NEW ANTIBACTERIAL AGENTS

MRB Maloba
National Health Laboratory services,(NHLS) DGMAH, Univ of Limpopo, MEDUNSA campus

Presentation outline

- Antibiotic pipeline
- Fidaxomicin
- Bedaquiline
- Daptomycin
- Conclusion

ANTIBIOTIC PIPELINE

- Antibiotics have saved countless lives since the discovery of sulfonamides and beta-lactams in the 1930s
- These breakthrough discoveries initiated a "golden era" of antibiotic research~40 years
- During 1970s -1999: innovative antibiotic pipeline dried up
- All launched antibiotics: analogues of existing drugs except mupirocin

ANTIBIOTIC PIPELINE

- Since 2000, 5 more new classes of antibiotics launched:

1. Linezolid (systemic, approved 2000)
2. Daptomycin (systemic, approved 2003)
3. Retapamulin (topical, approved 2007)
4. Fidaxomicin (*Clostridium difficile infections, approved 2010)*
5. Bedaquiline (systemic, approved 2012)

The Journal of Antibiotics(2013)66,571-591

ANTIBIOTIC PIPELINE

Recent years : evidence of return to pre-antibiotic era:

1. increasing threat of drug-resistant 'superbugs'
2. the dearth of new classes of antibiotics
3. disengagement of most pharmaceutical companies from antibiotic research:

- economic challenges-comparably poor returns
- regulatory challenges: costly phase-III trials-onerous recruitment requirements needed to fulfil non-inferiority conditions mandated by the FDA

ANTIBIOTIC PIPELINE

- In 1990: 18 large pharmaceutical companies actively engaged in antibiotic R&D, today= 4 :

1. AstraZeneca (London,UK)
2. Novartis (Basel, Switzerland)
3. GSK (London, UK)
4. Sanofi-Aventis (Paris, France)

- Pfizer (Groton, CT, USA), closed its antibiotic antibiotics R&D center, Connecticut: 2011

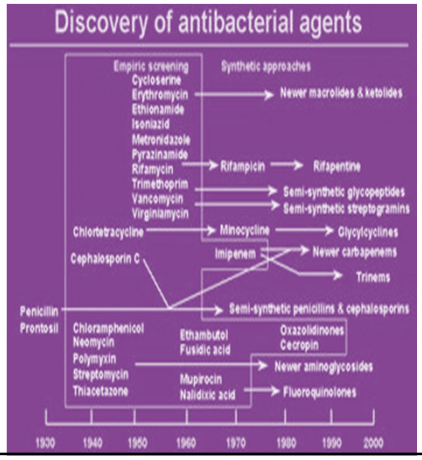


Table 1 Antibiotics of NP or S origin launched since 2000 with antibiotic class, activity against Gram-positive and/or Gram-negative bacteria, lead source and NP-lead source organism

Year approved	*Drug name*[a,b]	*Class*	*Bacteria type*[c]	*Lead source*	*NP-lead source organism*
2000	Linezolid	Oxazolidinone	G+ve	S	
2001	Telithromycin	Macrolide	G+ve/G−ve	NP derived	Actinomycete
2002	Biapenem	Carbapenem	G+ve/G−ve	NP derived	Actinomycete
2002	Ertapenem	Carbapenem	G+ve/G−ve	NP derived	Actinomycete
2002	Prulifloxacin	Fluoroquinolone	G+ve/G−ve	S	
2002	Pazufloxacin	Fluoroquinolone	G+ve/G−ve	S	
2002	Balofloxacin	Fluoroquinolone	G+ve/G−ve	S	
2003	Daptomycin[b]	Lipopeptide	G+ve	NP	Actinomycete
2004	Gemifloxacin	Fluoroquinolone	G+ve/G−ve	S	
2005	Doripenem	Carbapenem	G+ve/G−ve	NP derived	Actinomycete
2005	Tigecycline	Tetracycline	G+ve/G−ve	NP derived	Actinomycete
2007	Retapamulin[b,d,e]	Pleuromutilin	G+ve	NP derived	Fungus
2007	Garenoxacin	Quinolone	G+ve/G−ve	S	
2008	Ceftobiprole medocaril	Cephalosporin	G+ve/G−ve	NP derived	Fungus
2008	Sitafloxacin	Fluoroquinolone	G+ve/G−ve	S	
2009	Tebipenem pivoxil	Carbapenem	G+ve/G−ve	NP derived	Actinomycete
2009	Telavancin	Glycopeptide	G+ve	NP derived	Actinomycete
2009	Antofloxacin	Fluoroquinolone	G+ve/G−ve	S	
2009	Besifloxacin[e]	Fluoroquinolone	G+ve/G−ve	S	
2010	Ceftaroline fosamil	Cephalosporin	G+ve/G−ve	NP derived	Fungus
2011	Fidaxomicin (1)[b]	Tiacumicin	G+ve	NP	Actinomycete
2012	Bedaquiline (2)[b]	Diarylquinoline	G+ve (TB)	S	

