto 4-fold higher against anaerobes [21]. **RWJ-416457**, the pyrrolopyrozolyl-substituted oxazolidinone exhibits 2 to 4 fold greater potency than linezolid against susceptible and multi-drug resistant staphylococci, enterococci, and streptococci, *Haemophilus influenzae* and *Moraxella catarrhalis* and also the atypical intracellular respiratory tract pathogens *Chlamydia pneumoniae, Legionella pneumophila*, and *Mycoplasma pneumoniae* [22]. RWJ-416457 had 2 to 4 fold lower MICs than linezolid against linezolid resistant *S. aureus* and enterococci [23].

**Mechanism of Resistance—**Resistance to oxazolidinones results from mutations in ribosomal RNA (rRNA), all of which map near the PTC. They cluster in the vicinity of the central loop of domain V of 23S rRNA of the large ribosomal subunit [24]. Linezolid resistance is selected *in vivo* by prolonged drug treatment or reducing the dose. Most of the clinical resistant mutants have the G2576T mutation in domain V of 23S rRNA. More than one 23S rRNA gene must be mutated to confer resistance, leading to a rarity in resistance occurrence

23, as most bacteria contain 4–6 copies. The potency of torezolid against linezolid-resistant microbes is explained by additional hydrogen bond interactions with 23S rRNA (residues A2451 and U2484) and lesser requirement for residues associated with linezolid resistance [25]. Mutations in ABC transporter (efflux pump) genes causing overexpression as well as RNA methyltransferase mutations have led to linezolid resistance in *S. pneumoniae* [26].

### 1.2 Glycopeptides

**Mechanism of Action—**Glycopeptide antibacterial drugs are natural products introduced first in the 1950s (vancomycin) and are a heptapeptide core with an attached sugar moiety. Due to the emergence of vancomycin resistance, newer derivatives of glycopeptides with potency against the resistant microbes are being developed [27]. **Oritavancin** is a phenyl glycopeptide derivative and inhibits peptidoglycan biosynthesis by not only inhibiting transglycosylation, but also transpeptidation 28, 29. This antibacterial drug blocks utilization of D-Ala-D-Ala or D-Ala-D-Lac containing PG precursors. The selective action of glycopeptide antibacterial drugs is due to strong intramolecular interaction with D-amino acid-containing PG residues, not found in mammalian cells [30]. The alkyl and fatty acyl lipophilic side chains of the new glycopeptides cause effective membrane anchoring, increased dimerization (co-operative effects) and prolonged half-life [31–33]. **Telavancin**, another semisynthetic glycopeptide has an additional mode of action : depolarization and permeabilization of the bacterial membrane causing rapid bactericidal activity [34]. The mechanism by which this occurs is through interactions with lipid II [35].

**Spectrum of Activity/Improved Analogs—**These newer glycopeptides offer significant advantages over vancomycin: in addition to improved *in vitro* potency (Table 3), their pharmacokinetics allow less frequent dosing and possibly improved distribution. Oritavancin, a semisynthetic glycopeptide and **dalbavancin**, a second-generation lipoglycopeptide are two new glycopeptides in clinical development. The new glycopeptides show good potency towards *S. pneumoniae*, and also staphylococci, though dalbavancin is highly potent against *S. aureus* ($MIC_{50}$ 0.03–0.12 μg/ml) and coagulase-negative staphylococci ($MIC_{50}$ 0.03 μg/ml) [36, 37]. Dalbavancin is not potent against *vanA* vancomycin resistant enterococci, but highly potent ($MIC_{50}$ of 0.06 μg/ml compared to $MIC_{50}$ of 1 μg/ml for vancomycin) towards vancomycin susceptible enterococci [38]. Telavancin is very potent against MRSA, streptococci and also VRE due to its optimized lipophilic tail [39, 40]. Oritavancin is also potent against MRSA but not as potent against vancomycin intermediate *S. aureus* (VISA) [41]. Oritavancin, however, exerts concentration-dependent cell killing activity against vancomycin-intermediate isolates of *S. aureus* (VISA) including heterogeneous VISA (hVISA) [42, 43] and against vancomycin resistant staphylococci and *Enterococcus faecium* (VRE) which correlates to disruption of membrane integrity [44].

Dalbavancin is being developed for treatment of skin and soft tissue infections and catheter related bloodstream infections. In a phase II clinical trial for catheter-related bloodstream infection caused by staphylococci, 87% success rate in 75 adult patients was observed with dalbavancin compared to 50% with vancomycin [45]. In a phase III randomized, double blind, non-inferiority study dalbavancin was non-inferior to linezolid in a total of 854 patients with complicated SSTIs [46]. However worldwide marketing application for dalbavancin has been withdrawn as of September 2008 pending a global multicenter study for cSSTI, including those caused by MRSA [47].

Two Phase III clinical trials were conducted with telavancin in patients with focus on MRSA cSSTIs and were non-inferior compared to vancomycin [48]. Two ATTAIN (Assessment of Telavancin for Treatment of MRSA Pneumonia) Phase III studies have been conducted for telavancin in nosocomial pneumonia caused by Gram positive bacteria compared to

vancomycin. An overall clinical cure rate of 85% was observed for the telavancin group versus 76% for vancomycin group [49]. Telavancin clinical cure rate was statistically significantly higher for patients infected with *S. aureus* with a vancomycin MIC ≥1 μg/mL 50. Two randomized, double-blind, multicenter, phase III trials have been completed for oritavancin in cSSTIs and a total of 1763 patients received study medication (either oritavancin (3–7 days) or vancomycin/cephalexin (10–12 days)). The clinical cure rate in the clinically evaluable patients was 77.7% for the oritavancin group and 75.8% for the vancomycin group [51]. However the FDA Anti-infective drug advisory committee (AIDAC) decided that the data did not demonstrate efficacy or safety of oritavancin 52 and requested another phase III trial for cSSTI enrolling more patients with MRSA. Telavancin, on the other hand, received a favorable recommendation from AIDAC for cSSTI, requiring no additional trials but requiring a risk management strategy 53.

