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Review Article

REVIEW ON CLINICALLY DEVELOPING ANTIBIOTICS

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ABSTRACT

The world is running out of antibiotics. Between 1940 and 1962, more than 20 new classes of antibiotics were marketed. Since then, only two new classes of antibiotics were marketed. Now, not enough analogues are reaching the market to stem the tide of antibiotic resistance, particularly among gram-negative bacteria which indicates the need of novel antibiotics for their effective action. This review describes those antibiotics in late-stage clinical development. Most of them belong to existing antibiotic classes and a few with a narrow spectrum of activity are novel compounds directed against novel targets. The reasons for some of the past failures to find new molecules and a path forward to help attract investments to fund the discovery of new antibiotics are described.

Keywords: Antibiotics, Clinical development, Narrow spectrum

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INTRODUCTION

The antibiotics are the cornerstones of recent medicine after the entry of penicillin, which came into widespread use in the beginning of the 1940s. [1] By 1950s, multiple numbers of newer classes of antibiotics came into the scene, over the next twenty years. [2] Nowadays it is difficult to treat and do certain medical procedures which are extensively used, like chemotherapy, organ transplants, joint operations or the provision of care for premature babies without the antibiotics [1]. Moreover, they can control both morbidity and mortality rate in humans and animals. [3] To brief outing, they have become the lifesaving treatment for all types of infections in humans as well as animals. The timeline of new class antibiotics has been given in table 1.

Table 1: Time line of antibiotics

Year introduced	Class of drug
1935	Sulphonamides
1941	Penicillins
1944	Aminoglycosides
1945	Cephalosporins
1949	Chloramphenicol
1950	Tetracyclines
1952	Macrolides/lincosamides/streptogramins
1956	Glycopeptides
1957	Rifamycins
1959	Nitroimidazoles
1962	Quinolones
1968	Trimethoprim
2000	Oxazolidinones
2003	Lipopeptides

Now, however, two developments are resulting in more and more difficult to treat the bacterial infections with the antibiotics successfully, including the increasing number of antibiotic-resistant pathogens and the second one is that the number of new antibiotics developed since the 1970s has decreased [4]. It was estimated that infections that can be treated completely are also becoming more complicated to treat, increasing costs of healthcare facilities, and patient mortality is increasing with costs to the society. The antibiotic effectiveness has to decrease now and many of the microorganisms are resistant to multiple antibiotics [5]. The issue of antibiotic resistance, though not new, has amplified in the previous 10 to 15 y and creates a serious threat to the treatment of infections. Certain new investigational studies were reported that, among all the multidrug-resistant pathogens like S. *aureus and* P. *aeruginosa, Acinetobacter* species are the major infective organism which can cause even life-threatening resistant infections. The improper intake of antibiotic dosage or lack of sensitive antibiotic agents to fight against these types of organisms may be the reason for the occurrence of such infections [6].

Despite this increase in the multidrug-resistant pathogens, the development of antibacterial agents is declining, [7] that is, there are not enough antibiotics for treating such infections [4]. This antibiotic deficit will become more and more problematic in the years to come.

As per World Health Organization (WHO), the antibiotic resistance is one among the serious hazard to human health and the consequences of antibiotic-resistant bacterial infections are greater than ever [4]. So, new antibiotics are critically needed to alleviate the problems associated with this antibiotic resistance [8, 9]. The Infectious Diseases Society of America (IDSA, 2010) estimated that at least another 10 antibiotics, which are active against these superbugs, are required to enter the market within ensuing ten years [10]. It ought to be noted that antibiotics, which were already in market use are complex natural products with multiple binding sites on the target, making it less likely for resistance selection. Moreover, the prevalence of treatment difficulty for both resistant and multi-resistant nosocomial organisms are greatly rising, both for Gram-negative and Gram-positive bacteria among this; gram-negative organisms are producing a greater threat [11].

Thus, the demand for new antibiotics is critical for some gram-negative microbes as compared to gram-positive microbes since the new molecules or compounds will produce action in new pathways to eradicate such microbes [12]. Generally, small proteins are the greatest source of new antibiotics called antimicrobial peptides (AMPs) and many of these AMPs are derived from natural molecules [13]. The current study reviews all the current articles on clinically developing antibiotics and describes their needs and scope in the market.