The Journal of Antibiotics(2013)66,571-591

ANTIBIOTIC PIPELINE

- Bedaquiline: noteworthy- fast tracked through clinical trials for use in combination with other drugs to treat tuberculosis
- However all of these new antibiotic classes are mainly limited to Rx of Gram+ve infections
- New therapies capable of treating Gram-negative infections desperately needed

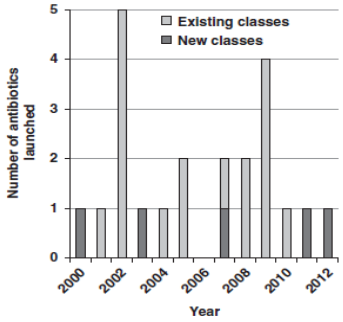
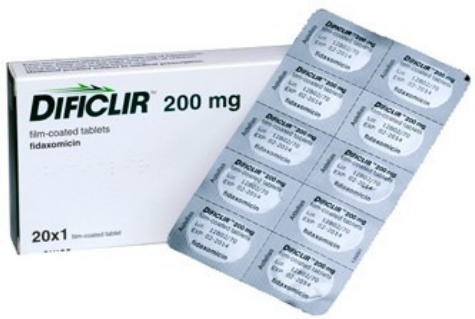


Figure 1 New antibiotic approvals 2000–2012 with new classes highlighted.



FIDAXOMICIN

- First drug for CDAD to be approved in nearly 25 years
- Contains a narrow spectrum 18-ring macrolide antibiotic, belongs to tiacumicin class
- Originally known as lipiarmycin A4
- Produced by fungus: *Actinoplanes deccanensis* [Coronelli et al. 1975]
- Approved by FDA -2010, launched-2011

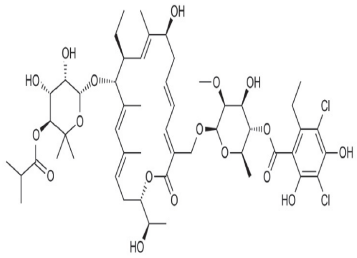


Figure 1. Molecular structure of fidaxomicin.

FIDAXOMICIN

- MOA: inhibits RNA transcription at the sigma subunit and mobile-clamp domain ß' of the RNA polymerase
- Has an inhibitory effect on sporulation

FIDAXOMICIN PHARMACOKINETICS

- Almost completely insoluble in water at pH value found in the GI tract with minimal systemic absorption
- Plasma blood levels mostly below 5 ng/ml
- Total fecal recovery of fidaxomicin and its metabolite = 100%.

FIDAXOMICIN CLINICAL STUDIES

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

Thomas J. Louie, M.D., Mark A. Miller, M.D., Kathleen M. Mullane, D.O., Karl Weiss, M.D., Arnold Lentnek, M.D., Yoav Golan, M.D., Sherwood Gorbach, M.D., Pamela Sears, Ph.D., and Youe-Kong Shue, Ph.D., for the OPT-80-003 Clinical Study Group*

