New Bugs? New Drugs!

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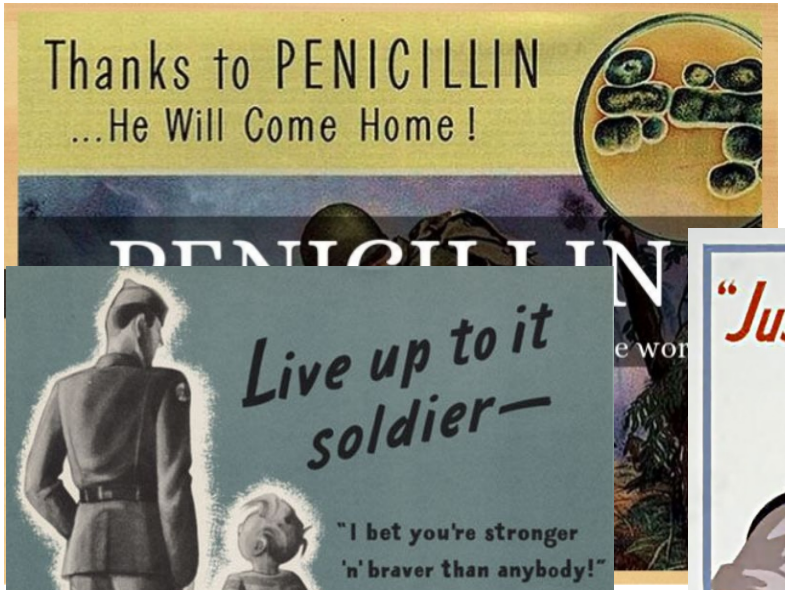
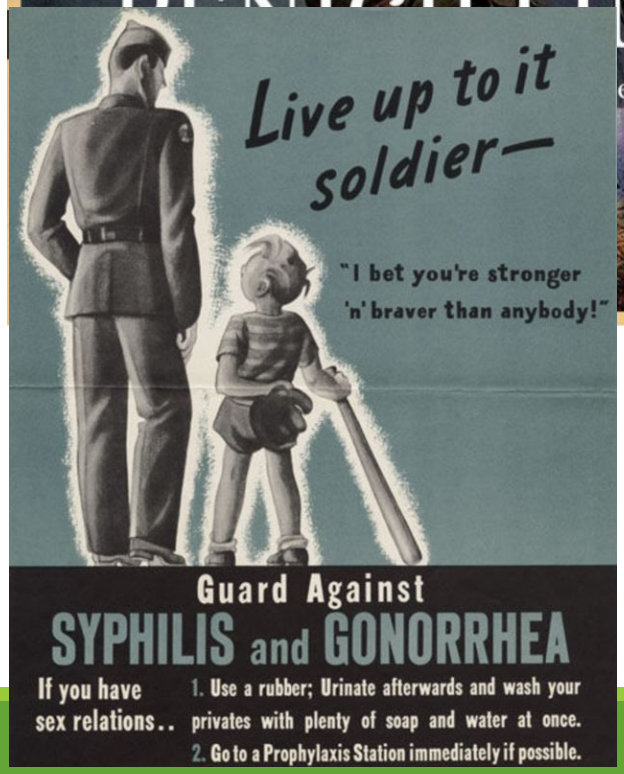
A long time ago, in a galaxy far, far away……





The Microorganisms Strike Back

- Urgent threat
  - *Clostridium difficile*
  - Carbapenem-resistant *Enterobacteriaceae*
  - Drug-resistant *Neisseria gonorrhoeae*
- Serious threat
  - Multi-drug resistant *Acinetobacter*
  - Drug-resistant *Campylobacter*
  - Fluconazole-resistant *Candida*
  - Extended spectrum β-lactamase producing *Enterobacteriaceae* (ESBLs)
  - Vancomycin resistant *Enterococcus* (VRE)
  - Multi-drug resistant *Pseudomonas aeruginosa*
  - Drug-resistant non-typhoidal *Salmonella*
  - Drug-resistant *Shigella*
  - Methicillin-resistant *Staphylococcus aureus* (MRSA)
  - Drug-resistant *Streptococcus pneumoniae*
  - Drug-resistant tuberculosis

https://www.cdc.gov/drugresistance/biggest_threats.html

Learning Objectives

1. Review recently FDA approved antimicrobials and antimicrobials in the pipeline
2. Discuss appropriate use of new antimicrobial agents and their niche in therapy
3. Assess various treatment options for patient cases

A New Hope?