Search criteria

Articles related to new antibiotics and their developments were reviewed for the study, most of them were from Pubmed databases. Articles between the years of 2000 and 2017 were selected for reviewing and the points were extracted. Primary resources were given the first preference for reviewing.

Approval and development of antibiotics from the 'Golden Era'

The response to the entry of any new antibiotic has lead to the development of resistant bacterial variants so, new antibiotic compounds should be needed constantly to alleviate the associated problems. During the "golden era" of antibiotic evolution, that is, in the years of 1940s to 1970s, new antibiotics with new actions were incessantly developed, which made it possible to manage the threat of gradually rising resistant strains. [8] The European Medicines Agency (EMA) and the American Food and Drug Administration (FDA) were the two agencies responsible for making the approval decisions for new antibiotics. The new antibiotics, which are approved in the year of 2000 and 2011, are listed below (table 2).

Table 2: Status of antibiotics approved by the FDA and the EMA between 2000 and 2011

Substance	Class	Rejected by FDA	Approved by FDA	Approved by EMA
Linezolid	Oxazolidinones		2000	
Ertapenem	Carbapenems		2001	2002
Cefditoren	Cephalosporines		2001	
Gemifloxacin	Fluoroquinolones		2003	
Daptomycin	Lipopeptides		2003	2006
Telithromycin	Macrolides		2004	
Tigecycline	Glycylcyclines		2005	2006
Faropenem	Penems	2006		
Retapamulin	Pleuromutilins		2007	2008
Dalbavancin	Glycopeptides	2007		
Doripenem	Carbapenems		2007	2008
Oritavancin	Glycopeptides	2008		
Cethromycin	Macrolides	2009		
Cethromycin	Macrolides	2009		
Iclaprim	Trimethoprims	2009		
Besifloxacin	Fluoroquinolones		2009	
Telavancin	Glycopeptides		2009	2011
Ceftobiprole	Cephalosporines	2009		
Fidaxomicin	Lipiarmycins		2011	2011
Colistimethate sodium	Colistin			2012
Ceftaroline	Cephalosporines		2010	2012

However, the world's capacity for antibiotic discovery is already reducing the rate of emergence of bacterial resistance, and which indicates the necessity of another new class of antibiotics to be introduced in the market (Figure1). Fig. 1 showed a line drawing of total number of newer classes of antibiotics that entered to the market in the years of 1940s and 1960s, the two new classes since 2000, and further 20-40 new classes were required to support medicine in the future years from now [6].

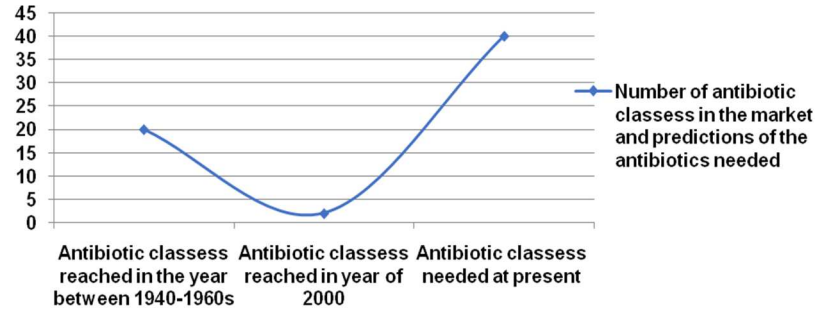

Fig. 1: Number of antibiotics in the market and the predictions of new antibiotics needed for the future

Novel antibiotics in recent years

The majority of new antibiotic substances is in the early phase of development is, phase 1 clinical trials [4]. The clinical trials for new antibiotics are believed to be cover disease indications even if it is the infection caused by more than one bacterial species [14]. The research updates showed that only two new classes of antibiotics were marketed in last 10 y and it may be due to the lack of development and almost all the pharmaceutical companies were concentrating only on analogue development which may be due to the high toxicity risks associated with the new classes [15]. At present, the environment has changed a little positively, and those who observing preclinical and clinical development strategies and activities have a reason to be more optimistic [11].

