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Recent Advances in the Development of Antibacterial Agents.

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ABSTRACT

Antibacterials are one of the most commonly prescribed groups of medications, especially in developing nations, owing to the vast number of microbial diseases prevalent in the community. Ever since the discovery of the phenomenal antibacterial, penicillin, there has been a great rise in the number of antibacterials in the market. In this era, where roadblocks like chemo-resistance and mutations plague medicine, scientists across the world are looking to adapt lateral approaches in encountering diseases. This review article brings to limelight, the recent advances in the field of antibacterial drug development, from the year 2007 till date.

Keywords: Oritavancin, Tedizolid, Dalbavancin, Raxibacumab, Bedaquiline, Ceftaroline

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INTRODUCTION

Infectious diseases are among the leading causes of mortality worldwide, especially in developing nations where second line antibacterial drugs against resistant bacteria are generally either unavailable or unaffordable. The emergence of multi-drug resistance (MDR) in both community-acquired and hospital-acquired infections has outpaced the development and delivery of new drugs to the clinic. While the market potential for new antibacterial drugs is estimated to be several billions of dollars, the discovery pipelines of most major pharmaceutical companies are running near empty. The paucity of new antibacterial drugs has led the Infectious Disease Society of America (IDSA) and other bodies to call for action in rebuilding the infrastructure and efforts to develop next generation drugs [1]. On an average, research and development of a single anti-infective drug takes around 15-20 years, and can cost more than 1000 million dollars per drug. The cost of bringing a new product to the market is increasing at a rate of at least 10% per annum [2].

Newer Antibacterial Drugs, Drug Combinations and Formulations (in reverse chronological order): (as listed in Table 1)

Table 1

S. No.	New Drug / New Drug Combination	Class of Drug	Month of Approval
1	Ceftazidime – Avibactam	Cephalosporin / Beta lactamase inhibitor	February 2015
2	Finafloxacin (Otic Suspension)	Fluoroquinolone	December 2014
3	Ceftolozane – Tazobactam	Cephalosporin / Beta lactamase inhibitor	December 2014
4	Oritavancin	Lipoglycopeptide	August 2014
5	Tedizolid	Oxazolidinone	June 2014
6	Dalbavancin	Lipoglycopeptide	May 2014
7	Raxibacumab	Monoclonal antibody	December 2012
8	Bedaquiline	Diarylquinoline	December 2012
9	Fidaxomicin	Macrocyclic	May 2011
10	Ceftaroline	Cephalosporin	November 2010
11	Telavancin	Lipoglycopeptide	September 2009
12	Retapamulin	Pleuromutilin	2007
13	Doripenem	Carbapenem	2007

Ceftazidime – Avibactam

Avibactam is a non-beta-lactam beta lactamase inhibitor that has been recently approved for use in combincation with ceftazidime, which is a third generation cephalosporin. Avibactam inhibits several classes of beta lactamases including *Klebsiella pneumonia* carbapenemases (KPCs), AmpC and class D beta lactamases. However, it is not active against metallo beta lactamases. The combination therapy is mainly used against Gram negative organisms. The most common application for the drug combination is in treating complicated UTIs and complicated intra-abdominal infections caused by antibiotic-resistant pathogens. Common adverse events are gastrointestinal upset, blood alkaline phosphatase increase, anxiety and giddiness [3].

Finafloxacin

Finafloxacin is a flouroquinolone antibiotic that has been approved recently by the US FDA for swimmer's ear, scientifically termed as acute otitis externa. It is highly active against *Pseudomonas aeruginosa* and *Staphylococcus aureus*. It is available as a topical formulation in the form of eardrops / otic suspension. Commonly reported adverse events include local pruritis and nausea. Also, hypersensitivity reactions may be seen with the drug. It is also being used for the treatment
of urinary tract infections [4,5].

Ceftolozane – Tazobactam

Ceftolozane is a fifth generation cephalosporin that is highly active against Gram negative bacteria. It is administered along with a beta lactamase inhibitor, tazobactam to prevent its destruction. The drug combination is indicated in severe urinary tract infections and intra-abdominal infections. It is also being tried

for ventilator-associated pneumonia. Usual adverse events include gastrointestinal disturbances, insomnia, headache, hypertension and infusion-site reactions [6,7].