**Mechanisms of Resistance—**Bacteria that have a VanA or VanB resistant phenotype synthesize an altered PG precursor with reduced vancomycin binding affinity [54, 55]. Vancomycin is unable to bind to D-Ala-D-Lac precursor substrate compared to D-Ala-D-Ala. Oritavancin, however, due to its hydrophobic side chain, co-operativity due to dimerization and binding to lipid II on the membrane, binds equally well to both substrates and therefore is useful against vancomycin resistant bacteria. Oritavancin resistant clinical isolates have not been reported. Telavancin is useful against vancomycin intermediate *S. aureus* (VISA), heterogenous VISA and also vancomycin resistant enterococci VRE expressing *vanB* [40, 56]. Dalbavancin is potent against strains of VRE expressing *vanB* and *vanC* gene products but inactive against VRE expressing *vanA* [38]. Dalbavancin resistance did not develop in staphylococci by direct selection and serial passage at subtherapeutic concentrations [57].

### 1.3 Ketolides

**Mechanism of Action—**Drug resistance in community acquired respiratory tract infections (CA-RTIs) has driven the discovery and development of ketolides. Ketolides are derived from 14 membered ring macrolides and have a carbonyl group at the C3 position, which is crucial in conferring sensitivity to macrolide resistant strains [58]. **Telithromycin** was approved by the FDA in 2004 for community acquired pneumonia, chronic bronchitis and acute sinusitis [5]. Crystal structure of macrolide bound to 50S ribosomal subunit revealed that this antibacterial drug occupies and blocks the peptide exit tunnel without affecting the peptidyl transferase activity [59]. The macrolides form hydrogen bonds with the 23S rRNA at domains II and V and thus inhibit bacterial protein synthesis. Ketolides are known to bypass macrolide resistant mechanisms by improving ribosome binding affinity, especially binding to domain II and evading macrolide efflux mechanisms [60, 61]. The structure-activity relationship is paramount in ketolide mechanism of action. For example, the aryl group enhances activity against macrolide resistance caused by ribosome methylation *erm* phenotype 60, [62]. The ketolides also have longer post-antibacterial effects (PAEs), compared to erythromycin [63].

**Spectrum of Activity/Improved Analogs—**Telithromycin and cethromycin are two ketolides derived from erythromycin. **Cethromycin** inhibits protein synthesis up to 50% at 2.5 ng/ml, in *S. pneumoniae* [61]. It has a 67-fold higher binding affinity to 50S ribosomes from *S. pneumoniae* than erythromycin and also accumulates at a higher rate within both susceptible and cells resistant due to efflux mechanisms [60]. Cethromycin has an $MIC_{50}$ of 0.008 to 0.016 μg/ml for different isolates of *S. pneumoniae* and was also more potent than telithromycin against macrolide-susceptible strains of *S. pneumoniae*, *Streptococcus pyogenes*, *S. aureus*, *Staphylococcus epidermidis*, enterococci, *Helicobacter pylori*, and *Mycobacterium avium* complex, and also against *Corynebacterium* spp., *M. pneumoniae*, *Chlamydia trachomatis*, *Borrelia burgdorferi*, *H. influenzae*, *M. catarrhalis*, *C. pneumoniae* and *Toxoplasma gondii* [63, 64]. Cethromycin was very potent against macrolide-resistant streptococci and enterococci

irrespective of their macrolide resistance mechanism but had little detectable activity against constitutively macrolide-resistant *S. aureus* [64]. Upon *erm* induction of ribosome methylation, cethromycin (at 100 μM) inhibited translation up to 75% compared to 25% by erthyromycin, in an *in vitro* transcription-translation assay, suggesting that at higher drug concentrations cethromycin has an affinity for methylated ribosomes, though 100 fold lower than for unmethylated ribosomes [60].

The FDA withdrew its approval of telithromycin in December 2006 for acute exacerbation of chronic bronchitis (AECB) and acute sinusitis because they determined that the balance of benefits and risks no longer support approval of the drug for those indications and also cited cases of safety risks (hepatotoxicity, visual disturbances and loss of consciousness), raising concerns over the future of this antimicrobial drug class [65]. In a phase III double blind, randomized, multi-center clinical trial of cethromycin compared to clarithromycin, for mild to moderate community acquired pneumonia, in 584 patients, non-inferior clinical cure rate was observed with no safety concerns 66.

**Mechanisms of Resistance—**Ketolides do not induce $MLS_B$ (Macrolide Lincosamide Streptogramin B) resistance phenotype which is attributed to the cladinose moiety in the C3 position of macrolides. $MLS_B$ resistance can arise by constitutive or inducible expression of methyl transferases that methylate the 23S rRNA [67].

The first ketolide resistant mutation was identified by *in vitro* selection of mutated rRNA operon and the U2609C mutation found in 23S rRNA was resistant to cethromycin [62]. Dimethylation of 23S rRNA at postion A2058 confers ketolide resistance in *S. pyogenes* which express *ermB* [68]. Ketolide susceptible strains of *S. pyogenes* that are macrolide resistant due to *erm* induction have monomethylated rRNA, implicating dimethylation as a ketolide resistance mechanism [68]. In a macrolide resistance surveillance study in Europe, 13% of erythromycin resistant *S. pneumoniae* isolates were telithromycin resistant by agar diffusion method [69], but this incidence of telithromycin resistance has not been found in other studies. A *S. pneumoniae* clinical isolate was found to be telithromycin resistant (MIC 8 μg/ml) due to a deletion in the leader sequence for *ermB*, causing a constitutive phenotype, leading to rRNA dimethylation [70]. Laboratory generated mutants of *S. aureus* that are telithromycin resistant were found to have mutations in *rplV* which led to amino acid duplications in L22 ribosomal protein and also a few gene conversion events between *rplV* and *rplB* (encoding ribosomal protein L2) [71].

### 1.4 Glycylcyclines

**Mechanism of Action—**Glycylcyclines are the newest member in the tetracycline class of antibacterial drugs and one member (**tigecycline**) was approved by the FDA (June 2005) [5] for complicated skin and skin structure infections and also for intra-abdominal infection. The novelty about glycylcyclines is their ability to subvert the common tetracycline resistance mechanisms acquired by genetically mobile element encoding the *tet* genes. The two major resistance mechanisms are tetracycline efflux pumps or ribosomal protection 72. The compound with t-butylglycylamido moiety at position 9 of minocycline (tigecycline) exhibits potent antibacterial activity and also potency against tetracycline resistant bacteria 73, 74. The glycylcyclines bind with a 5-fold to 100-fold higher affinity to 30S and and 70S ribosomes, respectively, than tetracyclines 75 and also inhibit protein synthesis of Tet(M) and Tet(O) tetracycline resistant bacteria 76, 77. Protein synthesis inhibition by tigecycline is 20-fold more efficient than tetracycline 75.

