Review Article

New and promising anti-bacterials: Can this promise be sustained?

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Abstract

The World Health Organization (WHO) announced antimicrobial resistance (AMR) as a major threat to public health which requires that new antimicrobials need to be developed faster than ever before. The rapid development of resistance has rendered many promising antibacterials useless in treating critically ill patients. This article discusses new antibacterials, which got Food and Drug Administration (FDA) approval in the last few years, along with their key pharmacokinetic and pharmacodynamic (PK/PD) advantages, added antimicrobial spectrum, indications, strengths and weaknesses of these drugs from an intensivist point of view. A brief mention has been made on antimicrobial peptides (AMPs), bacteriophages and nanoparticles, which are likely to dominate the future of antibacterials. Finally, it must be understood that the battle against AMR can only be won by a combination of innovative therapies, good infection control practices, strong antibiotic stewardship in the hands of informed healthcare workers.

Keywords: Antimicrobial resistance, critically ill, new antibacterials, pharmacodynamics, pharmacokinetics

Introduction

The advent of antibacterials heralded an important victory of mankind against disease and death. The timeline of antibacterials began with Alexander Fleming's serendipitous discovery of penicillin, and was followed by a period of rapid growth (till the 1970s') when streptomycin, sulphonamides, tetracyclines and fluoroquinolones were discovered.[1] Following this golden era, the discovery of newer antibacterials went hand in hand with the emergence of resistance mechanisms. The appearance of resistant strains followed the discovery of drugs in quick succession, such as penicillin resistant *Staphylococcus aureus* in 1940 and beta-lactamases isolated in Greece (TEM1,2) in 1948, soon after penicillin had come to clinical use.[1] Figure 1 depicts the discovery of antibacterials along with appearance of resistant strains. The appearance of extended spectrum beta-lactamases (ESBL) which are resistant to penicillin and cephalosporins; metallo-betalactamases (MBL) which are resistant to carbapenems, and later followed by Klebsiella pneumoniae carbapenemase (KPC) have threatened the clinical utility of antibacterials against gram negative micro organisms in developing countries.[2] Although methicillin-resistant *Staphylococcus aureus* (MRSA) is a major threat to antimicrobial resistance in developed countries it is of less concern in developing countries where infections due to gram negative bacteria (GNB) predominate.[3] Vancomycin resistant enterococci (VRE) are

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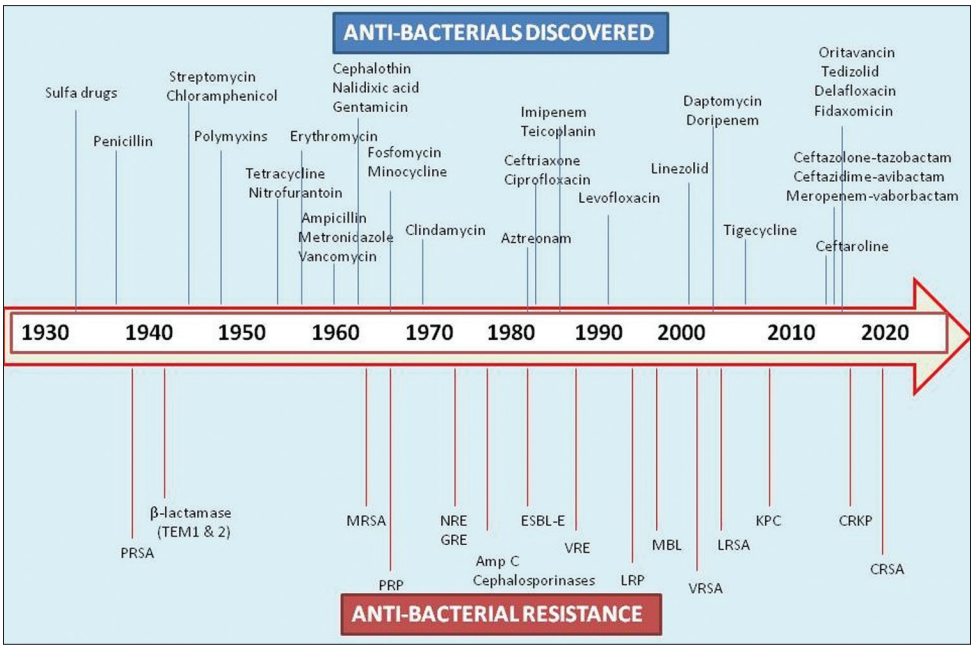