Oritavancin

Oritavancin is a phenyl glycopeptide derivative. It shares its structure with vancomycin, and inhibits peptidoglycan biosynthesis by inhibiting both transglycosylation and transpeptidation. It has a selective action due to its strong intramolecular interaction with D-amino acid-containing peptidoglycan residues, not found in mammalian cells. Its pharmacokinetic properties allow less frequent dosing and also improved distribution. The drug has good potency against *S.pneumoniae* and *Staphylococci*. It exerts concentration-dependent cell killing activity against vancomycin-intermediate isolates of *S. aureus* (VISA) including heterogeneous VISA (hVISA) and against vancomycin resistant *Staphylococci* and *Enterococcus faecium* (VRE). It may also have additional activity against *B.anthracis*. It has a long elimination half-life of around 393 hours. A single 1200-mg dose administered IV over 3 hrs is given for skin and skin structure infections [8-10].

Tedizolid (Torezolid)

Tedizolid is an orally administered novel oxazolidinone. It is 4–8 times more active than linezolid in linezolid-susceptible and resistant strains of *Staphylococci* and *Enterococci* and up to 4 times higher activity against anaerobic bacteria. It has an oral bioavailability of 91% and hence no dosage adjustment is needed between IV and PO doses. It has an elimination half-life of around 12 hrs. It inhibits bacterial protein synthesis at the initiation/elongation step. It binds to the peptidyl transferase center (PTC) of 50S ribosome. It also binds to LepA, a universal bacterial elongation factor. Oxazolidinones bind only to the mitochondrial 70S ribosomes and not the cytoplasmic 80S ribosomes, explaining the myelosuppression and toxic optic neuropathy observed in linezolid-treated patients for as little as 14 days. Tedizolid is indicated in skin and skin structure infections. It is administered as 200 mg oral/IV for 6 days. Adverse events associated may include nausea, headache, anaemia, flushing, hypertension and *C.difficile* colitis [11-13].

Dalbavancin

Dalbavancin is highly potent against *S.pneumoniae*, *S.aureus*, coagulase-negative *Staphylococci* and vancomycin susceptible *Enterococci*. It is approved for the treatment of acute bacterial skin and skin structure infections caused mainly by Gram positive bacteria. The drug is to be infused IV over 30 minutes, only with 5% Dextrose as it gets precipitated with normal saline. Rapid infusion rates can lead to infusion reactions in form of upper body flushing, urticaria, pruritus, rash and ALT elevations > 3 times the Upper Normal Limit. Diarrhoea should be evaluated for *Clostridium difficile*-associated diarrhea (CDAD). Dalbavancin is 93% bound to albumin. It has an elimination half-life of around 346 hours. It is currently in trials for catheter related bloodstream infections [14,15].

Raxibacumab

Raxibacumab is a recombinant human monoclonal antibody that has been recently developed against Anthrax infections. It can be used both as a prophylactic agent as well as a therapeutic agent. It is highly effective when given in combination with drugs used against *B.anthracis*. The drug targets the protective antigen component of the lethal toxin of the Anthrax bacillus. Common adverse events reported are headache, nausea, respiratory infections, pruritis and pain in the extremities [16-18].

Bedaquiline

The U.S. Food and Drug Administration (FDA) has approved Bedaquiline for use as part of a combination therapy in adults with pulmonary multidrug-resistant tuberculosis (MDR TB). It inhibits proton pump of mycobacterial ATP synthase by binding to the oligomeric and proteolipic subunit-C of mycobacterial ATP synthase. This leads to inhibition in ATP synthesis and hence bacterial death. Bedaquiline has a half-life of 4-5 months. Increased mortality, QT prolongation, raised liver enzymes, hemoptysis and chest pain are reported adverse events with bedaquiline. It is dosed as follows: Weeks 1 - 2: 400 mg (oral) once daily; Weeks 3 - 24: 200 mg (oral) three times in a week [19,20].

Fidaxomicin

Fidaxomicin is a narrow spectrum macrolide. It is mainly active against *Clostridium difficile*, and exerts limited activity against normal intestinal flora. It inhibits RNA polymerase sigma subunit that results in disruption of protein synthesis and cell death in susceptible organisms. It is purely bactericidal. It has minimal systemic absorption, has half-life of 9 hours and excreted mainly through faeces. It is given at a dose of 200 mg orally twice daily for 10 days. The most common adverse reactions reported in clinical trials are nausea, vomiting, gastrointestinal hemorrhage, abdominal pain, neutropenia and anaemia [21,22].