Several compounds have been developed in various antibiotic classes which are against resistant organisms in the whole spectrum of multidrug-resistant (MDR) bacteria (fig. 2) [11].

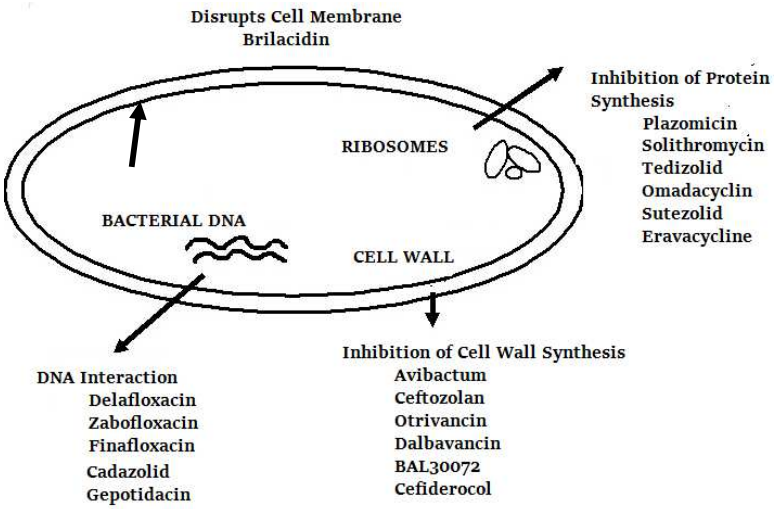

Fig. 2: New antibiotic compounds acting against resistant organisms

Source Reference: https:/www.google.co.in.novelantibiotics diagram [16]

Since most of the infections can be cured without antibiotic therapy, thus, new antibiotic approval is generally limited to complicated or more serious infections. The Infectious Diseases Society of America (IDSA) emphasizes that selecting the optimal drug regimen; dose, duration, and route of administration are a very important part in the stewardship practice. Furthermore, stewardship seeks to diminish the toxicity and other adverse events and also to lessen the costs of healthcare infections [16].

It is not easy to estimate the numbers of drugs in preclinical development, as most of them are not published or marketed [17]. Still, there are no antibiotics against the major gram-negative microorganisms such as *K. pneumoniae, P. aeruginosa and A. baumanii* in Phase II b and III and also the number of compounds (analogs of existing markets antibiotics) against these pathogenic organisms in earlier stages of development are also lessened. Since there are no new classes of antibiotics in the final phases of drug development, the new class antibiotics will not be introduced in the market in the short term [10, 18]. In the longer term, during the next 20 y, the probability of inventing twenty new antibiotic classes like many broad-spectrum antibiotics, as similar in 1940-1960s, looks to be remote, especially for multi-drug-resistant gram-negative microorganisms.

Novel compounds against microorganisms which are under clinical development

• Compounds against Gram-positive bacteria

Novel long-acting lipoglycopeptides-oritavancin and dalbavancin

Acute bacterial skin and skin structure infections (ABSSIs) are considered as the major bacterial infection and the frequent indications for antibacterial therapy, which are usually induced by Gram-positive bacteria like MRSA (Methicillin-resistant *Staphylococcus aureus*). With the introduction of the newer lipoglycopeptides with an extended elimination half-life, ABSSSI therapy may become more convenient. Oritavancin acts by inhibiting transglycosylation (like vancomycin), transpeptidation (like beta-lactams), and disruption of cell membrane integrity (like telavancin) [19] and results in quick bactericidal activity. It has a long elimination half-life of>300 h [20] and showed a strong bactericidal activity in a dose of 1200 mg in the *in vitro* PK/PD model [21].

Dalbavancin is another semisynthetic lipoglycopeptide which has been estimated for skin and soft tissue/skin structure infections, [22, 23] and also for catheter-associated bloodstream infections. Its half-life is about two weeks [24] also allowed for prolonged dosing intervals. Dalbavancin had a favorable safety profile with fewer adverse effects. It is estimated that the usage of dalbavancin was joined up with a significantly lower mortality (0.2 vs. 1.1 %). Finally, this has proceeded to the FDA approval of dalbavancin for ABSSSI caused by S. *Aureus* and S. *pyogenes* in May 2014.