**Spectrum of Activity/ Improved analogs—**Glycylcyclines have a broad spectrum of antimicrobial activity ranging from aerobic to anerobic bacteria, gram positive and gram

negative. Tigecycline is active against methicillin-resistant *S. aureus* (MRSA), vancomycin resistant enterococci (VRE), drug resistant *S. pneumoniae*, respiratory gram-negative pathogens such as *H. influenzae*, *M. pneumoniae*, *M. catarrhalis* and Enterobacteriaceae [73, 78]. Tigecycline is also active against other aerobes like *Neisseria gonorrhoeae*, mycobacteria, and anaerobes such as *Clostridium* spp.and *Bacteriodes* spp. [73, 79]. *Pseudomonas aeruginosa* is however resistant to tigecycline (MIC> 4 μg/ml) 80. Tigecycline is equally potent against both tetracycline susceptible and resistant clinical isolates 81. Tigecycline was more potent towards enterococci and streptococci (MICs<0.2 μg/ml) compared to staphylococci 81. Tigecycline was also effective against some carbapenamase producing *Acinetobacter baumannii* and Enterobacteriaceae [82]. Tigecycline is bacteriostatic in the rat and rabbit endocarditis models of *Enterococcus faecalis* infection, including vancomycin resistant strains [83]. Monotherapy with tigecycline (phase III, randomized, double blind clinical trials) have exhibited non-inferiority to standard therapy for complicated skin/ skin structure (comparator: vancomycin-aztreonam) and intra-abdominal infections (comparator: imipenem-cilastatin) [84, 85]. Significant incidence of nausea and vomiting has been noted in patients in 2 days of therapy and was a major reason for discontinuing treatment 84, 85. Tigecycline was found to be safe, effective and non-inferior in a double blind, randomized phase III trial conducted for community acquired pneumonia in 418 hospitalized patients given either intravenous tigecycline or comparator levofloxacin 86. Two randomized phase III multi-center double-blind clinical trials have been conducted to test i) the safety and efficacy of tigecycline compared to vancomycin or linezolid in hospitalized patients with MRSA or VRE [87] and ii) the safety and efficacy of tigecycline in hospitalized patients with serious infections caused by resistant gram negative pathogens such as *A. baumannii*, *K. pneumoniae* and *E. coli* who were unresponsive to previous antimicrobial therapy 88. In both the trials, tigecycline was found to be effective in hospitalized patients with serious infections 87, [88]. However side effects such as nausea/vomiting were common in tigecycline treated patients (41% compared to 18% with vancomycin) [87]. **PTK0796** is a new aminomethylcycline in development and has oral activity. In a phase II trial (randomized, double blinded, multicenter), for complicated skin and skin structure infection (cSSSI), PTK0796 had a clinical success rate of 98% compared to 93.2% for linezolid in the clinically evaluable population [89].

**Mechanisms of Resistance—**Tigecycline resistance has been reported in *Proteus* and *Providencia* species and in many strains of *Morganella morganii* due to the presence of constitutively overexpressed multidrug efflux pump systems (eg. AcrAB) which can transport tigecycline 90, 91. AcrAB belongs to the RND (resistance nodulation division) family of efflux pumps found in Gram negative bacteria e.g. *E. coli* and *K. pneumoniae* [92]. Tigecycline is also substrate of MATE (multidrug and toxic compound extrusion) family MepA pump from *S. aureus* [92] leading to reduced susceptibility.

### 1.5 Carbapenems

**Mechanism of Action—**Carbapenems are β-lactam antibacterial drugs related to penicillin (penam) and cephalosporine (cephem). They differ from the penams by the presence of a carbon at position 1 instead of a sulphur, and unsaturation in the 5-membered ring. **Doripenem** is the newest member of the carbapenems and received FDA approval in October 2007 for complicated urinary tract infections and intra-abdominal infections [93]. Carbapenems bind to penicillin binding proteins (PBPs) that are required for elongation and crosslinking the peptidoglycan of the cell wall, in both Gram positive and Gram negative bacteria. Carbapenems are capable of passing through porins in outer wall of Gram negative bacteria, have a high affinity to PBPs and are stable against most Ambler class A, C and D β-lactamases [94, 95], explaining their potency. Doripenem preferentially binds to PBP2 of *E. coli* and PBP2 and 3 of *Pseudomonas aeruginosa*, similar to meropenem [96].

**Improved Analogs/ Spectrum of Activity—**Doripenem is unique in that it has a spectrum against Gram-positive cocci similar to that of imipenem and activity against Gram-negative bacilli, similar to meropenem [97]. The presence of a side chain at position 2 leads to greater activity against non-fermentative Gram-negative multi drug resistant bacilli such as *P. aeruginosa*, *Acinetobacter spp.* and *Burkholderia cepacia*, unlike other antibacterial drugs [94, 97]. Doripenem is active against staphylococci, enterococci and streptococci [97, 98]. Doripenem is also active against the Enterobacteriaceae such as *E. coli spp*. (non-producers and producers of ESBLs), *Klebsiella spp*. (non-producers and producers of ESBLs), *Enterobacter spp*., *Proteus mirabilis*, *Salmonella spp*. and *Shigella spp*. 97, 98. Meropenem is a potent carbapenem as well and sometimes is more potent than doripenem especially in respiratory tract pathogens [97]. In addition to clinical trials conducted for diseases for which doripenem is FDA approved, trials have been conducted for ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP). Multicenter, randomized, open-label Phase III trials for ventilator-associated pneumonia and hospital-acquired pneumonia involving 1000 patients show that intravenous doripenem was at least as effective as standard comparator agents such as imipenem (68% vs 64% clinical cure rate in clinically evaluable patients) and piperacillin/tazobactam (81% vs 80% clinical cure rate in clinically evaluable patients), respectively [99, 100]. However, the FDA's anti-infective drug advisory committee disagreed with the selection of the noninferiority margins, not the margin that was met in the trial 101. The actual NI margin that was achieved was more favorable than the margin for which the study was designed.
**Razupenem** (**PZ-601)** is a novel carbapenem with activity against multi drug-resistant Gram-positive and Gram-negative (ESBL producers) bacteria [102] and is currently in Phase II clinical trial for complicated skin and skin structure infections (cSSSI) 103.

