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Antibiotics in pipeline till December 2019

Dr. Ashish Sadashiv Danane

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I. INTRODUCTION

"Antibiotic," is any substance produced by a microorganism, and subsequently by chemical synthesis, that inhibits growth of other microorganisms.[1]

An antimicrobial agent refers to all agents which kill or inhibits the growth of microorganisms.[2]

Rise in mortality is due to infection in more seriously ill or immunocompromised patients, there is a need for new strategies and new molecules to treat pathogens that are resistant to nearly the full range of contemporary antibiotics.[3]

A second indication of the need for novel antibacterials is the almost 40-year innovation gap between introductions of new molecular classes of antibiotics: fluoroquinolones in 1962 and the oxazolidinone (linezolid) in 2000[4].

A third indication is the recent trend by several large pharmaceutical companies to leave the antibacterial and antifungal therapeutic arenas, suggesting a future decrease in antibacterial-drug discovery and development skills.[5]

The need for new antimicrobial agents is now greater than before because of the emergence of multidrug resistance in common pathogens, the rapid emergence of new infections, and the potential for use of multidrug-resistant agents as bioweapons in wars[3]

Microorganisms are one of the richest source of antibiotics; with 99% of the known microbial species as yet uncultured, these clearly are untapped sources of novel antimicrobial agents. A recent example is the isolation of abyssomicin C, which inhibits folate biosynthesis in MRSA; the molecule is produced by the rare actinomycete Verrucosispora collected in a sediment sample from the Japanese sea at a depth of 867 ft [6].

The emerging field of metagenomics, in which the pooled genetic material of a bacterial community is sequenced without cultivating each individual member, offers the possibility of identifying novel product and biosynthetic pathways[7].

Attention should be paid to natural strategies used by prokaryotes and eukaryotes against microorganisms. Hosts respond to microbial infection by secretion of peptidic molecules, such as defensins, which act locally. Narrow-spectrum protein toxins (bacteriocins) are a predominant strategy in natural microbial communities for killing neighboring strains; Efforts should be focused on delivery strategies for peptides, bacteriocins, and phage-based lytic proteins[8].

Bacteria produce bioactive molecules through a series of biosynthetic steps. The idea behind combinatorial biosynthesis is to break the biosynthetic pathways down into modules and combine modules in host to generate novel end products.

Two promising techniques for generating greater diversity in synthetic-molecular construction are "click chemistry" and programming small molecules genetically. The "click chemistry" paradigm elaborated by Sharpless and colleagues [9]—such as the coupling of azides and alkynes with copper catalysis in aqueous solution under mild conditions—is a leading example of rapid modular combinatorial chemistry. Another strategy in chemical libraries is genetically programmable small molecules[10]. DNA tethering provides enhanced adjacency to promote new, high-yield chemistry and the creation of large libraries from which molecules can be selected for function.

Eskape pathogens: Eskape pathogens are important because they are commonly associated with resistance & easily escape commonly used antibiotics.

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Abbreviation	Full form
E	Enterococcus faecialis
S	Staphylococcus aureus
K	Klebsiella pneumonia
A	Acinetobacter spp.
P	Pseudomonas aeroginosa
E	enterobacter spp.

Antibiotics in pipeline

Beta-lactam antibiotics

M.O.A-Inactivation of transpeptidase & other penicillin binding proteins inhibits peptidoglycan biosynthesis weakening bacterial cell wall and makes organism vulnerable to rupture.

Name & class	Phase	Activity against ESKAPE	Changes for development	Added advantage & new indications	Route	Company
Cefiderocol (siderophore beta lactam)	NeA	DYes against KAPEnterobacter	catechol moiety is added on C-3 side chain which mimicks natural siderophore	Active against CRE, CRAB & CRPA ventilator-asso. pneumonia, bloodstream infections & sepsis	iv	Shionogi & Co. Ltd
ETX0282CP	1	Yes	Addition of Beta-lactamase broadens spectrum.	Active against CRE Urinary tract infections	po	Entasis Therapeutics Inc.
DP14/ ETX1317 (cephalosporin +Diazicyclooctane)		against KEnterobacter				
Imipenem/ cilastatin relebactam β-lactam (carbapenem)/ dehydropeptidase	NA	DKPEnterobacter	iridium-catalyzed H insertion series of transformations around bicyclo-urea	Active against CRE, CRPA. complicated intraabdominal	iv	Merck & Co. Inc.