Drugs to destroy gram-negative bacteria and broad-spectrum antibiotics

BAL30072

BAL30072 is a monosulfactam antibiotic, have an action against carbapenem-resistant Enterobacteriaceae and non-ferments [25]. It is chemically related to aztreonam and coming under the class of beta-lactam antibiotic and inhibiting the cell wall synthesis of bacteria. Certain *in vitro* studies has shown that the combination of BAL30072 with BAL29880 or clavulanate can result in susceptibility rates of more than 90%. A study conducted in Thailand, with its laboratory strains (1026b, 1710b) and several strains which are isolated, it was observed that more than 93% of the isolates were susceptible to BAL30072 with minimal inhibitory concentrations (MICs) between 0.004-0.016 µg/ml [26]. BAL30072 showed high activity through a MIC 90 of 0.016 µg/ml as compared to ceftazidime, meropenem, and imipenem.

Ceftolozane

Ceftolozane with tazobactam is presently undergoing certain investigational studies for testing its action in complicated urinary tract infections (cUTIs), complicated intra-abdominal infections (cIAIs) and ventilator-associated pneumonia (VAP). It is a new cephalosporin which is structurally similar to ceftazidime, which active against Pseudomonas and also against bacteria-producing beta-lactamases such as TEM-1. [11] Ceftolozanealone cannot destoy or kill the bacteria-producing ESBL and carbapenemases. However, along with tazobactam, it can destroy most of the bacteria-producing ESBL and some anaerobes. The FDA approved ceftolozane/ tazobactam to treat adultscIAI and cUTI in December 2014 [27].

Delafloxacin (fluoroquinolone)

Delafloxacin is a fluoroquinolone and its efficacy is undergoing through various investigational studies. As compared with others, it has a substituent on the seventh position of the quinoline ring system which is not protonatable and causes a pKa shift. Generally fluoroquinolones are zwitterionic except delafloxacin and as a result, they are neutrally charged only at a physiological pH. The neutral charge is essential for membrane penetration. Delafloxacin permeates the membranes at lower pH as seen in the inflamed tissue [28, 29]. Generally, the pH levels are mildly acidic (about 5.5-6) in the inflammatory tissue of soft tissue infections, abdominal infections, or urinary tract infections, under these conditions, e. g., 90% of moxifloxacin is in a cationic state, so it cannot permeate the

bacterial membranes. In contrast, delafloxacin is neutral at this pH and thereby leads to high cellular uptake [28].

Novel beta-lactamase inhibitors

The beta-lactamase inhibitors which are available for the clinical application includes sulbactam, clavulanate, tazobactam, etc. Recently, these beta-lactamases increases the resistance particularly to Gram-negative bacillieg. oxacillinasescephalosporinases and the metallo-beta-lactamases. Novel beta-lactamase inhibitors (e. g., diazabicyclooctane-related substances) are also able to inhibit these enzymes to a different extent. They, therefore, contribute substantially to meet the increasing need for new drugs against ESBL or Klebsiella pneumonia carbapenemases (KPCs)-producing bacilli [11].

Antibiotics currently under clinical development

SinceMarch 2017, about 41 novel antibiotics have been found to be under clinical investigation in the U. S. market for the management of potential bacterial infections. The achievement rate for such clinical drug development is low; the various study data showed that, generally, only 1 in 5 infectious disease products are entering into phase 1 clinical trial (human testing) [30]. The present antibiotic pipeline, on the basis of currently available information, is given in table 3. It will be revised in a periodic manner.

