

New antibiotics for antibiotic-resistant bacteria

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Abstract

The need for new antibiotics to effectively treat antibiotic-resistant infections remains unfulfilled. Despite the well-publicised concern over this issue, only two novel antibiotic classes have been introduced in the past 20 years alongside several new agents of existing classes. Accordingly, the current antibiotic armoury remains inadequate to meet the challenges posed by resistance today. More worryingly, there are very few new agents being developed that can be expected to replace existing antibiotics that succumb to the rising tide of resistance.

Introduction and context

Antibiotic resistance among pathogenic bacteria is a well-documented phenomenon that has severe consequences for the treatment of infections in the hospital setting and increasingly in the community. The Infectious Diseases Society of America recently published a hit list of bacterial pathogens [1] whose antibiotic resistance severely impacts the ability to treat infections in the US hospital setting. This list is comprised of *Staphylococcus aureus*, *Enterococcus faecium*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Enterobacter* spp. In addition, the emergence of community-acquired methicillin-resistant *S. aureus* (MRSA) [2] and extensively drug-resistant (XDR) *Mycobacterium tuberculosis* [3] demonstrates that problematic resistance is not limited to the confines of the hospital. This article attempts to evaluate recent therapeutic options available for the treatment of resistant infections and the progress being made in terms of discovery and development of the next generation of antibacterials that will be relied upon for treating such infections in the next decade.

Major recent advances

Current antibiotics

The emergence of MRSA and vancomycin-resistant enterococci (VRE) highlighted an urgent need for novel antibiotics that are not affected by existing mechanisms of resistance. In this decade, two antibacterials that

belong to new classes - linezolid (an oxazolidinone) and daptomycin (a lipopeptide) - were approved and have offered new options for the treatment of, for example, complicated skin and skin structure infections (cSSSIs) caused by resistant Gram-positive pathogens.

In addition, there are a few new agents that soon could be introduced for the treatment of Gram-positive infections in the hospital. The glycopeptide telavancin has been recommended for US Food and Drug Administration (FDA) approval for cSSSI [4] and currently is also being investigated for nosocomial pneumonia. Unfortunately, at the same time, several other pre-registration candidates - oritavancin, ceftobiprole, and iclaprim - have not yet received the same recommendation.

These new antibiotics emerged against a backdrop of reduced activity in the area of antibiotic discovery. Only five new antibiotics were approved from 2003 to 2007, compared with 16 in the period from 1983 to 1987 [1]. It is perhaps not surprising that there are a number of weak points in the current range of available antibiotics for the treatment Gram-positive infections, due to limitations in either efficacy or tolerability. Such therapeutic gaps include enterococcal bloodstream infections [5], oral drugs for infections due to community-acquired MRSA [6], and efficacy of treatment for invasive infections of critically ill patients [7].

The situation for the treatment of Gram-negative infections is even bleaker [8]. The reason for the especially slow introduction of new compounds may be in the inherent difficulties in discovering anti-Gram-negative agents. The impermeable nature of the Gram-negative envelope and presence of multiple efflux pumps in combination with other resistance mechanisms conspire to increase the difficulty of this task [9].

A few licensed antibiotics do hold some promise as Gram-negative therapies. Doripenem is a new-generation carbapenem that has demonstrated clinical efficacy against *P. aeruginosa* in investigational trials, and tigecycline is currently under investigation for *A. baumannii* infection [8]. Additionally, ceftobiprole could potentially become comparable to the intravenous cephalosporins (for example, ceftazidime) as a therapy against *P. aeruginosa* infection. However, it will be some years before the clinical efficacy of these agents in the face of existing and evolving resistance mechanisms is understood.

Future antibiotics

If the rise and spread of antibiotic resistance continue to follow the same worrying trend, it is reasonable to assume that resistance to the newer antibiotics will emerge. Reduced susceptibility to linezolid [10] and daptomycin [11] has already been encountered in the clinical setting. Given that (even despite prudent usage) the life span of a new antibiotic will be limited by emerging resistance, it is vital to have a continuous pipeline of new antibiotics in place that are not affected by existing resistance mechanisms. A number of

antibiotics that are currently in development to reach the market in 2011 to 2013 are listed in Table 1.