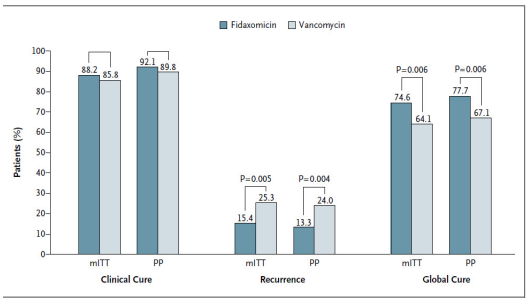
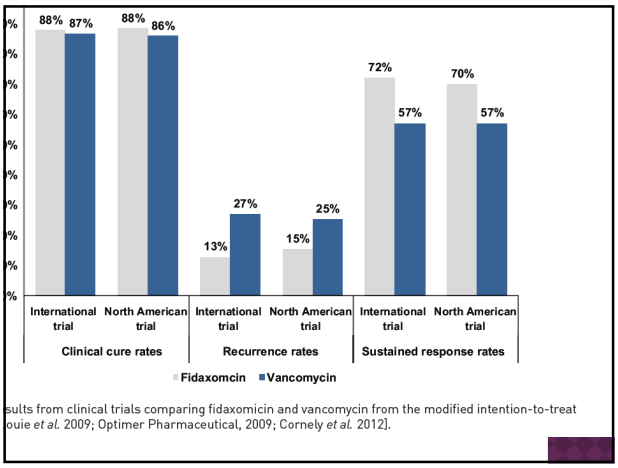


Figure 2. Rates of Primary and Secondary End Points.
For the primary outcome of clinical cure, the lower boundary of the 97.5% confidence interval for the difference in cure rates between fidaxomicin and vancomycin was −3.1 percentage points in the modified intention-to-treat (mITT) analysis and −2.6 percentage points in the per-protocol (PP) analysis. N Engl J Med 2011;364:422-31.



sults from clinical trials comparing fidaxomicin and vancomycin from the modified intention-to-treat ouie *et al.* 2009; Optimer Pharmaceutical, 2009; Cornely *et al.* 2012].

FIDAXOMICIN INDICATIONS

- Recommended dose: 200 mg tablet twice daily X 10 days with/without food [Optimer Pharmaceuticals, 2011]
- adults >18yrs old with suspected CDAD
- Safety and efficacy not studied in the pediatric population

FIDAXOMICIN SAFETY PROFILE

- Good safety profile in a wide population with minimal adverse side effects
- Minor GIT S/E, elevated transaminases and hyperuricemia
- No dose adjustment in elderlies/patients with impaired renal function
- Theoretical concern: interaction between cyclosporine and fidaxomicin due to the P-glycoprotein (P-gp) efflux pump

FIDAXOMICIN RESISTANCE

- *C. difficile* has minimal ability to develop spontaneous resistance to fidaxomicin in vitro and in clinical studies
- Resistance frequency= 2.8 × 10 at 4-8 X MIC: similar to both vancomycin and metronidazole
- However, in one single strain isolated from a cured patient, an elevated fidaxomicin MIC of 16 µg/ml was noted at recurrence
- At baseline, prior to receiving therapy, the same strain had MIC of 0.06 µg/ml
- A specific mutation in the RNA polymerase

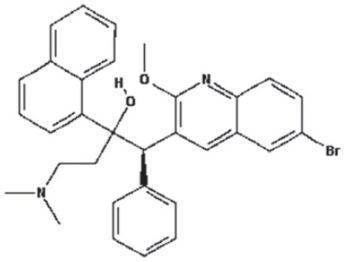
FIDAXOMICIN

- CDAD is a major cause of healthcare-associated diarrhea and with few treatment therapies
- Fidaxomicin narrow spectrum of activity and ease of administration make it an attractive alternative to current therapies

Sirturo™
bedaquiline
100mg tablets

BEDAQUILINE

- It is the first anti-TB agent to be approved by the FDA in more than 40 years
- A novel oral anti-mycobacterial agent, belongs to class diarylquinoline
- Compounded with fumaric acid (1:1) as bedaquiline fumarate (Sirturo, Janssen Products, LP)
- Originally developed thru Tibotec and the TB Alliance partnership