Table 3: List of compounds which are under clinical development

Drug name	Company	Drug class	Target	Expected activity against resistantGram-negativeESKAPE pathogens	Expected activity against a CDCurgent threat pathogen	Potential Indications
Baxdela(delafloxacin) Meropenem+Vaborbactam CRS3123	Melinta Therapeutics Inc. Rempex PharmaceuticalsInc Crestone Inc.	Fluoroquinolone β-lactam (carbapenem)+β-lactamase inhibitor(cyclic boronate) Diaryldiamine	Bacterial type IITopoisomerase PBP; β-lactamase MethionylTrna synthetase [17]	Possibl No	Possibly Yes Yes	ABSSIs, cUTI, Community-acquired pneumonia (CAP) [6] cUTI, cIAIs, Hospital-acquired bacterial pneumonia/ventilator associated bacterial pneumonia,Febrile neutropenia, Bacteremia.[6] *C. difficile*infections
ETX2514SUL10	Entasis Therapeutics Inc.	β-lactam (sulbactam)+β-lactamase inhibitor(diazabicyclooctane)	PBP; β-lactamase	Yes	No	Bacterial infections (caused by*Acinetobacterbaumannii*) [6]
GSK-334283010	GlaxoSmithKlinePLC (Shionogilicensee)	β-lactam (cephalosporin)	PBP	Possibly	Possibly	Bacterial infections
KBP-7072	KBPBioSciencesPharmaceuticalTechnical Co. Ltd.	Tetracycline	30S subunit ofbacterial ribosome	Possibly	No	CAP [6]
LCB01-037110	LegoChemBiosciences Inc.	Oxazolidinone	50S subunit ofbacterial ribosome	No	No	Bacterial infections
MCB3837	Morphochem AG	Oxazolidinone-quinolonehybrid	50S subunit of bacterial ribosome; bacterial type IItopoisomerase	No	Yes	*C. difficile* infections[6]
MGB-BP-310	MGBBiopharmaLtd.	Distamycin [16]	DNA minor groove	No	Yes	*C. difficile*-associated diarrhea
Nacubactam (OP0595/RG6080)	Meiji Seika PharmaCo. Ltd./FedoraPharmaceuticalsInc. (Rochelicensee)	β-lactamase inhibitor(diazabicyclooctane)	β-lactamase, PBP2	Possibly	Possibly	Bacterial infections
SPR74	Spero Therapeutics	Polymyxin	Cell membrane	Possibly	Possibly	Bacterial infections
TD-1607	TheravanceBiopharma Inc.	Glycopeptide-β-lactam(cephalosporin) hybrid	PG chainelongation; PBP	No	No	ABSSIs, hospital-acquired pneumonia/ventilator-associated bacterial pneumonia, bacteremia. [6]
TP-271	TetraphasePharmaceuticals inc	Tetracycline	30S subunit ofbacterial ribosome	Possibly	Possibly	Community-acquired bacterial pneumonia
TP-60766	TetraphasePharmaceuticals Inc	Tetracycline	30S subunit ofbacterial ribosome	Possibly	Possibly	Bacterial infections
WCK 2349	Wockhardt Ltd.	Fluoroquinolone (WCK771 pro-drug)	Bacterial type IItopoisomerase	No	No	Hospital-acquired bacterial pneumonia [6]
WCK 771	Wockhardt Ltd.	Fluoroquinolone	Bacterial	No	No	Hospital-acquired