Figure 1: Time line of anti-bacterials discovery and development of resistance. Annexure to Figure 1 of new and promising anti-bacterials. PRSA = penicillin resistant *Staphylococcus aureus*; MRSA: methicillin resistant staphylococcus aureus; PRP = penicillin resistant pneumococcus; NRE = nalidixic acid resistant enterococci; GRE = gentamicin resistant enterococci; ESBL-E = ESBL producing Enterobacteriaceae; VRE = vancomycin resistant enterococci; LRP = Levofloxacin resistant pneumococcus; MBL = metallo β-lactamases; VRSA = vancomycin resistant *staphylococcus aureus*; LRSA = Linezolid resistant *staphylococcus aureus*; KPC = Klebsiella pneumoniae producing carbapenamases CRKP = Colistin resistant Klebsiella pneumoniae; CRSA = Ceftaroline resistant *staphylococcus aureus*

also an important cause of healthcare associated infections for which treatment options need to be developed.[4] Fewer new antibacterials are being added in the last two decades – from 37 drugs in 1983-93 to 18 drugs in 1993-2003, with a progressive decline thereafter.[5] The present times have witnessed a revival of antimicrobials discovered before the 1970s—fosfomycin, minocycline and polymyxin—which have shown efficacy against the extensively drug resistant microbes (XDR) causing infections in intensive care units.[6] Worsening anti-microbial resistance (AMR) has forced innovative, yet disturbing strategies such as the use of suicidal agents like the double-carbapenem-based therapy in which ertapenem is being used as suicidal drug against KPC producing organisms.[7] Another example of an innovative strategy to counter AMR is stool transplantation (fecal microbiota transplantation) in recurrent *Clostridium difficile* infection.[8] Viruses (bacteriophage therapy),[9] plants (aromatic polyketolides)[10] and nanometals[11] are vying for a future role as antibacterials. AMR has been highlighted as a major threat by World Health Organization (WHO).[12]

This review highlights recent promising antibacterials – drugs which are Food and Drug Administration (FDA) approved after phase 3 randomized double-blinded non-inferiority trials.[13] The article highlights the added antimicrobial spectrum, pharmacokinetic and pharmacodynamic (PK/PD) advantages along with prescribed dosage, indications, strengths and weaknesses of these drugs along with landmark trials from an intensivist point of view [Table 1].

Antibacterials against Gram Positive Micro-organisms

Lipoglycopeptides

Dalbavancin and oritavancin are further modified glycopeptides (vancomycin and teicoplanin) with addition of lipid chain which confers the advantage of extended elimination half time of the drug. These drugs do not require drug concentration monitoring, need to be prescribed only once (or repeat doses weekly) and circumvent problems of drug compliance and prolonged requirement of invasive lines.[14] There is no necessity of dosage adjustment in renal and hepatic failure. These drugs are active against VRE (non-vanA mediated) including daptomycin- resistant species, MRSA (mec A and mec C), and some vancomycin intermediate *Staphylococcus aureus* and heteroresistant species (VISA/hVISA). Dalbavancin was non-inferior to vancomycin and linezolid when used for acute bacterial skin and skin structure infections (ABSSI) as in DISCOVER 1 and DISCOVER 2 studies.[15]

5th generation cephalosporins

The mechanism of penicillin resistance in *Staphylococococcus aureus* is predominantly by reducing binding affinity to penicillin binding proteins (PBP's), especially PBP2a.[16] This is circumvented by the new fifth generation