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+(diazabicyclooctane				infections, ventilator-asso. pneumonia		
Meropenem + nacubactam β-lactam (carbapenem)+ diazabicyclooctane	1	KEnterobacter	Diazicyclooctane-produced thermal reactions compds. of type H2NCH2CH2X (X = OH, NHR) presence of zeolitic catalysts	Active byagainst ofCRE hospital-inacquired pneumonia/ ventilator-asso. pneumonia	iv	NacuGen Therapeutics (joint venture of Meiji Seika Pharma Co. Ltd./Fedora Pharmaceuticals Inc.)
WCK 2252 (cefepime + zidebactam)	1	Yes: KAP, Enterobacter spp.; Possibly: S. aureus hospital- acq. asso. pneumonia	Diazicyclooctane	Active against CRE Indicated for complicated U.T.I, & venti.-asso. pneumonia	iv	Wockhardt Ltd.
BOS-228 (LYS228) β-lactam (monobactam)	2	Yes: Enterobacter spp.	monobactam—β-lactam compounds where β-lactam ring is not fused to another ring	Active against CRE Indicated for complicated	iv	Boston Pharmaceuticals Inc. (In-licensed from Novartis

				cases-U.T.I & Intra-abdominal cases		AG)
Cefepime AAI101 (cephalosporin) +(Enmetazobactam)	3	Yes,K Enterobacter spp.	methylation tazobactam's triazole moiety yielded enmetazobactam a zwitterion	Active against ESBL complicated intraabdominal infections,venti-asso. pneumonia	iv	Allecra Therapeutics GmbH
Cefilavancin (TD-1792) Glycopeptide-β-lactam (cephalo) hybrid	3	Yes: S. aureus	a hetero dimer antibiotic composed of vancomycin covalently tethered through a linker to cephalosporin moiety	ABSSSI, novel m.o.a-pg chain elongation	No devel opment updated since 2015	R-Pharm/ Theravance Biopharma Inc.
Ceftobiprole β-lactam (cephalosporin)	3	Yes: S. aureus, K. pneumoniae,	Ceftobiprole broad-spectrum, fifth-generation, pyrrolidinone cephalosporin	Active against skin and skin structur	iv	Basilea Pharmaceutica International Ltd.

		Enterobacter spp			e infection specially designed to enhance activity against MRSA		
Sulbactam-durlobactam (SUL- DUR) β-lactam (sulbactam) + (diazabicyclooctane)	3	Yes: baumannii	A.	Addition diazabicyclooctane	Complicated urinary tract infection including acute pyelonephritis	iv	Entasis Therapeutics Inc**.**
Sulopenem/ sulopenem-etzadroxil14 β-lactam (carbapenem)	3	Yes: pneumoniae, Enterobacter spp	K.	ester prodrug of sulopenem, thiopenem broad-spectrum antibacterial activity	Activity against n.gonorrhea and ESBL as well acute bacterial prostatitis, gonococcal urethritis, and pelvic inflammatory disease	po	Iterum Therapeutics PLC
Tebipenem-Pivoxil (SPR99414/ SPR859)7 β-lactam (carbapene	3	Yes: pneumoniae, aeruginosa	K P.	Tebipenem pivoxil is a member carbapenems and a pivaloyloxymethyl ester.	Diabetic foot infection, and acute pyelone	po	Spero Therapeutics Inc.

m)				phritis Has		
				against ESBL as well		
Cefepime + taniborbactam (VNRX-5133) β-lactam (cephalosporin) + β-lactamase inhibitor (cyclic boronate)	3	Yes: K. P, Enterobacter spp.	β-lactamase inhibitor containing a bicyclic boronate moiety,	Activity against CRE and CRPA Complicated U.T.I	iv	VenatoRx Pharmaceuticals Inc.

Tetracyclines
M.O.A.- tetracyclines inhibit protein synthesis by binding to 30S ribosomes. attachment of aminoacyl-t-RNA to mRNA-ribosome complex is interfered with.