**Mechanism of Resistance—**Carbapenems are susceptible to hydrolysis by serine carbapenemases and metallo-β-lactamases (MBLs). KPC carbapenemases (Class A) are most prevalent and are plasmid-borne in *K. pneumoniae* and in *Serratia marcescens*, *Enterobacter cloaecae* and other Enterobacteriaceae [104]. Class B carbapenemases are the metallo-β-lactamases and are found increasingly in Enterobacteriaceae [105]. Carbapenemase dissemination has changed pattern from chromosomally encoded to plasmid-borne eg. IMP-1 a metallo-β-lactamase in *P. aeruginosa* (over 20 IMP variants of metallo-β-lactamases) [105]. Efflux pumps and porin mutations are also responsible for carbapenem resistance 106.

## 2. Additional Promising Antibacterial drugs in the pipeline

Natural products produced by certain micro-organisms to survive in their natural environment (secondary metabolites) have been the stronghold of antibacterial drug discovery. Due to rampant drug resistance that has developed for virtually all antimicrobial drugs, despite antimicrobial conservation efforts, development of new drugs with novel mechanisms and increased potency towards resistant microbes is desirable (Table 2). Some of these new compounds have potent gram negative activity. Ceftobiprole and Ceftaroline are newer cephalosporins and are discussed here because of improved mechanism of action than older cephalosporins. Iclaprim, with improved mechanism of action compared to trimethoprim, is also discussed here.

**Ceftobiprole** is a novel engineered cephalosporin with activity against MRSA and penicillin-resistant streptococci. It was engineered to bind strongly to PBP2a (or PBP2') of methicillin-resistant Staphylococci [107]. Ceftobiprole due to its strong binding to *S. pneumoniae* PBP2x [107] has an MIC of 0.5μg/ml against penicillin-resistant *S. pneumoniae* 108. Ceftobiprole is stable against some enzymes (non-ESBL Class A) due to its C7 side chains, but is hydrolyzed by ESBLs and carbapenamases [109]. In two Phase III clinical trials for complicated skin and skin structure infections (cSSSI), ceftobiprole had 82% activity (<=4μg/ml) against all baseline pathogens, demonstrating its broad spectrum 110 and was as effective as comparator

vancomycin-ceftadizime or vancomycin alone 111, 112. **Ceftaroline** is a novel cephalosporin in Phase III development with broad spectrum activity against MRSA and multi-drug resistant *S. pneumoniae* 113. Ceftaroline inhibits PBP-2a, explaining its potency against MRSA 114. A double blind, randomized, phase III clinical trial has been conducted in 700 patients with cSSTI for the safety and efficacy of intravenous ceftaroline against vancomycin and aztreonam. Clinical cure rates were similar for both groups and ceftaroline was non-inferior to vancomycin-aztreonam combination [115]. Ceftaroline is synergistic with β-lactamase inhibitor tazobactam (upto 500 fold) against multi-drug resistant gram negative pathogens such as ESBL producing *E. coli* and *K. pneumoniae* [116].

Novel DHFR (Dihydrofolate reductase) inhibitors (e.g. **iclaprim**, a diaminopyrimidine) that inhibit DNA/RNA synthesis are antibacterial agents designed with the knowledge of trimethoprim resistance (transposon inserted DHFR isoforms) and have improved affinity to *S. aureus* DHFR [117]. Iclaprim has a broad spectrum of activity including trimethoprim and methicillin resistant as well as vancomycin intermediate *S. aureus* ($MIC_{90}$ is 0.5μg/ml) [118], penicillin resistant *S. pneumoniae* and Gram-negative bacteria such as *Enterobacter*, *Salmonella*, *L. pneumophila*, *H. influenzae*, *C. pneumoniae* etc. [118, 119]. In a large surveillance study including about 4500 *S. aureus* isolates (MSSA and MRSA), iclaprim was 16-fold more potent than trimethoprim and had activity similar to TMP/SMZ (trimethoprim/ sulfamethoxazole) combination [120]. Two Phase III trials for cSSSI with iclaprim and comparator linezolid have concluded in 2700 patients and demonstrate that iclaprim has high efficacy comparable to linezolid 121. However as of January 2009, the FDA requires additional clinical data to demonstrate efficacy to gain approval 122.

**NXL103 (XRP2868)** is a mixture of modified forms of quinupristin/dalfopristin streptogramins making it more water-soluble and permitting oral administration. NXL103 is also more inhibitory than nine other antibacterial drugs tested against Gram-positive clinical isolates including vancomycin, daptomycin, linezolid, clarithromycin, telithromycin, clindamycin, ampicillin, quinupristin/ dalfopristin and pristinamycin [123]. It is more effective (2–5 fold lower $MIC_{50}$ values) in inhibiting erythromycin resistant *S. pneumoniae*, methicillin-resistant *S. aureus* (MRSA) and β-lactamase-positive *H. influenzae*, compared to quinupristin/ dalfopristin [124]. NXL103 also inhibits vancomycin resistant enterococci (VRE) and cocci harboring resistance to streptogramins by different mechanisms [125]. *E. faecalis* is intrinsically resistant to streptogramin A but NXL103 displays MICs less than 1μg/ml [125]. Mutations in ribosomal proteins L4 and L22 in *S. aureus* and streptococci are sufficient to reduce potency of NXL103 and suppress in part the synergy between $S_A$ and $S_B$ [125].

**Nitazoxanide**, a nitro-thiazolide, exhibits broad spectrum activity against anaerobic bacteria and against anaerobic intestinal parasites. Nitazoxanide (brand name Alinia, Romark Laboratories Ltd, Tampa Florida) is FDA approved for the treatment of intestinal infections caused by *Giardia intestinalis* and *Cryptosporidium parvum* in adults and children [126]. This drug is increasingly being used (off-label) to treat infections caused by *Clostridium difficile* based on demonstration of clinical efficacy 127. In these studies, nitazoxanide was shown to be equivalent to comparator drugs metronidazole and vancomycin. The drug also exhibits some antiviral activity against rotavirus and hepatitis C 128, [129]. The wide spectrum has raised concerns of safety, but the drug is of low toxicity to humans, with few side effects, probably due to its high affinity for serum proteins. The concerns of safety arise because at different doses used to treat diseases caused by a variety of organisms, the drug will also inhibit other organisms (eg. disruption of flora) with unknown consequences, unless highly specific analogs are designed. Therefore, studying nitazoxanide's mechanism of action against different organisms is paramount.