Table 1: Comparative table of new and promising antibacterials

Name of the anti-bacterial	Oritavancin	Dalbavancin	Ceftaroline fosamil	Tedizolid	Delafloxacin	Fidaxomicin	Ceftolozane-Tazobactam	Ceftazidime-avibactam	Meropenem-vaborbactam
Added antimicrobial spectrum	VRE (non-van A mediated) including Daptomycin resistant; MRSA (mec A and mec C); VRSA and some VISA/hVISA		MRSA E. faecalis	NIL	NIL	Narrowed spectrum to *C .difficile*	CRPA > CRAB, CRE	CRE > CRPA and other KPC producing CRE	KPC producing CRE
PK/PD advantage	$t_{1/2}$: >250 h	$t_{1/2}$: >350 h	NIL	$t_{1/2}$: 12 h → Once daily dosage	Weak acidic property (↑ intracellular penetration and active in acidic pH). Clearance by non-renal pathways	Bactericidal property	NIL	Covalent reversible binding to serine β lactamases leading to increased potency	Covalent adduct formation between serine side of β-lactamase and Boron atom leading to destabilization of enzyme
Dose	1200 mg IV one dose	1000 mg first dos e followed by 500 mg on day 8	600 mg IV Q12H	200 mg IV (lyophilized powder) or E/R for 6 days	300 mg IV Q 12 h 450 mg E/R Q 12 h	200 mg Q 12 h through E/R route	3 g (2+1) Q8h	2.5 g [2+0.5] I.V Q8h	2+2 gm IV Q 8 h
Indications(FDA Approved)	ABSSI	ABSSI	ABSSI	ABSSI	ABSSI	CDI even first episode and first recurrence Severe CDI	c-IAI (with Metronidazole) c-UTI	c-IAI (with Metronidazole) c-UTI HAP VAP	c-UTI
Strengths	Long $et_{1/2}$ No dose adjustments in renal and hepatic failure No TDM requirement		Activity against MRSA with increased binding to PBP2a	↓myelosuppression ↓MAO inhibition ↓peripheral and optic neuropathy ↓lactic acidosis Not inactivated by cfr methyltransferase	Minimal QTc prolongation Very low frequency of spontaneous mutations Less dose modification in renal failure	Minimal systemic absorption High fecal concentrations with prolonged post antibiotic effect Limited activity on gut microbiota	Ambler class C (Amp C enzymes)	Active against KPC producing bacteria Active against few class D (OXA-24,48) enzymes	Active against KPC producing bacteria Active against few class D (OXA-24,48) enzymes
Weaknesses	Only IV route Cost		Not active against E. faecium, VRE, ESBL-E	Bacteriostatic Cost	Hypersensitivity like other FQ	Cost	Not active against MBL and KPC producing microbes	Not active against MBL Not active against CRAB	Not active against MBL

PK/PD=Pharmacokinetic and pharmacodynamic; FDA=Food and Drug administration; VRE=vancomycin resistant enterococci; MRSA=methicillin resistant staphylococcus aureus; VRSA=vancomycin resistant staphylococcus aureus; VISA=vancomycin intermediate staphylococcus aureus; hVISA=hetero-resistant staphylococcus aureus; E. faecalis=Enterococcus feacalis; E. faecium=Enterococcus faecium; ABSSI=acute bacterial skin and skin structure infection; TDM=therapeutic drug monitoring; $et_{1/2}$=elimination half time; ESBL-E=ESBL producing Enterobacteriaceae; FQ=fluroquinolone; CDI=Clostridium difficile infection; CRPA=Carbapenem resistant Pseudomonas aeruginosa; CRAB=Carbapenem resistant Acinetobacter baumannii; KPC=Klebsiella pneumoniae producing carbapenamases; IV=intravenous; E/R=enteral route; Q 12 h=every 12 hours; Q24 h=once in every 24 h; Q8 h=every 8 hours; c-IAI=complicated intraabdominal infection; c-UTI=complicated urinary tract infection; MBL=metallo β-lactamases; HAP=hospital acquired pneumonia; VAP=ventilator associated pneumonia; ↓ = decreased