Ceftaroline

Ceftaroline is a novel fifth generation cephalosporin. It is available as Ceftaroline fosamil (a prodrug). It is converted to the bioactive form, ceftaroline in plasma by phosphatases. It is a broad-spectrum antibiotic that is highly effective against Methicillin Resistant *Staphylococcus aureus* (MRSA), penicillin and cephalosporin resistant *S. pneumoniae*, Vancomycin-intermediate *S. aureus* (VISA), and Vancomycin-resistant *S. aureus* (VRSA). Ceftaroline acts by binding to penicillin binding proteins 1-4. It shows high affinity for PBP2a present in *Staphylococcus aureus* that is responsible for methicillin resistance. In *S. pneumonia*, ceftaroline binds to all 6 PBPs identified. It is bactericidal. It is 20% bound to plasma proteins. It has a half-life of around 2.6 hours and excreted mainly through kidneys[1]. For community-acquired pneumonia, a regimen of 600 mg IV twice daily for 5-7 days is used. A course of 5-14 days is preferred for acute skin and skin structure infections. Dosing adjustment is to be done in renally impaired patients. Nausea, dysgeusia, vomiting, diarrhea and headache are common adverse events [23-25].

Telavancin

Telavancin is highly potent against MRSA, *Streptococci* and Vancomycin resistant Enterococcus (VRE). The drug has been approved for complicated skin and skin structure infections, and for ventilator-associated bacterial pneumonia caused by *S. aureus*. It is 90% protein bound and has an elimination half-life of around 8 hours. It is 76% excreted in urine. Hence, dosage adjustment is required in patients with severe renal impairment. For complicated skin and skin structure infections, an IV dose of 10 mg/kg is administered once a day for a period of 7 to 14 days. Adverse effects include taste disturbance, vomiting and foamy urine. Rapid IV infusion can cause "red man syndrome" like reactions. Diarrhea should be investigated for *Clostridium difficile*-associated diarrhea (CDAD). Possible additive effects with other drugs that prolong the QT interval have been seen [26-28].

Retapamulin

Retapamulin is a pleuromutilin that has been approved for the treatment of skin and soft tissue infections caused by drug-resistant *S.pyogenes* and *S.aureus*. Retapamulin is isolated from *Clitopilus scyphoides*, an edible mushroom. It is a protein synthesis inhibitor that acts by binding to 50-S subunit of bacterial ribosomes. It is bateriostatic at MIC while it becomes bactericidal at 1000x MIC. It is 94% bound to plasma proteins and is metabolized mainly by CYP3A4. Pruritus at application site, bacterial or fungal superinfection on prolonged use including *Clostridium difficile* associated diarrhea (CDAD) and pseudomembranous colitis have been reported [29,30].

Doripenem

Doripenem is a beta-lactam antibiotic. It is grouped under the carbapenem group. It has a broad spectrum of activity but it is inactive against MRSA. It is highly stable against most beta-lactamases. Doripenem is also seen to be active against *Pseudomonas aeruginosa* than other carbapenems. It has a lower risk of causing or precipitating seizures than other carbapenems. It acts by inhibiting the synthesis of cell wall by attaching itself to penicillin-binding proteins that are normally required for cross-linking the peptidoglycans of the cell wall. Doripenem is metabolized by dehydropeptidase-1 into an inactive metabolite. The elimination half-life is around 0.95 hr, and 75% of the drug is excreted unchanged in the urine, thus necessitating dosage adjustment in patients with renal impairment. It is administered as a 500 mg IV infusion, thrice daily for 5-14

days. Adverse events include anaemia, anaphylactic reactions, seizures, neutropenia, toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome [31-33].

Drugs Currently In Clinical Trials [34,35]: (as listed in Table 2)

Table 2

Drug	Development Phase	Drug Class	Potential Indications
Plazomicin	Phase 3	Aminoglycoside	Bloodstream infections and nosocomial pneumonia caused by carbapenem-resistant Enterobacteriaeceae
Solithromycin	Phase 3	Macrolide (Ketolide)	Community-acquired bacterial pneumonia, uncomplicated urogenital gonorrhea
Surotomycin	Phase 3	Lipopeptide	Clostridium difficile-associated diarrhea
Eravacycline	Phase 3	Tetracycline	Complicated intra-abdominal and urinary infections. Hospital acquired bacterial pneumonia
Delafloxacin	Phase 3	Fluoroquinolone	ABSSSI, CABP, Uncomplicated gonorrhea
JNJ-Q2	Phase 2	Fluoroquinolone	Community Acquired Bacterial Pneumonia
Taksta (Fusidic acid)	Phase 2	Fusidane	Prosthetic joint infections
Ramoplanin	Phase 2	Lipoglycopeptide	Cl. difficile associated diarrhea
Radezolid	Phase 2	Oxazolidinone	ABSSSI, CABP
Omadacycline	Phase 2	Tetracycline	Complicated UTI, ABSSSI, CABP
Nemonoxacin	Phase 2	Quinolone	CABP, ABSSSI, Diabetic Foot Infection
Lefamulin	Phase 2	Pleuromutilin	ABSSSI, CABP
Brilacidin	Phase 2	Defensin- mimetic	ABSSSI
Debio 1452	Phase 2	FabI inhibitor	ABSSSI
POL-7080	Phase 2	Macrolide (protein epitope mimetic) LptD inhibitor	Ventilator associated bacterial pneumonia, Anti pseudomonal antibiotic
EDP-788	Phase 1	Bicyclolide	Bacterial Infections
ACHN-975	Phase 1	LpxC inhibitor	Bacterial Infections
CRS-3123	Phase 1	Methionyl tRNA synthetase (MetRS) inhibitor	C. difficile infections
Carbavance	Phase 1	Carbapenem (biapenem) + novel boronic beta-lactamase inhibitor	Febrile Neutropenia