Bedaquiline fumarate

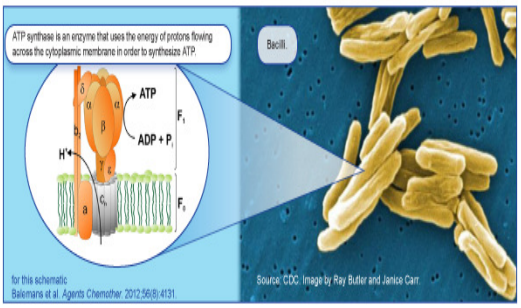
Chemical Formula: $C_{36}H_{35}BrN_2O_6$

Molecular Weight: 671.5769

BEDAQUILINE

- MOA: Inhibits the proton pump activity of adenosine triphosphate (ATP) synthase in MTB
- Unlike in many other bacteria, ATP synthase is essential for the optimal growth of MTB
- Targets the central region of the c subunit of the enzyme, halting the energy production process, inhibiting reproduction, lt cell death

SIRTURO™ Mechanism of Action



BEDAQUILINE SOA

- It exerts a bactericidal and sterilizing activity against MTB, including MDR strains, non replicating dormant strains and selected NTMs
- *M leprae* in a murine leprosy model

BEDAQUILINE PHARMACOKINETICS

- Bio- availability: incr. ~2-fold with meal containing approx 22 g of fat
- Plasma protein binding >99.9%
- CYP3A4 of the cytochrome P450 system metabolised
- Long t ½ =approx 5.5 months independent of the administered dose (slow release of bedaq and M2 from peripheral tissues-phospholipidosis)
- Primarily eliminated in the stools

BEDAQUILINE INDICATION/DOSING

- The FDA granted fast approval, an "orphan drug" designation to Rx adults(>18yrs) with MDR-PTB as part of a combination therapy when an effective treatment regimen cannot otherwise be provided (Dec 2012)
- Recommended dose =400 mg orally once daily 1st 2 wks, 200 mg 3x/ week thereafter for a total of 24 weeks with food (DOT)

Chahine et al

Table 1. In Vitro Activity of Bedaquiline[a] Against *Mycobacterium tuberculosis*.[18,19]

Organism	Isolates, n	Range of MICs (µg/mL)
M tuberculosis		
Drug susceptible[b,c]	41	0.002-0.12
Multidrug resistant[b,c]	44	0.004-0.13

[a]Susceptibility to bedaquiline was determined using an agar dilution method.
[b]MIC_{50} = minimum inhibitory concentration for 50% of tested isolates = 0.03 µg/mL.
[c]MIC_{90} = minimum inhibitory concentration for 90% of tested isolates = 0.06 µg/mL.

Table 2. In Vitro Activity of Bedaquiline[a] Against Nontuberculous *Mycobacterium* Species.[11,18,19]

Organism	Isolates, n	Range of MICs (µg/mL)
Mycobacterium avium complex[b]	22	0.03-0.25
M abscessus[c]	1	NR
M chelonae	3	0.06-0.5
M conspicuum	1	0.13
M fortuitum	3	0.13-0.25
M gordonae	1	0.03
M hiberniae	1	0.03
M interjectum	1	0.03
M kansasii	1	0.03
M mageritense	1	0.03
M malmoense	1	0.5
M marinum[d]	1	NR
M phlei	2	0.03-0.13
M simiae	2	0.03
M smegmatis	7	0.003-0.01
M scrofulaceum	1	0.03
M szulgai	2	0.03-0.06
M terrae	2	0.03-0.13
M ulcerans[e]	1	NR
M vaccae	2	0.03

BEDAQUILINE SAFETY CONCERNS

- Nausea, arthralgia, headache, hemoptysis, and chest pain
- QT prolongation: C/I pts with cardiac conduction abnormalities and those on other QT-prolonging agents,e.g. macrolides, fluoroquinolones, azole antifungals
- CYP3A4 interactions warrant pt monitoring, particularly when prescribed with rifamycins and/or antiretrovirals

BEDAQUILINE RESISTANCE

- MTB resistance: missense mutations of the atpE gene, disrupts capacity to bind to the c sub-unit of the F0 domain of ATP synthase
- The mutation either occurs at pos 63 with a proline substituting alanine or at pos 66 with a methionine substituting a leucine