RECENTLY APPROVED

- 2015
  - Ceftazidime-avibactam
  - Isavuconazonium sulfate
- 2016
  - Obiltoxaximab
  - Bezlotoxumab
- 2017
  - Meropenem/vaborbactam*
  - Delafloxacin*
  - Ozenoxacin*
  - Secnidazole

PHASE 3 CLINICAL TRIALS

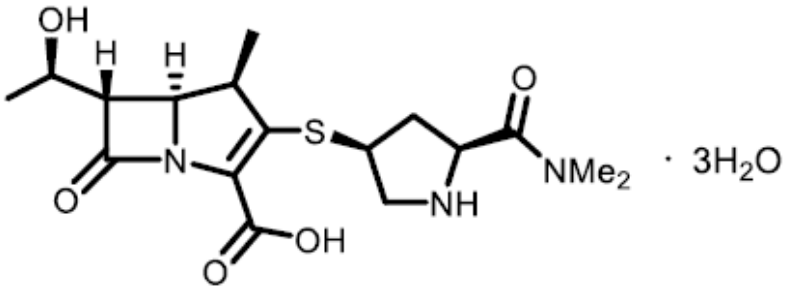
- Cadazolid
- Cefiderocol*
- Ervacycline
- Iclaprim*
- Imipenem/cilastatin/relebactam*
- Lefamulin*
- Omadacycline
- Plazomicin
- Zolithromycin
- Fusidic acid
- Zabofloxacin

https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf
http://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2013/11/07/gain-how-a-new-law-is-stimulating-the-development-of-antibiotics

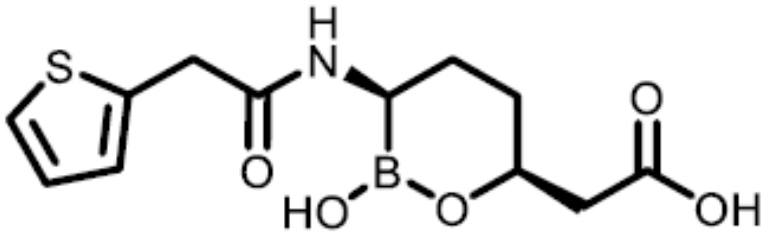
FDA Approved Antibacterials

Meropenem/vaborbactam (Vabomere™)

- Indication: complicated UTI in adults including pyelonephritis
  - Qualified infectious disease product: cUTI, IAI, HABP, VABP, NF, and CRBSI
- Mechanism of action:
  - Meropenem – binds to PBP to inhibit cell wall synthesis
  - Vaborbactam – non-suicidal β-lactamase inhibitor
- Dose: 4g (2g meropenem and 2g vaborbactam) IV over 3 hrs q8h
  - Renal adjustment required for both meropenem and vaborbactam



· $3H_2O$



Vabomere™. [Package insert]. Parsippany, NJ: The Medicines Company; 2017

Meropenem/vaborbactam

Indicated Bacteria	Possible Bacteria
Enterobacter cloacae species complex	*Citrobacter freundii*
Escherichia coli	*Citrobacter koseri*
Klebsiella pneumoniae	*Enterobacter aerogenes*
	Klebsiella oxytoca
	Morganella morganii
	Proteus mirabilis
	Providencia species
	Pseudomonas aeruginosa
	Serratia marcescens

Vabomere™. [Package insert]. Parsippany, NJ: The Medicines Company; 2017

Ambler Classification

Class	Active Site	Enzyme Type	Example
A	Serine	- Penicillinase - Broad Spectrum - Extended-Spectrum - Carbapenemase	- TEM1, SHV-1 in *E. coli* and *K. pneumoniae* - CTX-M in *P. aeruginosa* - KPC-1 in *K. pneumoniae*
B	Metallo-β-lactamases (Zn^{2+})	- Carbapenemase	- NDM-1 in Enterobacteriaceae
C	Serine	- Cephalosporinase	- AmpC in Enterobacteriaceae
D	Serine	- Broad-Spectrum - Extended- Spectrum - Carbapenemase	- OXA- family in *P. aeruginosa*

MOLECULAR MECHANISMS OF ANTIBIOTIC RESISTANCE IN BACTERIA. IN MANDELL, ED. PRINCIPLES AND PRACTICE OF INFECTIOUS DISEASES. 8TH ED.
BLAIR JM, ET AL. *NATURE* 2015;13: 42-51
MAYO CLIN PROC 2011;86(3):250-259
MAYO CLIN PROC 2015;;90(3):395-403