Antimicrobial Metallopolymers and Their Bio Conjugates [36]

Conventional antibacterial agents have exhibited activity against methicillin resistant *S.aureus* by modification with polymers. However, these strategies have been limited by their high toxicity, poor release, and low bacteria-specific targeting efficiency. Organometallics have been in use as anticancer agents, enzyme inhibitors and targeting agents. Their antimicrobial potential still remains in early stages and most of them have not yet achieved a balance between toxicity and bioavailability. Charged metallopolymers show good efficacy in reducing β-lactamase activity in addition to effectively lysing the bacterial cells. Metallopolymers target β-lactamase enzymes and cell walls, hence protecting the conjugated antibiotics by means of ion-pairing between antibiotics and polymers.

Charged metallopolymers are composed of cationic cobalt celenium-containing polymers. Due to the special ability of these polymers to complex with carboxylate anions, several β-lactam antibiotics (like Penicillin G, amoxicillin, ampicillin, cefazolin) can be protected from β-lactamase by forming ion-pairs with the polymers. They are efficacious against multidrug-resistant MRSA, while showing non-haemolytic activity and minimal

adverse events. Hexafluorophosphate paired cobalt celenium-containing polymer, Halide anion (Cl^-, Br^-, and I^-) are being subjected to trials.

Peptide-Conjugated Phosphorodiamidate Morpholino Oligomers (PPMO) [37,38]

Antisense phosphorodiamidate morpholino oligomers (PMOs) and their derivatives down-regulate gene expression (in a sequence-dependent manner) by interfering with the binding of ribosomes to mRNA. By doing so, they inhibit protein translation. The PMO backbone is made of morpholino rings with phosphorodiamidate linkage that protects them from nuclease degradation while still maintaining complementary base pairing. Covalent conjugation of the PMO with membrane-penetrating peptides has enhanced their cellular uptake by mammalian cells as well as bacterial cells. The advantage of PPMOs is that they specifically target the underlying genes of a bacterium, whereas conventional antibiotics just disrupt its cellular function and often have broader, unwanted impacts. As they are further developed, PPMOs should offer a completely different and more precise approach to managing bacterial infection, or conceptually almost any disease that has an underlying genetic component.

Some of the attractive targets for antisense antibacterial therapy include essential genes such as Acyl carrier protein (acpP) encoding fatty acid biosynthesis protein, bacterial RNA polymerases.

Newer Targets For Antibacterials To Prevent Resistance

Bacterial Proteins as drug target [2]

Antibiotics can target novel bacterial proteins like β-ketoacyl-acyl-carrier-protein synthase I/II enzyme required for fatty acid biosynthesis. Platensimycin is one such drug in preclinical trials that acts by blocking these enzymes involved in the condensation steps in fatty acid biosynthesis.

Virulence factors as drug target [2]

Virulence inhibitors could target

- *B. anthracis* lethal factor catalytic activity
- Virulence gene regulators that control virulence genes
- Bacterial adhesion to host cells: e.g., inhibition of the formation of pili (pilicides).

Modulating the host response pathways [2]

Toll-like receptor activators and modulators could potentially have an antimicrobial role by producing antimicrobial peptides that activates the adaptive immune response to combat the infection.

Use of bacteriophages[2]:

Small acid-soluble protein (SASPs) genes can be delivered to *S. aureus* via a *S.aureus*-specific delivery bacteriophage, thus producing SASPs which can bind to and inactivate bacterial DNA. These proteins have been shown to be rapidly bactericidal and active against a range of *S. aureus* strains, irrespective of existing antibiotic resistance.

Combining β-lactamase enzyme with β-lactam antibacterial drug [2]

It can significantly reduce emergence of resistant microbes by taking advantage of the natural phenomenon of inactivation of antibacterial drugs by enzymatic hydrolysis. 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.