Name & class	Phase	Activity against ESKAPE	Changes	Added advantage & indications	Route	Company
Omadacycline Tetracycline	Approved oct. 2 2018	Yes: SK E. faecium, Enterobacter spp	is semisynthetic aminomethyl-cycline antibacterial derived from the tetracycline	ABSSSI, complicated and uncomplicated urinary tract infections	po, iv	Paratek Pharmaceuticals Inc.
Eravacycline Tetracycline	Approved Aug. 27, 2018 (U.S. FDA)	Yes: E. faecium, S. aureus, K. pneumoniae, Enterobacter spp	is a synthetic fluorocycline antibiotic the tetracycline class	active against ESBL, CRE, CRAB Complicated intra-abdominal infections	iv	Tetraphase Pharmaceuticals Inc.
KBP-7072	1	Possibly	a novel third-	Can be	2	KBP

Tetracycline		: E. Faecium, S. aureus, A. baumanni	generation tetracycline (aminomethylcycline) antibacterial	used for ventilator-associated pneumonia & CRAB	phase 1 trial completed in 2015	BioSciences Pharmaceutical Technical Co. Ltd
TP-271 **Tetracycline**	1	Yes: S. aureus, A baumannii	a novel, fully synthetic fluorocycline antibiotic	Activity against CRAB	po, iv	Tetraphase Pharmaceuticals Inc.
TP-6076 **Tetracycline**	1	Yes: pneumoniae, baumannii, Enterobacter spp. K. A.	TP-6076 novel, fully synthetic fluorocycline antibiotic	Activity against CRE & CRAB	iv	Tetraphase Pharmaceuticals Inc.

Fluoroquinolones

M.O.A-FQs inhibit the enzyme bacterial DNA gyrase (primarily active in gram negative bacteria), which nicks double-stranded DNA, introduces negative supercoils and then reseals the nicked ends. This is necessary to prevent excessive positive supercoiling & permit replication or transcription. Hence replication is inhibited.

Name & class	**Phase**	**Activity against ESKAPE**	**Changes for development**	**Added advantage & new indications**	**Route**	**Company**
Lascufloxacin (KRP-AM1977) Fluoroquinolone	NDA	Yes: S. aureus; Possibly: K. pneumoniae, A. baumannii	NIL	Priority indication is respiratory unlike conventional FQ'S Community-acquired	po	Kyorin Pharmaceutical Co. Ltd.

			bacterial pneumonia		
Finafloxacin	2	Yes: S. aureus, K. pneumoniae, A. baumannii	fluorinated quinolone derivative with 8-cyano-substituent and 7-pyrrolo-oxazinyl moiety	Active against ESBL ABSSSI, complicated intra-abdominal infections	Topical; otic	MerLion Pharmaceuticals Pte Ltd
Levonadifloxacin Fluoroquinolone		Yes: S. aureus	a Novel Broad-Spectrum Anti-MRSA Benzoquinolizine Quinolone Agent	diabetic foot infection, and community-acquired bacterial pneumonia	po, iv	Wockhardt Ltd
Quinolones-OPS-2071		Nil		Active against C.Difficile	po	Otsuka Pharmaceutical Co. Ltd.
Taigexyn (Nemonoxacin)		Yes: S. aureus	novel C-8-methoxy nonfluorinated quinolone	Diabetic foot, ABSSSI & CAP are new indications	po, iv	TaiGen Biotechnology Co. Ltd.
DNV3837 Oxazolidinone-quinolone hybrid		nil	Oxazolidinone-quinolone hybrid	Active against C.Difficule infections	iv	Deinove SA
TNP-2092		Yes,	TNP 2092 is	Acts	po, iv, o	TenNor

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Rifamycin-quinolone hybrid	S.Aureus	a non-cleavable, hybrid antibiotic comprised of a rifamycin and quinolizinone pharmacophore	n multiple topical & hence can act more efficiently RNA polymerase, DNA gyrase, DNA topoisomerase IV		Therapeutics Ltd.

ABSSSI

Oxazolidinone

M.O.A-Oxazolidinones act by inhibiting initiation of protein synthesis. Because of its unique binding site (on 50S subunit), there is no cross resistance with other drug classes.

Name & class	Phase	Activity against ESKAPE	Changes for development	Added advantage & new indications	route	Company
Oxazolidinone-Oxazolidinone Delpazolid Group	1	Yes: E. faecium, S. aureus	A novel oxazolidinone with cyclic amidrazone	Active against E.faecium	po	LegoChem Biosciences Inc. (Shanghai Haihe Pharmaceutical Co., Ltd./CSPC Pharmaceutical
Contezolid (MRX-I) & contezolid acefosamil Oxazolidinone	3	Yes: E. faecium, S. aureus	potent oxazolidinone antibiotic against Gram-positive pathogens	Active against E.faecium	po, iv	MicuRx Pharmaceuticals Inc.