Amp-C

- Primarily chromosomal

- Common organisms:
  - *Morganella morganii*
  - Yersinia sp.
  - ***Serratia sp.***
  - *Providencia sp./ Pseudomonas sp./ Proteus sp.*
  - Acinetobacter sp./ Aeromonas sp.
  - ***Citrobacter freundii***
  - ***Enterobacter sp.***

Opal S, Pop-Vicas A. Molecular Mechanisms of Antibiotic Resistance in Bacteria. In Mandell, ed. Principles and Practice of Infectious Diseases. 8th ed.
Blair JM, et al. *Nature* 2015;13: 42-51
Kanj S, Kanafani Zeina. *Mayo Clin Proc* 2011;86(3):250-259
Vasoo *Mayo Clin Proc* 2015;;90(3):395-403

Meropenem/vaborbactam

- Susceptibility Interpretation for meropenem/vaborbactam

	S	I	R
Enterobacteriaceae	≤4/8	8/8	≥16/8

- β-lactamase activity
  - Effective against KPC, SME, TEM, SHV, CTX-M, CMY, and ACT
  - NOT active against: metallo-β-lactamases or oxacillinases with carbapenemase activity

Vabomere™. [Package insert]. Parsippany, NJ: The Medicines Company; 2017

Meropenem/vaborbactam

- PK/PD:
  - PK:

Parameter	Meropenem	Vaborbactam
C_{max} (mg/L)	57.3 (23)	71.3 (28.6)
CL (L/h)	10.5 (6.4)	7.95 (4.3)
AUC_{ss} (mg*h/L)	650 (364)	835 (508)
$T_{1/2}$ (h)	2.3 (2.5)	2.25 (2.1)

  - PD parameter:
    - Meropenem: time over MIC
    - Vaborbactam: AUC:MIC
  - Meropenem and vaborbactam are removed by dialysis

Vabomere™. [Package insert]. Parsippany, NJ: The Medicines Company; 2017

Tango 1 - Methods

- Study Design:
  - Phase 3, multicenter, double-blind, double-dummy, randomized comparing meropenem/vaborbactam vs piperacillin/tazobactam in the treatment of cUTI and acute pyelonephritis
- Intervention:
  - Meropenem/vaborbactam 4g IV over 3 hrs q8h vs piperacillin/tazobactam 4.5g IV over 30 min q8h for 10-14 d
  - After 5 days allowed to switch to levofloxacin
- Outcomes:
  - Primary: m-MITT overall success at end of IV therapy
    - Overall success = clinical cure or improvement and eradication of baseline pathogen to $<10^4$ CFU/mL

Tango 1 - Results

Table 4: Results by Primary Endpoint[2]

Primary Endpoint	VABOMERE (n=192) n (%)	piperacillin/ tazobactam (n=182) n (%)	Difference (95% CI)
FDA*			
Overall success rate at EOIVT			
m-MITT Population	189/192 (98.4)	171/182 (94.0)	4.5 (0.7, 9.1)
EMA**			
Overall eradication rate at TOC			
m-MITT population	128/192 (66.7)	105/182 (57.7)	9.0 (-0.9, 18.7)
ME population	118/178 (66.3)	102/169 (60.4)	5.9 (-4.2, 16.0)

CI = confidence interval; EOIVT = end of intravenous treatment; m-MITT = Microbiological Modified Intent-to-Treat, ME = microbiological evaluable; TOC = Test of Cure.
*Per FDA criteria, a microbiologic outcome of Eradication is defined as the demonstration that the bacterial pathogen(s) found at baseline is reduced to <104 CFU/mL of urine.
**Per EMA Criteria, a microbiologic outcome of Eradication is defined as the demonstration that the bacterial pathogen(s) found at baseline is reduced to <103 CFU/mL of urine.
Overall success = clinical outcome of cure or improvement and microbiologic outcome of eradication.