cephalosporins, ceftaroline and ceftabiprole with increased binding to PBP2a. When compared to a combination of vancomycin and aztreonam in complicated skin and soft tissue infections, ceftaroline fosamil acheived higher clinical cure and microbiological success rates.[15] Ceftaroline also demonstrated good tolerability and success rates[17] in treating hospital acquired pneumonia. An important limitation of these drugs is their lack of activity on *Enterococcus faecium (E. faecium)* and ESBL-E (ESBL producing Enterobacteriaceae).

Tedizolid

This oxazolidinone has a number of PK/PD advantages over linezolid such as availability as a lyophilized suspension and $et_{1/2}$ of 12 hours (compared to linezolid $et_{1/2}$ of 5-6 hours), which allows for once daily dosing. Linezolid accounts for around 600 ml volume infusion per day which can be reduced with the lyophilized preparation of this drug.[14] Moreover, mitochondrial toxicity (lactic acidosis) seen with prolonged linezolid therapy and myelosuppresion are less frequently observed. Tedizolid has a lower risk of drug interaction with catecholamines, and precipitating serotonin syndrome due to monoamine oxidase inhibition when compared with linezolid. The enzyme cfr methytransferase accounts for development of resistance to linezolid therapy in MRSA, but does not reduce tedizolid concentrations. This drug has shown promising results in the setting of ABSSI and pneumonia due to MRSA.[18] However, like its predecessor, tedizolid shares the limitation of being bacteriostatic.

Delafloxacin

Delafloxacin has been developed by removing a protanatable substituent (anionic fluroquinolone) making it weakly acidic, thereby conferring the drug with enhanced intracellular penetration along with heightened bactericidal activity.[19] Another unique property of delafloxacin is "balanced target enzyme inhibition" – both DNA gyrase (usual target in gram negative bacteria) and topoisomerase IV (usual target in gram positive infections) are equally inhibited, which limits the frequency of spontaneous mutations leading to development of resistance during the therapy. The PK/PD advantages are its major metabolism through glucuronidation, which is less affected in critically ill patients when compared to phase 1 reactions (oxidation, reduction and hydrolysis) and non-renal clearance accounting for 35-50% of drug elimination leading to lesser dose modifications in renal failure. This drug was non-inferior to a combination of vancomycin and aztreonam in ABSSI with fewer adverse effects leading to drug discontinuation.[20]

Fidaxomicin, Actoxumab and Bezlotoxumab

Fidaxomicin, a macrocyclic antibiotic has revolutionized the management of *Clostridium difficile* infection (CDI) due to its bactericidal property against C. *difficile*, unlike vancomycin and metronidazole which are bacteriostatic.[13] This drug is 8-10 times more potent than vancomycin with minimal systemic absorption and achieving high colonic concentrations after enteral absorption along with prolonged post antibiotic effect. This drug is active against resistant strains of C. *difficile* (NAP1/BI/027).[21] The Infectious Disease Society of America (IDSA) revised their guideline in 2017 to include fidaxomicin as the first line option in severe CDI and first recurrence, replacing the previous role of metronidazole.[22] Fidaxomicin had better cure rates and lower recurrence, when compared with vancomycin in acute CDI as reported by Louie *et al*.[23] Further advancement in the management of CDI (apart from fecal microbiota transplant) is the development of humanized monoclonal antibodies targeting toxin A (actoxumab) and toxin B (bezlotoxumab) respectively.[24] Bezlotoxumab therapy has shown promising results in reducing recurrence rates, when compared to combination therapy and actoxumab therapy alone, in MODIFY I and MODIFY II trials.[24] This shows that inhibiting the toxin to bind to the cell (toxin B) by bezlotoxumab halts the key step in the pathogenesis of CDI, providing an alternative/bridge to FMT in recurrent CDI. The PK/PD advantage of this antibody is its long $t_{1/2}$ (19 days) leading to single dose of 10 mg/kg intravenous dosage which can prevent recurrence upto 12 weeks.[24]