It is striking that all of the listed development compounds belong to established antibiotic classes to which resistance is already prevalent among key pathogens. These nevertheless may offer advantages over their predecessors in terms of safety, tolerability, pharmacokinetics (dosing), and antibacterial spectrum or improvements in potency with the potential to overcome at least some of the resistance problems originally attributed to that class. By way of example, there appears to be renewed interest in new quinolone antibiotics. The approaches involved vary and include testing of more potent quinolones to overcome resistance (for example, delafloxacin and nemonoxacin) or investigating more specialised indications (for example, finafloxacin for *Helicobacter pylori* eradication and WCK771 as an intravenous MRSA active quinolone).

Also of note is that there are no new agents in development for tuberculosis (TB). Current investigations into new treatments are focused on using antibiotics of existing classes that have not yet been used against TB. Fluoroquinolones and linezolid are two such examples [12]. Whether these options will provide a long-term solution for XDR TB is uncertain and clearly much more needs to be done to prevent this disease becoming untreatable.

Future directions

The current shortage of effective antibiotics and the lack of novel agents in development imply that future treatment strategies for resistant bacteria may have to

Table 1. Development pipeline for antibiotics in phase II clinical trials and beyond

Product	Class	Main segment	Status	Indication
Delafloxacin	Quinolone	Hospital	Phase II	CAP, SSSI
Nemonoxacin	Quinolone	Community	Phase II	CAP, DFI
WCK 771	Quinolone	Hospital	Phase II	SSSI
Finafloxacin	Quinolone	Specialised indication	Phase II	<i>Helicobacter pylori</i> , UTI
PZ-601	β -lactam	Hospital	Phase II	SSSI
NXL 104/ceftazidime	β -lactamase inhibitor	Hospital	Phase II	cUTI, cIAI
Ceftaroline	β -lactam	Hospital	Phase III	CAP, SSSI
Oritavancin	Glycopeptide	Hospital	Phase III	SSSI
Dalbavancin	Glycopeptide	Hospital	Phase III	SSSI, CR-BSI
Telavancin	Glycopeptide	Hospital	Phase III	SSSI, HAP
PTK0796	Glycylcycline	Hospital	Phase III	CAP, SSSI
Iclaprim	Trimethoprim	Hospital	Phase III	SSSI, HAP
Torezolid	Oxazolidinone	Hospital	Phase II	SSSI
Radezolid	Oxazolidinone	Hospital	Phase II	CAP, SSSI
Cethromycin	Macro-/ketolide	Community	Phase III	CAP
NXL 103	Streptogramin	Community	Phase II	SSSI, CAP

CAP, community-acquired pneumonia; cIAI, complicated intra-abdominal infection; CR-BSI, catheter-related bloodstream infection; cUTI, complicated urinary tract infection; DFI, diabetic foot infection; HAP, hospital-acquired pneumonia; SSSI, skin and skin structure infection; UTI, urinary tract infection.

rely on therapeutic approaches that disable existing resistance mechanisms. Inhibitors of extended-spectrum β -lactamases (ESBLs) could improve the life span of existing or new β -lactams; one such example is ESBL inhibitor NXL 104, which is currently under investigation in combination with ceftazidime [12] and in the future will be investigated in combination with ceftazoline [13]. Another interesting approach has been taken by Mpex Pharmaceuticals (San Diego, CA, USA), whose efflux pump inhibitor technology could one day offer a substantial improvement to the treatment of Gram-negative infections [14].

Despite the relatively recent introduction of two new antibacterial classes, the current range of treatment options for infections caused by antibiotic-resistant bacteria is far from adequate. Most of the recent advances have been for infections caused by Gram-positive bacteria; however, there are still large gaps in the therapeutic scope of these new drugs. Neglect in the areas of Gram-negative and TB antibacterial discovery has opened a potential window in which certain infections may become untreatable before new drugs become available.

It is clear that antibiotic resistance will continue to emerge and spread and that sustained research efforts to identify and develop new therapeutic options are required in order just to keep pace with the bacteria. The situation we face with resistance today and, more importantly, in the future will be manageable only with considerable efforts from the research community, pharmaceutical industry, and regulatory bodies, to improve the productivity of new antibiotics and treatment options for resistant bacteria.

Abbreviations

cSSSI, complicated skin and skin structure infection; ESBL, extended-spectrum β -lactamase; FDA, Food and Drug Administration; MRSA, methicillin-resistant *Staphylococcus aureus*; TB, tuberculosis; VRE, vancomycin-resistant enterococci; XDR, extensively drug-resistant.

Competing interests

WS is an employee of MerLion Pharmaceuticals Pte Ltd (Singapore); HL is an employee of MerLion Pharmaceuticals GmbH (Berlin, Germany) and holds stock options in MerLion Pharmaceuticals Pte Ltd (Singapore).

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