Tango 1 – Results by pathogen

Table 12: Overall Success Rates by Baseline Pathogen and Beta-lactamase Status at EOIVT and TOC (m-MITT Population)[2,20]

		Overall Success at EOIVT		Overall Success at TOC	
Pathogen	**Beta-lactamase Status**	**VAB (N=192) n/N' (%)**	**PIP/TAZO (N=182) n/N' (%)**	**VAB (N=192) n/N' (%)**	**PIP/TAZO (N=182) n/N' (%)**
Escherichia coli	+	27/27 (100.0)	25/27 (92.6)	19/27 (70.4)	16/27 (59.3)
	-	92/94 (97.9)	82/87 (94.3)	77/94 (81.9)	66/87 (75.9)
Klebsiella pneumonia	+	20/21 (95.2)	15/15 (100.0)	12/21 (57.1)	6/15 (40.0)
	-	8/8 (100.0)	10/11 (90.0)	5/8 (62.5)	7/11 (63.6)
Enterobacter cloacae species complex	+	7/7 (100.0)	3/3 (100.0)	5/7 (71.4)	3/3 (100.0)
	-	2/2 (100.0)	1/1 (100.0)	2/2 (100.0)	0/1 (0.0)
Proteus mirabilis	+	4/4 (100.0)	2/2 (100.0)	3/4 (75.0)	2/2 (100.0)
	-	2/2 (100.0)	10/10 (100.0)	0/2 (0.0)	7/10 (70.0)
Pseudomonas aeruginosa	+	2/2 (100.0)	6/8 (75.0)	2/2 (100.0)	3/8 (37.5)
	-	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)	1/2 (50.0)

VAB=VABOMERE; PIP/TAZO=piperacillin/tazobactam

Tango 2

- Study Design:
  - Phase 3, multicenter, open-label, randomized trial of adult patients with CRE serious infections and an anticipated 7 days of IV therapy
    - Serious infection: bacteremia, cUTI, AP, HABP, VABP, cIAI
- Intervention:
  - Meropenem/vaborbactam 4g IV over 4 hrs q8h vs best available therapy
  - Excluded patients with class B metallo-β-lactamases or class D oxacillinases
- Outcomes:
  - Proportion of patients with clinical cure at EOT and TOC
  - All cause mortality at Day 28

Tango 2 - Results

Table 2. Sensitivity Analysis – Clinical Outcomes by Visit Across All Indications (mCRE-MITT Population)[1,2]

	Outcomes Across All Indications		Sensitivity Analysis	
	VABOMERE N = 28 n (%)	BAT N = 15 n (%)	VABOMERE N = 19 n (%)	BAT N = 15 n (%)
Clinical Cure at EOT	18 (64.3)	5 (33.3)	16 (84.2)	5 (33.3)
Clinical Cure at TOC	16 (57.1)	4 (26.7)	13 (68.4)	4 (26.7)
Microbiologic Cure* at EOT	18 (64.3)	6 (40.0)	-	-
Microbiologic Cure* at TOC	14 (50.0)	5 (33.3)	-	-
Day-28 Mortality	5 (17.9)	5 (33.3)	1 (5.3)	5 (33.3)

BAT = best available therapy; mCRE-MITT = microbiological carbapenem-resistant Enterobacteriaceae Modified Intent to Treat; EOT = end of therapy; TOC = test of cure

* Microbiologic eradication of baseline pathogen at respective visit or absence of culture result at respective visit

Unpublished information request from The Medicines Company

Where does vaborbactam fit in?

	ESBL producer	Amp-C producer	Carbapenamase
Ampicillin-sulbactam	R	R	R
Piperacillin-tazobactam	V	R	R
Ceftazidime-avibactam	S	S	V
Ceftolozane-tazobactam	S	S	V
Aztreonam-avibactam	S	S	V
Meropenem-vaborbactam	**V**	**S**	**V**

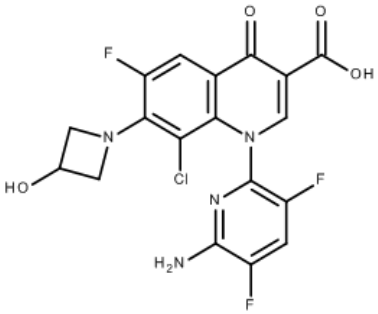
R = resistant
S = sensitive
V = variable

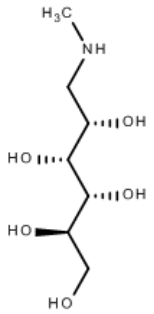
Mayo Clin Proc 2015;90(3):395-403
Unpublished information request from The Medicines Company

Potential Niche?