Antibacterials against Gram Negative Micro-organisms

New betalactam/betalactamase inhibitors (BL-BLI)

Tazobactam based BL-BLI combinations can inhibit few beta lactamases like 2a, 2b, 2be, 2c, 2e which belong to group 2 in Bush-Jacoby classification or Ambler class A and few class D or group 2 (2d and 2de) enzymes.[25] For efficacy against carbapenem resistant *Pseudomonas aeruginosa* (CRPA), ceftolozone, a third generation anti-pseudomonal cephalosporin with more potency than other anti-pseudomonal cephalosporins is paired with tazobactam.[26] This drug demonstrates activity against Ambler class C (Amp C) enzymes which are traditionally not inhibited tazobactam combinations, and also shows efficacy in treating infections due to ESBL-E and CRPA.[27] Ceftolozone-tazobactam was non-inferior in treating complicated intra-abdominal infections[28] and complicated urinary tract infections[29] when compared with meropenem and levofloxacin, respectively. The main limitation of this combination is its lack of activity on KPC. This problem has been circumvented by the development of ceftazidime-avibactam combination.[25] Avibactam has higher potency than other BLIs due to its covalent reversible binding property to serine

β lactamases.[26] This drug holds promise in carbapenem resistant Enterobacteriaceae (CRE) infections, albeit with lower activity against CRPA. Ceftazidime-avibactam has also demonstrated activity on few class D (OXA-24,48) enzymes, not seen with previous BL-BLI combinations. This drug was tested in combination with metronidazole in patients with complicated intra-abdominal infections in two non-inferiority studies, RECLAIM 1 and 2, and showed comparable cure rates to meropenem.[30] Similar results have been reported in treating complicated urinary tract infections as well.[31] This BL-BLI may have a role as carbapenem-alternatives in the management of hospital-acquired and ventilator-associated pneumonias, as evaluated in the REPROVE study.[32] The Achilles' heel of this drug is its lack of activity against metallo-betalactamases (MBL).

Carbapenem- betalactamase inhibitors (C-BLI)

Meropenem-vaborbactam is a new C-BLI which has been evaluated in TANGO trial with piperacillin-tazobactam in c-UTI which has shown promising results.[33] The unique structure of vaborbactam with a boron side chain leads to the formation of covalent adduct formed between serine side of β-lactamase and Boron atom causing destabilization of the KPC enzyme.[25] Inhibition of few class D enzymes (OXA-24,48) and lack of activity against MBL are features that this drug shares with ceftaroline-tazobactam previously discussed. The other C-BLI is imipenem-relebactam, which is yet to be approved by the FDA.

Antibacterials for Future

Recently, there has been renewed focus on developing alternative antibacterials with inherently lower risks of resistance. These include antimicrobial peptides (AMPs), bacteriophages and nanoparticles. It is likely that some of these may find active clinical use as future antibacterial therapies.[1]

Antimicrobial peptides

Biofilm formation plays an important role in various hospital acquired infections like catheter associated urinary tract infection (CAUTI), VAP and central line associated blood stream infection (CLABSI). "Quorum sensing" is a form of molecular communication in bacteria, which enhances virulence.[34] "Communication molecules" such as acyl-homoserine lactone in gram negative bacteria (GNB) and oligopeptides in gram positive bacteria (GPB) are the targets of these AMPs, respectively.[35] The exact mechanism of action of these AMPs is not yet fully understood although they may have predominant activity on cytoplasmic membrane and intracellular structures. Specifically targeted anti-microbial peptides (STAMPs) are modified AMPs in which the AMP is attached to a flexible linker with target domain that attaches specifically to the pathogen and not to the commensal flora thereby preserving normal gut microbiota. This is an important advantage as the gut microbiome has a proven role in metabolic functions, immune function and body homeostasis (Gut-Brain Axis).[36] M8(KH)-20 against *Pseudomonas aeruginosa* and *Streptococcus* mutants, Agplectasin against MRSA are the STAMPs currently in phase 1 and 2 level of studies, respectively. Peptides which are developed by post translational modification with introduction of cyclic structures to lanthionine (a thio-ether aminoacid) are labelled "Lantibiotics".[37] In general, lantibiotics are active in gram positive infections and have potent *in vitro* and *in vivo* activity. Challenges in developing lantibiotics for clinical use include improving antimicrobial activity and physical parameters such as solubility and protease resistance, while curtailing costs.[38] At present, these preparations are available as topical applications used in dental caries.