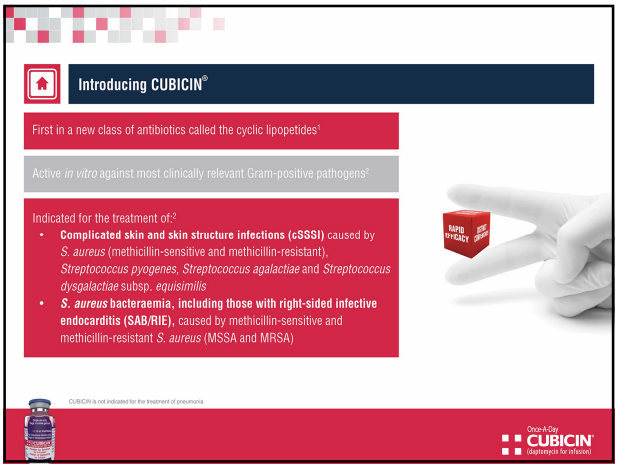
BEDAQUILINE RESISTANCE

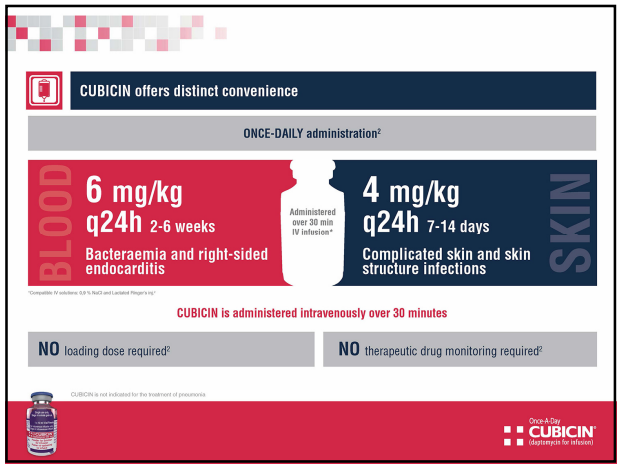
Three species of NTMs found to be intrinsically resistant:

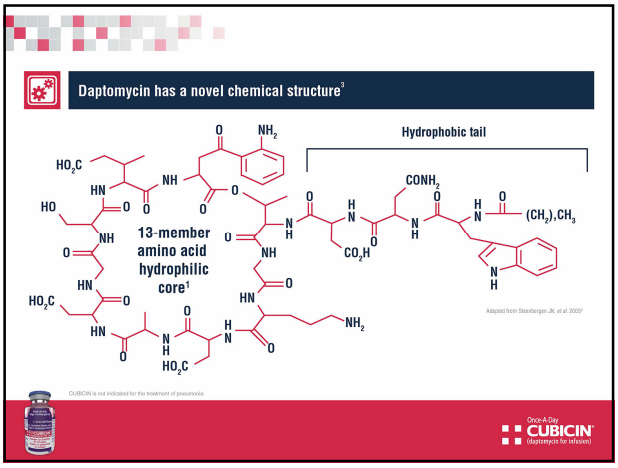
- *M novocastrense* (MIC of 8.0 µg/mL)
- *M shimoidei* (MIC of 8.0 µg/mL)
- *M xenopi* (MIC 4.0-8.0 µg/mL)

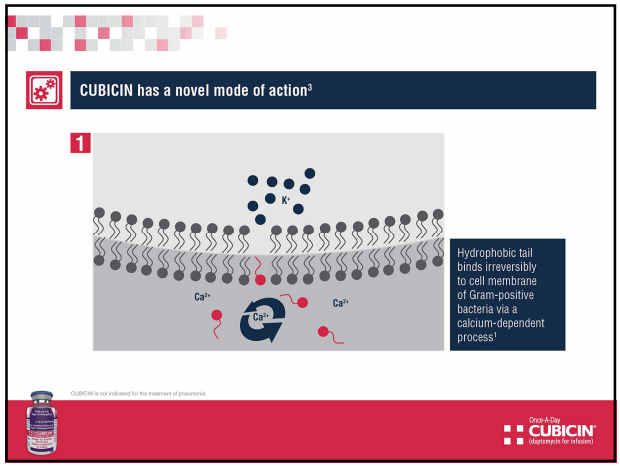
BEDAQUILINE

- Phase 3 studies needed to further evaluate safety, efficacy, and tolerability in TB pts
- Cost may represent a burden in resource-limited countries: 24-wk course of therapy, cost= $36 000.00