- Additional trials on clinicaltrials.gov
  - HABP/VABP – not yet recruiting
  - Dose finding study for serious bacterial infections in pediatrics - recruiting
  - Serious infections due to CRE in adults - completed
- Clinical thoughts
  - Since it doesn't cover metallo-β-lactamases would like susceptibilities prior to use
  - For hospitals not doing extended infusions, this drug could be a gateway for other extended infusion β–lactams
  - Interesting that the coverage for *Enterobacter* sp was so much lower than piperacillin-tazobactam when β-lactamases were present
  - Would reserve this drug for multi-drug resistant gram negative organisms with susceptibilities

Delafloxacin (Baxdela™)





- Indication: acute bacterial skin and skin structure infections (ABSSSI)
- Mechanism of action: inhibits both topoisomerase IV and II
  - Inhibits DNA replication, transcription, repaid, and recombination
- Dose:
  - IV: 300mg IV q12h over 60 min x 5-14 d
    - eGFR 15-29: 300mg q14h OR switch to PO after IV dose, not recommended for eGFR < 15
  - PO: 450mg PO q12h x 5-14 d
    - No dose adjustment for renal disease, not recommended for eGFR < 15
  - Switching: 300mg IV q12h over 60 min then switch to 450mg PO q12h at the discretion of the physician for 5-14d
- Warnings
  - Tendinitis, tendon rupture, peripheral neuropathy, central nervous system effects, exacerbation of myasthenia gravis, and CDI
  - No QTc warning

Baxdela™. [Package Insert]. Lincolnshire, Illinois: Melinta Therapeutics; 2017

Delafloxacin

Gram Positive Bacteria	Gram Negative Bacteria
Staphylococcus aureus (including MSSA and MRSA)	*Escherichia coli*
Staphylococcus haemolyticus	*Klebsiella pneumoniae*
Staphylococcus lugdunensis	*Enterobacter cloacae*
Streptococcus pyogenes	*Pseudomonas aeruginosa*
Streptococcus agalactiae	*Enterobacter aerogenes**
Streptococcus anginosus group	*Haemophilus parainfluenzae**
Enterococcus faecalis	*Klebsiella oxytoca**
*Streptococcus dysgalactiae**	*Proteus mirabilis**

*Efficacy in treating clinical infections with these organisms is unknown

Baxdela™. [Package Insert]. Lincolnshire, Illinois: Melinta Therapeutics; 2017

Delafloxacin

	Minimum Inhibitory Concentrations (mcg/mL)		
Pathogen	**S**	**I**	**R**
Staphylococcus aureus (methicillin-resistant and methicillin-susceptible isolates)	≤ 0.25	0.5	≥ 1
Staphylococcus haemolyticus	≤ 0.25	0.5	≥ 1
Streptococcus pyogenes[a]	≤ 0.06	-	-
Streptococcus agalactiae	≤ 0.06	0.12	≥ 0.25
Streptococcus anginosus Group[a, b]	≤ 0.06	-	-
Enterococcus faecalis	≤ 0.12	0.25	≥ 0.5
Enterobacteriaceae[c]	≤ 0.25	0.5	≥ 1
Pseudomonas aeruginosa	≤ 0.5	1	≥ 2

Baxdela™. [Package Insert]. Lincolnshire, Illinois: Melinta Therapeutics; 2017

Delafloxacin

- PK/PD:
  - PK:

Parameter	Tablet Steady State	IV Steady State
C_{max} (mg/L)	7.45	9.29
CL (L/h)	16.8	13.8
AUC_{ss} (mg*h/L)	30.8	23.4
$T_{1/2}$ (h)	4.2-8.5	

    - Distribution: 30-48L (~TBW)
    - Metabolism through UGT 1A1, UGT1A3, UGT2B15
  - PD parameter: AUC:MIC however the PI also notes that it has a concentration dependent bactericidal activity in vitro

Baxdela™. [Package Insert]. Lincolnshire, Illinois: Melinta Therapeutics; 2017

Proceed Study

- Study Design:
  - Phase 3, multicenter, stratified, randomized, double-blind trial to evaluate IV delafloxacin vs vancomycin/aztreonam for ABSSSI
- Intervention:
  - Delafloxacin 300mg IV or vancomycin 15mg/kg (actual body weight) with aztreonam 2g q12h
    - Aztreonam discontinued if cultures did not have gram negative organisms
  - Duration: 5-14 days
  - Excluded diabetic foot infections
- Outcomes:
  - Primary: 48-72hr (±2) response of ≥ 20% reduction in erythema of lesion without evidence of clinical failure
  - Secondary:
    - Investigator assessed success at follow up visit