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Macrolides

M.O.A- Macrolides acts by inhibiting bacterial protein synthesis. It combines with 50S ribosome subunits and interferes with '<u>translocation</u>'.

Name & class	Phase	Activity against ESKAPE	Changes for development	Added advantage & new indications	Route	Company
Nafithromycin Macrolide	2	Yes: S. aureus	Nafithromycin, second-generation lactone ketolide compound	anil	po	Wockhardt Ltd
T-4288 (solithromycin) Macrolide	3	Yes (N. gonorrhoeae)	new ketolide antibiotic, based on the macrolide antibiotic structure	Uncomplicated urogenital gonorrhea is a new primary indication	po, iv	Toyama Chemical Co. Ltd

Polymyxin

M.O.A- polymyxins are rapidly acting bactericidal agents; have a detergent-like action on the cell membrane.

Name & class	pha se	Activity against ESKAPE	Changes for development	Added advantage & new indication	Route	Company
SPR206 Polymyxin	1	Yes: KAPEnterobacter spp	Aminoacyl polymyxin nonapeptides	Aminoacyl polymyxin nonapeptides	iv	Spero Therapeutics Inc
SPR741 Polymyxin	1	Possibly: A. baumannii	SPR741 (NAB7 41) is a cationic peptide derived from polymyxin B	Active againstiv CRE, CRPA, CRAB		Spero Therapeutics Inc**.**

Novel classes of antibiotics

Name & class	Target	Phase	Activity against ESKAPE	Changes for development	Added advantage & new indications	Route	Company
Iclaprim dihydrofolate reductase (DHFR) inhibitor	Dihydro-folate reductase	ND A	Yes: S. aureus	Iclaprim is a selective bacterial dihydrofolate reductase (DHFR)	acomplicatedpo, iv estructure skin infections, orphan		Motif Bio PLC

				inhibitor	drug for cystic fibrosis		
Lefamulin Pleuromutilin	50S ribosomal subunit at the peptidyl transferase center	NDA	Yes: S. aureus	novel systemic pleuromutilin antibiotic	ABSSSI, cervicitis, and urethritis	po, iv	Nabriva Therapeutics PLC
ACX-362E DCBG {(dichloro-benzyl) guanine	C. difficile DNA polymerase IIIC	1	NIL	Ibezapolstat (ACX-362E) is the first DNA polymerase IIIC inhibitor	C. Difficile infections, no adverse events reported	po, topical	Acurx Pharmaceuticals LLC
CRS3123 Diaryldiamine	Methionyl-tRNA synthetase	1	Yes: E. faecium, S. aureus	CRS3123 is a small molecule protein synthesis inhibitor that acts on the novel target methionyl-tRNA synthetase	Highly potent against all clinical isolates of C. difficile;	po	Crestone Inc.
Afabicin (Debio 1450) Benzofuran naphthyridine	FabI	2	Yes: S. aureus	Afabicin (Debio 1450), a prodrug of the small-molecule, enoyl ACP reductase (FabI) inhibitor Debio 1452	Selective bone and joint infections (Staphylococcus specific)	po, iv	Debiopharm International SA
ARV-1801 Fusidane	Elongation factor G	2	Yes: S. aureus		Orphan drug for cystic fibrosis, prosthetic joint infection	po	Arrevus Inc. (acquired from Melinta Therapeutics Inc.)

					s		
Brilacidin Defensin mimetic	Cell membrane	2	Yes: S. aureus		ABSSSI	No recent information	Innovation Pharmaceuticals Inc.
CG-549 Benzyl pyridinone	FabI	2	Yes: S. aureus		ABSSSI, Indicated for Methicillin-resistant Staphylococcus aureus (MRSA).	No recent information	CrystalGenomics Inc
Gepotidacin Triazaacenaphthylene	Bacterial type topoisomerase (novel subunit site	2	Yes: S. aureus	a novel, first-in-class triazaacenaphthylene antibacterial	uncomplicated urogenital gonorrhea	po	GlaxoSmithKline PLC
MGB-BP-3 Distamycin	DNA minor groove binder	2	Possibly: E. faecium, S. aureus	derived chemical-synthesis and from Distamycin	C. Difficile infections	po, topical	MGB Biopharma Ltd.
Murepavadin Antimicrobial peptide mimetic	LptD	3	Yes: P. aeruginosa	It is synthetic cyclic beta hairpin peptidomimetic based the cationic antimicrob	bloodstream infection	Inhalaion, iv	Polyphor AG