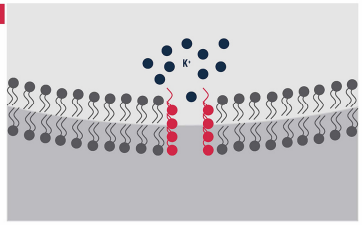






CUBICIN has a novel mode of action[3]

2



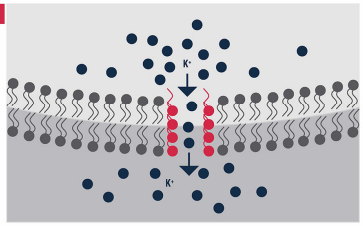
An ion channel is formed through the cell membrane[3]

CUBICIN is not indicated for the treatment of pneumonia

Once-A-Day CUBICIN (daptomycin for infusion)

CUBICIN has a novel mode of action[3]

3



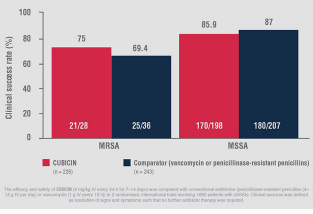
Efflux of potassium ions causes rapid depolarisation of the cell membrane and rapid cell death due to arrest of DNA, RNA and protein synthesis[1,3]

CUBICIN is not indicated for the treatment of pneumonia

Once-A-Day CUBICIN (daptomycin for infusion)

CUBICIN – proven effective for treatment of cSSSIs[16]

Clinical success against MRSA and MSSA in cSSSIs[16]



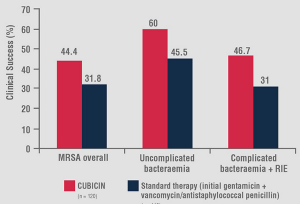
CUBICIN was not inferior to standard therapy for the treatment of cSSSI caused by MSSA or MRSA[16]

CUBICIN is not indicated for the treatment of pneumonia

Once-A-Day CUBICIN (daptomycin for infusion)

CUBICIN – proven effective for treatment of SAB/RIE[23]

Clinical outcomes in MRSA bacteraemia/RIE[23]



CUBICIN was not inferior to standard therapy for the treatment of SAB/RIE[23]

CUBICIN is not indicated for the treatment of pneumonia

Once-A-Day CUBICIN (daptomycin for infusion)

ESCMID/ISC: suitability of other agents for MRSA bacteraemia/endocarditis[21]

Agent	First-line treatment for severe MRSA bacteraemia/endocarditis	Recommendations
Teicoplanin[21]	NO	• Even with a loading dose, 2-3 days are required to reach a therapeutic plasma level, making it less suitable for treating acute severe infection and more appropriate for long-term therapy • Limited role in severe MRSA infections where there is particular concern over nephrotoxicity
Linezolid[21]	NO	• Warning against use in catheter-related blood stream infections or catheter-site infections
Tigecycline[21]	NO	• Secondary 'rescue' role only
Older agents[21] Tetracycline, chloramphenicol, cotrimoxazole, rifampicin, fosfomycin	NO	• Chloramphenicol to be used only as last resort owing to its myelotoxicity

ESCMID: European Society of Clinical Microbiology and Infectious Diseases; IDC: International Society of Chemotherapy; MIC: minimum inhibitory concentration; MRSA: methicillin-sensitive S. aureus; MRSA: methicillin-resistant S. aureus

CUBICIN is not indicated for the treatment of pneumonia

Once-A-Day CUBICIN (daptomycin for infusion)

CUBICIN has an established safety and tolerability profile[25]

Adverse events are comparable to that of standard therapy*[16]

Adverse events that occurred in ≥ 2 % of **CUBICIN**-treated patients and the comparator group[16]