Combining antibiotics with bioenhancers [2]

A bioenhancer is an agent capable of enhancing the bioavailability and efficacy of a drug with which it is co-administered, without any pharmacological activity of its own at the therapeutic dose used.

Cow urine distillate (CUD) can act as a potential therapeutic target to enhance the activity of antibacterial agents. CUD when combined with rifampicin increased the activity of rifampicin by about 5-7 times against Escherichia coli and 3-11 times against gram-positive bacteria.

Newer Strategies in Antibacterial Drug Discovery

Most of the current antibacterial drugs were discovered by means of traditional approaches, which are now saturated. This has led to the emergence of drug resistance as well as the emergence of new pathogens, requiring the development and exploration of newer strategies and sources in antibacterial drug discovery [2].

Antimicrobial peptides derived from vertebrates, invertebrates and microorganisms [2]

These act by interfering with metabolism, targeting cytoplasmic components and disrupting cell membranes. They may also enhance the immunity by functioning as immunomodulators, thus serving as a novel potential therapeutic target. Examples are:

- Dermaseptin derived from frog skin
- Defensin and crustin from crustacean family
- Bacteriocin derived from bacteria.

Drugs in the pipeline include omiganan and pexiganan.

Alternative form of drug delivery methods[2]

Unconventional form of drug delivery methods can be used. For instance, inhalational amikacin is available as nanoscale liposomal formulation showing potential for the treatment of chronic *P. aeruginosa* lung infections in cystic fibrosis by offering advantages such as biofilm penetration and sustained release from liposomes.

Pharmacometric approach [39]

Pharmacometrics is the scientific discipline that uses mathematical models based on biology, pharmacology, physiology, and disease for quantifying the interactions between drugs and patients. Data and information from various sources are bridged together and quantitatively related to each other.

Computer-based modeling and simulation of pharmacokinetic (PK) and pharmacodynamic (PD) data (denoted as PK/PD M&S) forms the basis of the pharmacometric analysis, but is frequently supplemented by models characterizing other important aspects of drug efficacy and/or safety in a given situation, such as disease progression, adherence to therapy or bacterial growth and infection.

Pharmacometrics aims at establishing models that provide guidance and decision support in drug development such as trials design, efficacy comparisons, dosage regimen optimization and endpoint analysis, but also in supporting regulatory decisions and improving clinical care in specific patient populations. In addition, increasing emphasis is more recently being placed on dose selection of approved antibiotics already in clinical use, with heavy reliance on quantitative benefit-risk evaluations.

Difficulties in Antibacterial Discovery

The failure of discovery can be attributed to the combined effects of several interacting factors, as listed below.

Failure of Discovery [40]

The challenge posed by the fact that an anti-infective, unlike any other pharmaceutical product, needs

- to have multiple targets in terms of bacterial species
- to work in multiple different infection types, arising in different body compartments

The genuine rarity of drug classes that can effectively permeate Gram negative bacteria and evade their endogenous efflux. This challenge is particularly important for *Acinetobacter sp.* and *P. aeruginosa*. This challenge is compounded if one further accepts that any single-target drug is likely to be vulnerable to mutational target-mediated resistance and that a desirable drug therefore should have multiple targets, as do β-lactams, aminoglycosides and fluoroquinolones

Over-optimism in the 1990s for genomics, which identified targets but not compounds and, even where compounds were found, underestimated the challenge of getting these molecules into bacteria or preventing their efflux. The corollary of this shift was an abandonment of tried-and-trusted methods of antibacterial discovery, notably natural product screening

Failure to bring agents into the market [40]

Lack of return of investment: The push for prudent antibiotic prescribing to reduce resistance rates and the policy of preserving newer agents as last line treatment options do little to encourage the industry to invest in newer drugs

High complexity and cost of conducting Phase 3 trials

The regulatory environment [41]

Demanding phase 3 study protocols

Necessity for all licensed indications to be microbiologically documented

Increased stringency of safety requirements for pre-licensing and post-licensing procedures (Despite these stringent requirements, risk/benefit definition remains unclear)

Higher standards for efficacy and safety trials

Prolonged evaluation/decision time which in turn affects return on investment

Failure of harmonization of regulatory requirements

Slow updating of existing guidelines

CONCLUSION

The future of antibacterial treatment seems promising, as several drugs with novel mechanisms of action are in development. Moreover, newer targets have also been identified. In the near future, the challenge will be to identify newer agents for the treatment of multidrug‑resistant pathogens that are emerging at a rapid rate. Further, measures should be taken to minimize the development and spread of resistance, which will in turn reduce the economic burden on the healthcare provider as well as on the patient.

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