Several investigations have identified the pyruvate:ferredoxin oxidoreductase (PFOR) as the major target for nitazoxanide and this enzyme is both common and essential to all of the intestinal parasites and anaerobic bacteria, including *C. difficile* [130, 131]. Other targets for this drug include nitroreductases in *Giardia* sp. and protein disulfide isomerases in parasites [132, 133]. Most microorganisms, systemic parasites and humans oxidize pyruvate via pyruvate dehydrogenase, which is not a target for the drug. Recent studies on mechanism have provided evidence to suggest that nitazoxanide inhibits an early step in the PFOR reaction by a non-competitive inhibition of the interaction of pyruvate with the thiamine pyrophosphate (TPP) cofactor [130]. In this study it was determined that nitazoxanide is biologically active as an anion which becomes protonated by abstraction of a proton from the TPP-pyruvate intermediate resulting in no substrate catabolism and inactivation of the drug via protonation. Inhibition of PFOR by nitazoxanide stops the conversion of pyruvate to acetate, a key component of fatty acid biosynthesis, amino acid biosynthesis and energy production. This novel mode of action by nitazoxanide illustrates several fundamental points that might be of value in the design of future therapeutics. First, nitazoxanide interacts with the TPP vitamin cofactor and not with the PFOR enzyme, thus diminishing mutation based drug resistance mechanisms and second, PFOR is unique in mechanism to the target group of pathogens and not present in humans. In over 10 years of clinical use there has been no reported drug resistance and attempts to produce drug resistance under laboratory conditions have generally not met with much success. Nitazoxanide may be the first antimicrobial drug for which the mechanism of action against a small vitamin cofactor precludes development of drug resistance, a model that might hold promise with enzyme targets containing other classes of vitamin cofactors. **Fidaxomicin (OPT-80)** is a novel macrocycle which is non-absorbed systemically and has potency against anaerobes such as *C. difficile* (MICs ranging between 0.016–0.25 μg/ml) [134]. It demonstrated a clinical cure rate of 91% in a Phase II clinical trial of patients with *C. difficile* infection [135].

**Sulopenem** is an orally active penem in current clinical development and is potent against multi-drug resistant pathogens including penicillin-resistant *S. pneumoniae* and ESBL-producing Enterobactericeae ($MIC_{50}$ 0.015–0.125 μg/ml) [136]. Novel prodrugs of sulopenem exhibit *in vivo* efficacy when administered orally in three different animal infection models of organisms including $ESBL^+$ *K. pneumoniae*, *E. coli* and *H. influenzae* [137].

New **β-lactamase inhibitors** such as imidazole-substituted 6-methylidene-penem molecules have high *in vitro* activity against Class A and C β-lactamases and can be used with β-lactams as combination therapy [104]. **BAL30376** is an antimicrobial combination of monobactam **BAL19764**, Class C β-lactamase inhibitor **BAL29880** and clavulanic acid (an oxapenem, a class A β-lactamase inhibitor). It has *in vitro* activity against carbapenem-resistant strains of *P. aeruginosa*, among other multi-drug resistant gram-negative bacteria and in *in vivo* murine lethal peritonitis and sepsis models [138]. **BAL30072** is a new siderophore monobactam that bypasses porin mutations and inhibits PBPs and has broad spectrum Gram-negative activity including multidrug resistant *Acinetobacter*, *Burkholderia*, *Pseudomonas* and *Stenotrophomonas* spp. [139, 140]. **NXL104** is a small molecule that inhibits serine β-lactamases and is potent in combination with extended-spectrum cephalosporins and aztreonam against Gram negative infections (including *Klebsiella*) [141]. It is in clinical trials in combination with ceftazidime in patients with complicated urinary tract infections [142]. NXL104 is the first β-lactamase inhibitor to be studied in clinical trials since tazobactam in the 1980s. The novel bicyclic penem inhibitor, **BLI-489** has demonstrated activity as an inhibitor against Class A (including ESBLs), and Class D as well as Class C β-lactamase enzymes and *in vitro* potency of BLI-489:Piperacillin combination against several bacteria, including ESBL and AmpC producing strains, makes BLI-489 a strong candidate for further development [143].

**JNJ-Q2** is the newest member of the fluoroquinolone family of type II topoisomerase inhibitors. It is 8-fold more potent than moxifloxacin against Gram-positive pathogens,

including MRSA and levofloxacin-resistant *S. pneumoniae*. It also has Gram-negative activity against *H. influenzae*, *E. cloacae* and *K. pneumoniae* [144]. **Finafloxacin** is a novel 8-cyano fluoroquinolone exhibiting optimal activity at acidic pH and is potent against urinary tract pathogens and can be used for *H. pylori* eradication [145].

Bacterial cell division inhibition is an unexploited antibacterial target. **PC190723**, identified by structure based molecular docking, binds to FtsZ (analogous to anti-cancer drug Taxol binding to tubulin), inhibiting septum production during cell division and has activity against *S. aureus* in mice [146, 147]. Structure based design has also led to the discovery of novel pyrimidine-based compounds (**Rx100472**) with Gram positive antibacterial activity that target methionyl-tRNA synthetase (MetRS) [148]. Components of membrane biogenesis in bacteria such as FabI involved in fatty acid biosynthesis have several identified inhibitors 149. Novel aryloxy-phenol **Fab I inhibitors** derivatized from triclosan (eg. **MUT7307**) have potent Gram-positive (MIC 0.06μg/ml against MRSA) and Gram-negative activities (MIC 0.003–0.5 μg/ml) [150]. Pyrrolamides are novel DNA gyrase inhibitors discovered by structure guided design and are bactericidal againt MRSA, *S. pneumoniae* and respiratory tract pathogens, making pyrrolamides a potential drug for the treatment of nosocomial pneumonia [151]. Antimicrobial peptides (eg. **Omiganan**) with direct killing action or a host modulatory effect during innate immunity hold promise as an entirely new class of antibacterial drugs which would mitigate the growing problem of drug resistance. Several peptides and peptidomimetics are in commercial development and resolving their issues of poor pharmacokinetics and toxicity could be in sight [152]. Some other attractive antibacterial compounds include quorum-sensing blockers (such as **LED209**, read below), lipid II binding compounds, bacterial efflux pump inhibitors and bacterial 2- component signal transduction inhibitors [153].