				ial peptide prot egrin I			
Ridinilazole Bis-benzimidazole	Inhibition of division and reduction of t oxin production	3	nil	novel narrow-spectrum nonabsorba ble antibiotic	specific action against c.difficule and long post-antibiotic effect	po, topical	Summit Therapeutics PL
Zoliflodacin Spiropyrimidinetrione	Bacterial type topoisomerase (GyrB)	3 II	Yes: S. aureus	Spiropyrimidinetrione antibiotic	Fast track designation by U.s.fda for gonococcal infection	po	Entasis Therapeutics Inc

ABSSSI acute bacterial skin and skin structure infections, CABP community-acquired bacterial pneumonia, CDI C. difficile infection, cIAI complicated intra- abdominal infections, cUTI complicated urinary tract infections, DHFR dihydrofolate reductase, iv intravenous, MRSA methicillin-resistant S. aureus, NP natural product, PBP penicillin binding protein, po per orem (oral), S synthetic, SSSI skin and skin structure infections, TB tuberculosis, VABP ventilator-associated bacterial pneumonia, CDIC. difficileinfections, G−veGram-negative, G+ve Gram-positive, MRSA methicillin-resistantS.aureus

Tables compiled from- 1. The pew charitable trusts SEP2019 Antibiotics Currently in Global Clinical Development

2. **World health organisation 2019 ANTIBACTERIAL AGENTS IN CLINICAL DEVELOPMENT an analysis of the antibacterial clinical development pipeline**
3. **Mark S. Butler, David L. Paterson Review article Antibiotics in the clinical pipeline in October 2019**

II. CONCLUSION

Despite taking efforts for developing new antibiotics with novel mechanisms or developing antibiotics in existing class, the problem of antimicrobial resistance remains inevitable. Funding to pharmaceutical companies and concern towards antimicrobial resistance may prove fruitful in this situation. Hopefully we will have a number of novel antibiotics to tackle antimicrobial resistance in near future.

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Conflicts of interest

The authors declare no conflict of interest.

REFERENCES

[1]. Robert L. Zimdahl, in Six chemicals that changed agriculture, 2015
[2]. Asif M (2017) Antimicrobial Agents. J Anal Pharm Res 4(3): 00104. DOI: 10.15406/ japlr.2017.04.00104
[3]. Brad Spellberg,1 John H. Powers,3 Eric P. Brass,1,2 Loren G. Miller,1,2 and John E. Edwards, Jr.1,2 Trends in Antimicrobial Drug Development: Implications for the Future
[4]. Walsh & Wright. Introduction: Antibiotic resistance Chem. Rev. 2005, 105, 2, 391–394
[5]. Projan 2003; Shlaes 2003. Why is Big Pharma getting out of antibacterial drug discovery? Curr Opin Microbiol 2003;6:427–30
[6]. Bister et al. 2004 Bojan Bister, Daniel Bischoff, Markus Strobele, Julia Riedlinger, Andreas Reicke, Falko Wolter, Alan T. Bull, Hans Zahner, Hans-Peter Fiedler, and Roderich D. Sussmuth* Abyssomicin C—A Polycyclic Antibiotic from a Marine Verrucosispora Strain as an Inhibitor of the p-Aminobenzoic Acid/Tetrahydrofolate Biosynthesis Pathway**
[7]. Patrick d schloss & JO Handelsman 2005 Metagenomics for studying unculturable microorganisms : cutting the Gordon knot
[8]. Pauline Yoong, Raymond Schuch, Daniel Nelson, Vincent A. Fischetti 2004 Identification of a Broadly Active Phage Lytic Enzyme with Lethal Activity against Antibiotic-Resistant Enterococcus faecalis and Enterococcusfaecium
[9]. Kolb et al. 2001 Click Chemistry: Diverse Chemical Function from a Few Good Reactions
[10]. Li and Liu 2004; Halpin et al. 2004; Halpin and Harbury 2004a,b DNA Display III. Solid-Phase Organic Synthesis on Unprotected DNA