			type IItopoisomerase			bacterial pneumonia [6]
Cefepime+Zidebactam(WCK 5222)	Wockhardt Ltd.	β-lactam (cephalosporin)+β-lactamase inhibitor(diazabicyclooctane)	PBP; β-lactamase	Yes	Possibly	cUTIs,hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia[6]
Aztreonam+Avibactam [7,10](ATM-AVI)	Pfizer Inc./AllerganPLC	β-lactam (monobactam)+β-lactamase inhibitor(diazabicyclooctane)	PBP; β-lactamase	Yes	Yes	cIAIs
Brilacidin	Cellceutix Corp.	Defensin mimetic16	Cell membrane	No	No	ABSSIs
CG400549	CrystalGenomicsInc.	Benzyl pyridinone	Fab1 inhibitor	No	No	ABSSIs, osteomyelitis [6]
Afabicin(Debio 1450)	DebiopharmInternational SA	Benzofurannaphthyridine	Fab1 inhibitor	No	No	ABSSIs and osteomyelitis (*Staphylococcus*-specific)
Finafloxacin	MerLionPharmaceuticalsPvt Ltd.	Fluoroquinolone	Bacterial type II topoisomerase	Yes	Possibly	cUTIs, acute pyelonephritis, cIAIs, ABSSIs
Gepotidacin(GSK2140944)15	GlaxoSmithKlinePLC	Triazaacenaphthylene[16]	Bacterial type II topoisomerase(novel A subunitsite) [17]	No	Yes	cUTIs, uncomplicatedUTI, ABSSIs uncomplicated urogenital gonorrhoeaand CAP [6]
MRX-I 14	-	-	50S subunit of bacterial ribosome	No	No	ABSSIs
Nafithromycin (WCK 4873)	Wockhardt Ltd.	Macrolide	50S subunit of bacterial ribosome	No	No	CAP
Nemonoxacin	TaiGenBiotechnology Co. Ltd.	Quinolone	Bacterial type IItopoisomerase	No	No	CAP, diabetic foot infection, ABSSIs
Murepavadin (POL7080)	Polyphor Ltd.	Antimicrobial peptide mimetic	Targeting Pseudomonas LPS-assembly protein (OstA; LptD; Imp)	Yes (Pseudomonas)	No	Ventilator-associated bacterial pneumonia (caused by *Pseudomonas aeruginosa*), lower respiratory tract infection, Bronchiectasis
Ramoplanin	Nanotherapeutics Inc.	Lipodepsipeptide	Lipid I,II	No	Yes	*C. difficile* infection[6]
Ridinilazole(SMT19969)	SummitTherapeutics Inc.	Bis-benzimidazole[1]	Unknown	No	Yes	*C. difficile* infection [26]
Zoliflodacin(ETX0914)	EntasisTherapeutics Inc.	Spiropyrimidenetrione[16]	Bacterial type IItopoisomerase(GyrB)	No	Yes	Uncomplicated gonorrhea
Cadazolid	ActelionPharmaceuticalsLtd.	Oxazolidinone-quinolonehybrid	50S subunit of bacterial ribosome; bacterial type Iitopoisomerase	No	Yes	*C. difficile* infection
Cefiderocol (S-649266)30	Shionogi and Co. Ltd.	Siderophore-β-lactam(cephalosporin)	PBP	Yes	Yes	cUTI, carbapenem-resistant Gram-negative bacterial infections
Eravacycline	TetraphasePharmaceuticalsInc.	Tetracycline	30S subunit of bacterial ribosome	Yes	Yes	cIAIs, cUTI
Iclaprim	Motif Bio PLC	2,4 diaminopyrimidine	Dihydrofolate reductase	No	No	ABSSIs, hospital-acquired bacterial pneumonia
Imipenem/cilastatin+relebactam (MK-7655)	Merck and Co. Inc.	β-lactam (carbapenem)+β-lactamase inhibitor(diazabicyclooctane)	PBP; β-lactamase	Yes	Yes	cUTI,Acutepyelonephritis, cIAIs,hospital-acquired bacterial pneumonia/ventilator-associated bacterial

Lefamulin (BC-3781)	NabrivavTherapeutics AG	Pleuromutilin[16]	50S subunit ofbacterial ribosome	No	No	pneumonia ABSSIs,CAP, hospital-acquired bacterial pneumonia/ventilator-associatedbacterial pneumonia, Osteomyelitis, prosthetic jointinfections [6]
Omadacycline	ParatekPharmaceuticalsInc.	Tetracycline	30S subunit of bacterial ribosome	Yes	Possibly	CAP, ABSSIs

CONCLUSION

There are many promising antibiotic compounds which are currently under clinical development which will be open up the possibilities for treating various life-threatening infections, but among them very few are reaching the stage of human testing. The resistance mechanisms are the main problem associated with the antibiotic therapy, but this will not stop with the entry of the new drugs into the market. Therefore, the race must continue, and drugs with new actions need to be investigated and tested for human use. The requirements should include that, the product is within the scope of combination regimes, should be made possible as this could help to delay the development of resistance.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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