Bacteriophages

Seeking help from viruses (which are the most abundant microbes on the planet) to fight drug resistant bacteria is seemingly logical, and bacteriophages seem to be well suited for the purpose. Bacteriophages offer advantages like rapidity in killing bacteria, specificity to target pathogen, lower chances for developing resistance, synergistic activity with other antibiotics and lysins, apart from their excellent activity on biofilms.[9] Phage lysins are being developed for specific gram positive pathogens (*S. pneumoniae*, *S. aureus*, *S. pyogenes*) and gram negative bacilli too (*P. aeruginosa*, *A. baumanni*, Enterobactericiae).[39]

Nanoparticles

Silver and metal oxides of copper, zinc and iron of 1-100 nm size have been evaluated and utilized in preventing hospital-acquired infections, especially for their role in biofilm prevention as demonstrated by the role of utilization of silver coated endotracheal tubes in NASCENT trial in preventing VAP.[40] Nanoparticles act through multiple mechanisms like oxidative stress induction (release of reactive oxygen species), inhibition of electron transport chain, damage to DNA and other interactions with bacterial metabolism.[11] Cefiderocol is an application of nanomedicine in which the cephalosporin is hidden inside an iron containing shell (catechol siderophore containg ferric iron), which helps to penetrate the outermembrane of GNB inside which the drug is released as "Trojan Horse".[26,27] At present, nanoparticles are being developed for use as coating agents to prevent biofilms and as drug transporters.[11]

Laupland *et al.*, reviewed new and promising antimicrobials just a decade ago and the drugs they enlisted, are all in clinical use now and we are already looking beyond them for

newer options due to development of AMR against these drugs.[41] While new drugs might play an important role in infections caused by resistant organisms, we should focus on using existing antimicrobials effectively through stringent implementation of antibiotic stewardship.[42] This requires implementation of core elements of stewardship program along with use of resistance tracking platforms globally.[43] To maximize the effect of antibacterials, the prescriber should have a thorough knowledge of local microbiology and susceptibility patterns, bacterial status (inoculum size) along with site of infection, antimicrobial concentration and dosing required, minimum inhibitory concentration (MIC), mutant spectral window (MSW), mutant prevention concentration (MPC) and minimum bactericidal concentration (MBC).[44] The prescriber should assess the influence of host factors such as the volume of distribution, presence of hypoproteinemia and organ dysfunctions (renal/hepatic), while addressing pharmacological aspects (hydrophilic/lipophilic, molecular weight and protein binding) and type of killing properties (time dependent/concentration dependent; bacteriostatic/bactericidal) to decide appropriate dose and duration of therapy.[45] To tackle antibiotic resistance, every hospital should monitor quality indicators of stewardship program including structural (establishment of stewardship teams, computerized physician order entry), process (antibiotic time outs) and outcome (defined daily dose: DDD, duration of therapy: DOT) measures with frequent audits.[46,47]

Conclusion

Bacteria which have dominated ecological systems for millennia cannot be vanquished for good. Therefore, we conclude that new antibacterials cannot remain new or promising for long. Using existing antibacterials along with strong adherence to infection control practices and antimicrobial stewardship is the best option to redeem our species from the threat of AMR.

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Conflicts of interest
There are no conflicts of interest.

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