Event	CUBICIN (n=534)	Comparator* (n=558)
Headache	5.4	5.4
Diarrhoea	5.2	4.3
Rash	4.3	3.8
Abnormal liver function tests	3.0	1.6
Elevated creatine phosphokinase level	2.8	1.8
Hypotension	2.4	1.4
Urinary tract infection	2.4	0.5
Dizziness	2.2	2.0
Dyspnoea	2.1	1.6

*vancomycin and penicillinase-resistant penicillins (cloxacillin, flucloxacillin, nafcillin, oxacillin)

The majority of adverse events were considered unrelated to therapy and mild-to-moderate in intensity[16]

CUBCIN has no significant CYP450 drug-drug interactions[2]

CUBICIN is not indicated for the treatment of pneumonia

Once-A-Day CUBICIN (daptomycin for infusion)

AAC
Journals.ASM.org

Evaluation of Telavancin Activity versus Daptomycin and Vancomycin against Daptomycin-Nonsusceptible *Staphylococcus aureus* in an *In Vitro* Pharmacokinetic/Pharmacodynamic Model

Molly E. Steed,[a] Céline Vidaillac,[a] and Michael J. Rybak[a,b,c]
Anti-Infective Research Laboratory, Eugene Applebaum College of Pharmacy and Health Sciences,[a] School of Medicine, Wayne State University,[b] and Detroit Receiving Hospital,[c] Detroit, Michigan, USA

Daptomycin-nonsusceptible (DNS) *Staphylococcus aureus* strains have been reported over the last several years. Telavancin is a lipoglycopeptide with a dual mechanism of action, as it inhibits peptidoglycan polymerization/cross-linking and disrupts the membrane potential. Three clinical DNS *S. aureus* strains, CB1814, R6212, and SA-684, were evaluated in an *in vitro* pharmacokinetic/pharmacodynamic (PK/PD) model with simulated endocardial vegetations (starting inoculum, $10^{8.5}$ CFU/g) for 120 h. Simulated regimens included telavancin at 10 mg/kg every 24 h (q24h; peak, 87.5 mg/liter; $t_{1/2}$, 7.5 h), daptomycin at 6 mg/kg q24h (peak, 95.7 mg/liter; $t_{1/2}$, 8 h), and vancomycin at 1 g q12h (peak, 30 mg/liter; $t_{1/2}$, 6 h). Differences in CFU/g between regimens at 24 through 120 h were evaluated by analysis of variance with a Tukey's *post hoc* test. Bactericidal activity was defined as a ≥3-$\log_{10}$ CFU/g decrease in colony count from the initial inoculum. MIC values were 1, 0.25, and 0.5 mg/liter (telavancin), 4, 2, and 2 mg/liter (daptomycin), and 2, 2, and 2 mg/liter (vancomycin) for CB1814, R6212, and SA-684, respectively. Telavancin displayed bactericidal activities against R6212 (32 to 120 h; −4.31 $\log_{10}$ CFU/g), SA-684 (56 to 120 h; −3.06 $\log_{10}$ CFU/g), and CB1814 (48 to 120 h; −4.9 $\log_{10}$ CFU/g). Daptomycin displayed initial bactericidal activity followed by regrowth with all three strains. Vancomycin did not exhibit sustained bactericidal activity against any strain. At 120 h, telavancin was significantly better at reducing colony counts than vancomycin against all three tested strains and better than daptomycin against CB1814 ($P < 0.05$). Telavancin displayed bactericidal activity *in vitro* against DNS *S. aureus* isolates.

REVIEW ARTICLE
Drugs 2012; 72 (11): 1473-1493
0012-6667/12/001-1473/$58.95/0
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Ceftaroline Fosamil in the Treatment of Community-Acquired Bacterial Pneumonia and Acute Bacterial Skin and Skin Structure Infections

Thomas P. Lodise[1] and *Donald E. Low*[2]
1 Albany College of Pharmacy and Health Sciences, Albany, New York, NY, USA
2 Mount Sinai Hospital/University Health Network, Toronto, ON, Canada