## 3. New Targets for the Next Generation of Antimicrobial drugs

While most antimicrobial drugs in current clinical use inhibit essential processes such as protein or cell wall biosynthesis, many of these drugs are also bacteriostatic, which may contribute to development of resistance. One way of developing novel antibacterial drugs with minimal potential for resistance development could be to target bactericidal functions of bacterial proteins (eg. essential enoyl-ACP reductase FabI required for fatty acid biosynthesis) [149]. Targeting of essential proteins must take into consideration the structural constraints within substrate binding and catalytic domains and the mitigating effects of mutations on enzyme function. Alternatively, targeting virulence factors 154 or host-microbial response pathways might lead to rapid clearance of infecting organisms. An example of virulence factor based therapy arises by the recent discovery of a cholesterol reducing agent (**BPH-652**, a phosphonosulphonate) which is an inhibitor of MRSA [155]. CrtM from *S. aureus* is an enzyme required for biosynthesis of staphyloxanthin, a virulence factor which acts as an antioxidant to evade host reactive oxygen species response. Interestingly BPH-652 inhibits CrtM which is structurally related to SQS (squalene synthase), being targeted by cholesterol lowering drugs [155]. Fungi possess a nuclear receptor-like pathway that activates multi-drug resistant efflux pumps and could be a new therapeutic target against multidrug resistant pathogenic fungi 156. These examples illustrate the analogies of mammalian pathways to microbial pathways which can be targeted for therapeutic purposes. However, the drugs must be stringently designed to specifically inhibit only the bacterial target to prevent toxicity eg. novel linkers or scaffolds in bacterial proteins. Precedent exists in the design of antibacterial drugs against targets also found in humans, eg. iclaprim selectively inhibits bacterial DHFR at submicromolar concentrations with no inhibition of the human enzyme at over 5-fold higher concentrations 157.

Type III secretion system (T3SS) of Gram negative pathogens such as *Chlamydia*, *Escherichia coli*, *Pseudomonas*, *Salmonella*, *Shigella*, and *Yersinia* play an essential role in virulence by

evading the host innate immune response. Salicylidene acylhydrazines are small molecule inhibitors of T3SS that affect invasion-associated SPI1 effector proteins in *Salmonella* and the related enterobacterial flagellar motility system [158]. These small molecules were originally identified in a bacterial reporter assay as inhibitors of expression of Yop effector proteins in *Yersinia* [159]. Another interesting example of antivirulence targeting is to target bacterial defences that render it vulnerable to the host innate immune response [160]. In Gram-negative organisms, the outer bacterial membrane composed of LPS is required for resistance to complement and cationic peptides. RfaE is a core LPS biosynthesis enzyme and pathogenic *E. coli rfaE* mutants are sensitive to complement killing, but fully colonize mouse intestine. Inhibitors of RfaE have been identified that inhibit synthesis of LPS but do not affect bacterial growth. Antivirulence drugs can have an *in vivo* antibacterial effect as demonstrated by inhibitors of DltA, an enzyme which causes D-alanylation of lipotechoic acid in Gram-positive pathogens. This D-alanylation is correlated to survival of bacteria against cationic peptides, cell killing and cell invasion. Inhibitors of *Streptococcus agalactiae* and *S. pyogenes* DltA are ineffective *in vitro* unless a cationic peptide is present. In an experimental model of systemic infection of mice by *S. agalactiae*, the DltA inhibitors were able to affect the bacterial multiplication in the host, as shown by a dose dependent decrease of bacteremia. The *in vivo* antibacterial effects of the compounds were at doses that are comparable to the effective doses of classic antibacterial drugs [160]. Inhibition of signaling is another proposed strategy; a bacterial adrenergic receptor QseC histidine kinase is a target for antibacterial compound **LED209** which blocks QseC-dependent virulence gene activation in *S. typhimurium* and *Francisella tularensis* [161].

Bacterial infections such as tuberculosis are difficult to treat due to dormant bacteria that are 50-fold resistant to antibacterial drugs that target growth and division. *Mycobacterium tuberculosis* is 8-fold more sensitive to ATP synthesis inhibitors than standard anti-TB drugs, since they reduce ATP synthesis while adjusting to the hypoxic conditions while establishing an infection. Disruption of the PMF (proton motive force), by specific inhibitors, which is necessary for ATP generation, is also bactericidal [162]. **TMC207** is a novel anti-mycobacterial drug belonging to the diarylquinoline class of compounds and is an ATP synthase inhibitor [163]. In a phase II randomized clinical trial with 47 patients with newly diagnosed multi-drug resistant pulmonary tuberculosis, addition of TMC207 to the standard second-line 5 drug anti-TB regimen reduced the time of conversion to negative sputum and increased number of patients with sputum conversion (48% vs 9%) [164].

A growing trend in antimicrobial drug targets has been the host response pathways; modulating them could reduce the persistence and severity of infectious disease. The TLR (Toll-like receptor) family of proteins is activated during innate immune response and leads to production of antimicrobial peptides and activates the adaptive immune response to combat infection [165]. TLR activators and modulators could potentially have an antimicrobial role. Along the same line, macrolides such as clarithromycin have immunomodulatory properties in sepsis in experimental models and clinical trials. In a rabbit model of sepsis and acute pyelonephritis caused by multi-drug resistant *P. aeruginosa*, increased animal survival was seen upon treatment with clarithromycin which was attributed to its anti-TNFα and antioxidant properties [166]. In a clinical trial conducted in patients with sepsis due to Ventilator-associated pneumonia (VAP), intravenous clarithromycin was beneficial as it hastened resolution of VAP and prolonged life [167].

Intracellular pathogens such as *S. typhimurium* and *M. tuberculosis* are capable of activating a host kinase network around Akt/PKB by virulence factors eg. SopB [168]. Some Akt kinase inhibitors have antibacterial properties, while other inhibitors are currently in clinical trials as anticancer drugs. Kinase inhibitors are being developed as anticancer drugs because of aberrant kinase signaling in cancerous cells, however due to the importance of certain host kinases in

intracellular infection, host kinase inhibitors that specifically inhibit intracellular bacterial growth but not host cell proliferation during anticancer drug discovery will also be found. Thus, it is expected that the development of anticancer drugs against these host pathways controlled by Akt may lead to future discovery of antibacterial drugs [168]. Moreover, chronic infections sometimes lead to development of cancers eg. *Salmonella typhi* infections cause gallbladder cancer [169], *H. pylori* infections cause gastric cancer [170], and therefore development of anticancer drugs against these cancers would also lead to discovery of antibacterial inhibitors.