Table 2 Compounds in phase-III clinical trials or under NDA/MAA evaluation

Name (synonym)[a]	Lead compound (lead source)	Mode of action	Bacteria type	Indication and development status (developer)
Small molecule antibiotics				
Dalbavancin (3)	Glycopeptide (A40926) (NP)	Cell wall inhibition	G + ve	Two ABSSSI completed (Durata Therapeutics)
Oritavancin (4)	Glycopeptide (chloroeremomycin) (NP)	Cell wall inhibition	G + ve	One ABSSSI completed, one in progress (The Medicines Company)
Omadacycline (5)	Tetracycline (NP)	Protein synthesis inhibition	G + ve/G − ve	ABSSSI (Paratek)
Eravacycline (6)	Tetracycline (NP)	Protein synthesis inhibition	G + ve/G − ve	cIAI (Tetraphase)
Solithromycin (7)	Erythromycin (NP)	Protein synthesis inhibition	G + ve/G − ve	CAP (Cempra)
Surotomycin (8)	Lipopeptide (daptomycin) (NP)	Membrane depolarization	G + ve	CDAD (Cubist)
Tedizolid phosphate (9a)	Oxazolidinone (S)	Protein synthesis inhibition	G + ve/G − ve	ABSSSI completed (Trius Therapeutics)
Delamanid (10)	Nitroimidazole (S)	DNA and cellular damage	G + ve (TB)	NDA and phase-III, TB (Otsuka Pharmaceuticals)
Perchlozone (11)	Thiosemicarbazone (S)	Unknown	G + ve (TB)	TB completed (USC Pharmasynthe)
SQ109 (12)	Ethambutol (S)	Cell wall synthesis	G + ve (TB) / G-ve	TB; also *H. pylori*-associated duodenal ulc (Sequella/Infectex)
Finafloxacin (13)	Fluoroquinolone (S)	DNA gyrase and topoIV	G + ve/G − ve	Acute Otitis Media; also completed phase- *H. pylori* and UTI (MerLion)
Delafloxacin (14)	Fluoroquinolone (S)	DNA gyrase and topoIV	G + ve/G − ve	ABSSI (Rib-X Pharmaceuticals)
Avarofloxacin (15)	Fluoroquinolone (S)	DNA gyrase and topoIV	G + ve/G − ve	Irritable bowel syndrome; phase-II CABP, ABSSSI completed (Furiex)
Zabofloxacin (16)	Fluoroquinolone (S)	DNA gyrase and topoIV	G + ve/G − ve	CAP (Dong Wha Pharmaceutical)
Nemonoxacin (17)	Quinolone (S)	DNA gyrase and topoIV	G + ve/G − ve	CAP (TaiGen Biotechnology)
Ozenoxacin (18)	Quinolone (S)	DNA gyrase and topoIV	G + ve	Impetigo (Grupo Ferrer Internacional) acn topical (Maruho Co)
β-Lactam/β-lactamase inhibitor combinations				
CXA-201 (ceftolozane (19)/ tazobactam (20))	Cephalosporin (NP)/ clavulanic acid (NP)	Penicillin-binding protein/ β-lactamase inhibitor	G + ve/G − ve	cUTI, cIAI; also phase-II HABP/ VABP (Cubist)
CAZ104 (ceftazidime (21)/ avibactam (22))	Cephalosporin (NP)/ diazabicyclooctane (S)	Penicillin-binding protein/ β-lactamase inhibitor	G + ve/G − ve	cIAI; UTI (AstraZeneca)

The Journal of Antibiotics(2013)66,571-591

CONCLUSION

Efforts to improving antibiotic research atmosphere :

- the US Generating Antibiotic Incentives act
- the Innovative Medicines Initiative New Drugs for Bad Bugs (IMI ND4BB), a $280 million fund~R&D of new antibiotics, basic research: how antibiotics penetrate G-ve bacteria
- the IDSA 10'20 initiative: development of 10 new safe, efficacious systemically admin antibiotics by 2020: to treat G-ve bacteria

CONCLUSION

- Emerging alternative approaches for prevention and Rx of bacterial infections: non-antibiotic-based therapies:
  - vaccines
  - neutralizing antibodies
  - probiotic therapy
  - phage therapy
  - immune stimulation
  - -virulence factor neutralization
- Emerging initiatives to support antimicrobial stewardship