## 4. New Strategies for Antibacterial Drug Discovery

Most of the current antibacterial drugs were discovered between 1940 and 1980 by traditional approaches which are now saturated, and the emergence of drug resistance as well as the emergence of new pathogens calls for new strategies in antibacterial drug discovery due to the inadequacies of screening libraries for novel antibacterial compounds as described in this section [171]. Antibacterial drugs have unique physicochemical properties which are dependent on their spectrum of activity [172]. Natural products are proposed to be an optimal antibacterial drug screening library as they have optimal cellular penetration and privileged structures to interact with finite structural spaces in protein folds [173]. Identifying feasible drug targets given the vast microbial genomics information by comparing different pathogen genomes and narrowing the targets based on essentiality, novelty of target or mechanism, absence of human homolog and low likelihood of resistance development is a failed strategy, and requires a chemically diverse compound collection [171]. Improving the quality of synthetic libraries by using core scaffolds to introduce natural product like characteristics could be a way to generate a chemically diverse compound collection. Comparative bacterial genomics has yielded knowledge of previously unknown biosynthetic pathways absent in humans which can be specifically targeted to discover antibacterial drugs for a specific microbe [174]. New microbial species from marine sediments or associated with plants are an untapped source of novel antibacterial drugs [175]. Harnessing “unculturable” micro-organisms in the laboratory has yielded novel quinone and glycosylated macrolactam antibacterial drugs [176]. A new trend in antibacterial drug discovery is the resurrection of undeveloped antibacterial drugs and overcoming their previously attributed physicochemical/pharmacokinetic deficiencies [175]. One such example is the increasing use of colistin, a polymyxin antibiotic, as a last-line therapeutic option in critically ill patients despite nephrotoxicity, because of its efficacy against multi-drug resistant *P. aeruginosa* and *A. baumanii* infections [177–179]. However, modern clinical trials would provide insight into the dosing regimen and the extent of adverse effects.

Discovery of lytic phages specific to pathogenic bacteria especially MRSA has potential as natural and ecological treatment against pathogens [180]. Systemic administration of bacteriophage therapy is efficacious in a mouse *Burkholderia cepacia* lung infection model 181. Inactivation of antibacterial drugs by enzymatic hydrolysis or formation of inactive derivatives causes widespread drug resistance 182. This natural phenomenon has been taken advantage of in the following strategy and follows the principle of antibacterial drug conservation: A combination of β-lactamase enzyme and a β-lactam antibacterial drug can significantly reduce emergence of resistant microbes 183. In a Phase II study of 112 patients treated for serious respiratory infections, 54 patients treated with P1A (β-lactamase product) and ampicillin had a 20% change in gut microflora compared to 50% in patients treated with ampicillin alone 180. The β-lactamase would inactivate any unused β-lactam antibacterial drug in the GI tract, thus maintaining the gut microflora. Emergence of ampicillin resistance was also 7-fold lower in patients treated with the enzyme/lactam combination compared to antibacterial drug alone 180. Another strategy would be if antibacterial drugs were engineered (prodrug or anti-antibacterial drug) such that a highly potent drug would result upon enzymatic action within a microbe, then common resistance mechanisms could be bypassed.

Antibacterial drugs could also be engineered to introduce two pharmacophores for high potency against two targets. Examples of such hybrid antibacterial drugs include the mutilin-quinolone hybrid **AM-3005** which is a Type II topoisomerase inhibitor and also a protein synthesis inhibitor [184]. **CBR-2092** is a rifamycin-quinolone hybrid which is a RNA polymerase inhibitor and also a DNA gyrase and topoisomerase IV inhibitor and demonstrates potency against gram positive cocci [185, 186]. Improved formulations of alternative drug delivery methods such as inhaled anti-infectives (**Amikacin** nanoscale liposome formulation) show potential for treatment of chronic *P. aeruginosa* lung infections in cystic fibrosis patients by offering advantages such as biofilm penetration and sustained release from liposomes [187]. MP-376 is a new formulation of levofloxacin for inhalation and is effective in mouse models of acute and chronic lung infections caused by *P. aeruginosa.* The high concentrations of drug delivered to the lung tissue causes increased bacterial clearance than inhaled tobramycin or aztreonam leading to increased mice survival [188]. Inhaled ciprofloxacin/levofloxacin is in phase II clinical trials for chronic lung infections in cystic fibrosis patients [189, 190].

Passive immunization is a strategy which activates the host immune response leading to pathogen clearance by attacking the organism directly, enhancing phagocytosis or altering the immune system, but this strategy is yet to encounter success in clinical trials [191]. Finally, host factors/ enzymes that play an important role in host innate immunity could be engineered for stability and used for antimicrobial therapy.

## 5. Conclusion

The number of new antibacterial medicines entering the clinic has been declining for years, while the emergence of drug resistance and especially multi-drug resistance continues to rise at an alarming rate 1. The more traditional approaches of generating new derivatives of old drugs or finding new ecosystems to mine for natural products are giving way to more innovative non-traditional strategies to develop next generation drugs 154, 175, [176]. The future does not seem bleak as several promising antibacterial drugs with novel mechanisms of action are in development and new types of targets (Type III secretion systems) have emerged [158]. The scourge of drug resistance in microbes will have to be fully understood and the choice of “good targets”, both new and old will be vital to the discovery of new antibacterial drugs as we progress forward into the 21st century.

## 6. Expert Opinion

Finally, since anti-infective research over the past 15 years has underperformed other therapeutic areas, there is little incentive to throw good money after bad. Since the new biology “genomics” has failed, augmented by development of resistance to antibacterial drugs in a short time period compared to decades of drug development and short courses of infectious disease treatment, there is considerable reluctance by the industry to initiate new strategies 192. In the absence of the pharmaceutical industry, it is now left to government sponsored research in universities and small biotech companies to produce next generation therapeutics. However, the pace of discovery in these venues will be slow when compared with the resource rich pharmaceutical industry. If society regards new life saving medicines as beneficial, then should society contribute to such discovery efforts? In an attempt to bridge this issue, as an incentive, the U.S. Congress proposed a 2-year wild card patent extension on existing blockbuster drugs to increase protected sales; and, under the US Bioshield II legislation, a drug company would qualify for a wildcard patent if the antimicrobial is licensed for military or antiterrorism use 5. The revenue from such sales would support an antimicrobial development program. The STAAR (Strategies to Address Antimicrobial Resistance) Act, a recent public health bill was introduced in November 2007 in the U.S. Senate and addresses management and monitoring of antimicrobial resistance, prevention and control and increasing federal funding for research

and development of new antibacterial drugs [193]. The Infectious Diseases Society of America's Antimicrobial Availability Taskforce (AATF) has reported a lack of antimicrobials for emerging pathogens as well as those displaying multi-drug resistance 3. While the antibacterial drug market is expected to grow to over US$ 45.0 billion by 2012, worldwide, 2 advances in other areas of medicine will contribute to an ever increasing population of individuals susceptible to infectious disease that will drive up demand, and the need for newer and better antibacterial drugs will continue to rise.

In view of the fact that new compounds for multi-drug resistant Gram-negative bacilli (MDRGNB) will unlikely be available for more than 10 years, infection control measures to limit spread of these organisms within institutions, and potentially into the community, are paramount. In addition, antimicrobial stewardship programs should be put in place to preserve the few remaining compounds with some activity against MDRGNB, e.g. colistin or tigecycline etc, through surveillance, monitoring, and restriction policies at all inpatient facilities.

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**Table 1**

Overview of new analogs of existing antibacterial drug classes

| CLASS OF COMPOUND | PHASE OF DEVELOPMENT | ANALOGS | MECHANISM OF ACTION | SPECTRUM OF ACTIVITY | RESISTANCE MECHANISM | DRUG COMPANY |
|---|---|---|---|---|---|---|
| Oxazolidinones | FDA Approved 2000 | Linezolid, Radezolid, Torezolid, RWJ-416457 | Inhibits protein translation (initiation/elongation) | Gram -positives, some anaerobes, *M. tuberculosis* | rRNA mutations | Pfizer, Rib-X, Trius Therapeutics, Johnson & Johnson |
| Glycopeptides | Phase III | Oritavancin, Dalbavancin, Telavancin | Inhibit peptidoglycan biosysnthesis/ transglycosylation | Gram-positive | unidentified | Targanta/The Medicines Co., Pfizer, Theravance |
| Ketolides | Phase III | Cethromycin | Inhibits protein synthesis | Gram-positive | rRNA dimethylation, ribosomal protein mutations | Advanced Life Sciences |
| Glycylcyclines | FDA Approved 2005 | Tigecycline, PTK0796 | Inhibits protein synthesis | Gram- positive, Gram- negative, aerobes, anaerobes | Efflux pumps | Wyeth, Paratek Pharmaceuticals |
| Carbapenems | FDA Approved 2007 | Doripenem, Razupenem | Inhibits peptidoglycan biosynthesis | Gram-positive, Gram-negative, anaerobes | Carbapenemases, Efflux pumps, Porin mutations | Johnson & Johnson, Protez Pharmaceuticals |
| Streptogramins | Phase II | NXL103/XRP2868 | Inhibits protein translation | Gram-positive, Gram-negative | unidentified | Novexel |
| Fluoroquinolones | Preclinical | JNJ-Q2, finafloxacin | Inhibit type II topoisomerase | Gram-positive, Gram-negative | gyrA, parC mutations | Johnson & Johnson, MerLion Pharmaceuticals |

**Table 2**

Overview of new antibacterial drugs in development with novel mechanism of action

| DRUG NAME | TARGET/ MECHANISM OF ACTION | SPECTRUM OF ACTIVITY | PHASE OF DEVELOPMENT | DRUG COMPANY OR INNOVATOR |
|---|---|---|---|---|
| Ceftobiprole | Tight binding to PBP2a | Gram-positive, Gram-negative | Phase III | Johnson & Johnson |
| Ceftaroline | Tight binding to PBP2a | Gram-positive, Gram-negative | Phase III | Forrest Laboratories |
| Iclaprim | Increased affinity to bacterial DHFR | Gram-positive, Gram-negative | Phase III | Arpida |
| Sulopenem | Binding to PBPs | Gram-negative | preclinical | Pfizer |
| BAL30376 | Monobactam/β-lactamase inhibitor combination | Multi-drug resistant Gram-negative | preclinical | Basilea |
| Rx100472 | Methionyl tRNA synthetase inhibitor | Gram-positive | preclinical | Trius Therapeutics |
| PC190723 | Cell division protein FtsZ | *S. aureus* | preclinical | Prolysis |
| MUT7307 | Enoyl-ACP FabI reductase (fatty acid biosynthesis) | Gram-positive, Gram-negative | preclinical | Mutabilis |
| Nitazoxanide | Inhibits vitamin cofactor of pyruvate:ferredoxin oxidoreductase (PFOR) | *C. difficile* | Phase II | Romark Laboratories |
| Fidaxomicin (OPT-80) | Inhibits RNA synthesis | *C. difficile* | Phase II | Optimer Pharmaceuticals |
| LED209 | Quorum sensing | *S. typhimurium* *F. tularensis* | preclinical | University of Texas South Western Medical Center, Dallas |
| BPH652 | Virulence factor (antioxidant) | MRSA | preclinical | University of Illinois, Chicago |
| Omiganan | Antimicrobial peptide; Depolarizes cytoplasmic membrane of bacteria | Gram-positive, fungi | Phase III | MIGENIX, Cadence pharmaceuticals |
| TMC207 | ATP synthase inhibition | *M. tuberculosis* | Phase II | Johnson & Johnson, Tibotec |
| CBR2092 | Dual pharmacophore | Gram-positive | Phase I | Cumbre |
| Amikacin | Novel drug delivery: inhaled nano-liposomes | *P. aeruginosa* biofilm | Phase II | Transave Inc. |

## Table 3

Newer Glycopeptides

| | **Dalbavancin** | **Telavancin** | **Oritavancin** |
|---|---|---|---|
| Potency against Vancomycin resistant microbes | VRE (VanB, VanC) | VISA/hVISA, VRE (VanB) | VRE (VanA, VanB), VRSA, VISA, hVISA |
| MIC range (μg/ml) | 0.03–0.25 | 0.125–1, 0.06–2 | 0.008–0.5, 0.12–1, 0.5–4, 0.12–2 |
| Reference for MICs | 38 | 40, 56 | 42, 44 |

VRE: Vancomycin-resistant enterococci; VISA: Vancomycin-intermediate *S. aureus*; hVISA: heterogenous Vancomycin-intermediate *S. aureus* VRSA: Vancomycin-resistant *S. aureus*