Proceed - Results

	Delafloxacin	Vancomycin/ Aztreonam	Percentage difference (95% CI)
48-72 hr objective response	78.2%	80.9%	-2.6 (-8.78,3.57)
Cure at follow-up	52%	50.5%	1.5 (-6.11, 9.11)
Success at follow-up	81.6%	83.3%	-1.7 (07.55, 4.13)
Microbiologic response	97.8%	98.4%	Not provided
MRSA Cure at last follow up	83.6%	72.7%	10.9 (-3.71, 25.11)
Cure in obese patients at last follow up	71.7%	57.4%	14.2 (1.34, 26.9)

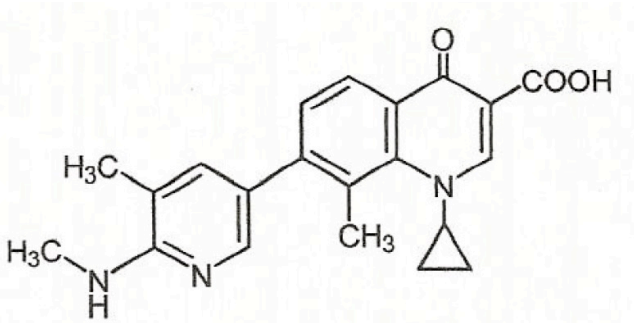
Proceed – Results Additional Comments

- Baseline demographics similar between the groups
- *Staphylococcus aureus* identified in 65.4% and 66.8% of patients with positive cultures in the delafloxacin and vancomycin/aztreonam arms respectively
- No cases of *Clostridium difficile* occurred, one patient had an incidence of hypoglycemia, two patients had hyperglycemia
- Rate of target attainment with vancomycin was not provided
- Only 2 patients in the delafloxacin and 5 patients in the vancomycin/aztreonam group had *Pseudomonas aeruginosa*

Potential Niche?

- Additional trials on clinicaltrials.gov
  - Delafloxacin vs. moxifloxacin for CABP recruiting
  - Delafloxacin vs ceftriaxone for uncomplicated Gonorrhea - terminated
- Clinical thoughts
  - Potentially in obese patients where a gram positive organism is identified
  - There are rumors that it could be used for polymicrobial infections like diabetic foot ulcers but there is not literature to support it yet
  - Concern for resistance development during treatment
  - Interesting that it doesn't have an effect on QTc – potential treatment opportunities
  - Cheaper than vancomycin/aztreonam for patients with beta lactam allergy
  - No CDI

Ozenoxacin (Xepi™)



- Indication: topical treatment of impetigo due to *Staphylococcus aureus* or *Streptococcus pyogenes* in patients > 2 months of age
- Mechanism of action: inhibits topoisomerase II and IV
- Dose:
  - Apply a thin layer to the affected area twice daily for 5 days
  - Each gram contains 10mg of ozenoxacin 1%
- Warnings
  - Bacterial overgrowth
- Negligible to no systemic absorption
- Antagonistic relationship between ciprofloxacin and ozenoxacin for *Staphylococcus aureus*

Xepi™. [Package Insert]. Fairfield, NJ: Medimetriks Pharmaceuticals; 2017

Ozenoxacin Clinical Trial

- Study Design:
  - Multicenter, randomized, placebo-controlled, parallel, blinded, superiority phase 3 study to ozenoxacin, retapamulin, and placebo for nonbullous or bullous impetigo
- Intervention:
  - Ozenoxacin 1% cream vs placebo cream applied twice daily
  - Retapamulin 1% ointment vs placebo applied twice daily
  - Duration: 5 days
- Outcomes:
  - Primary: clinical response at end of therapy (visit 3, day 6-7)
  - Secondary:
    - Clinical response in non-ITT populations
    - Clinical response at day 3-4 (visit 2) and day 10-13 (visit 4)
    - Size of affected area at visits 2,3, and 4
    - Microbiologic response
    - Time to clinical response

Ozenoxacin - Results

- Demographics were similar

	Ozenoxacin (n=155)	Placebo (n=156)	P-value	Retapamulin (n=154)	Placebo (n=156)	P-value
Clinical success at visit 3	54 (34.8%)	30 (19.2%)	0.003	58 (37.7%)	30 (19.2%)	0.189
Micro success at visit 3	122 (79.2%)	86 (56.6%)	P < 0.0001	125 (81.7%)	86 (56.6%)	P < 0.001

Phase 3 Pipeline

Iclaprim

- Synthetic diaminopyrimidine
- Mechanism of action: selectively inhibits dihydrofolate reductase (DHFR)
- Spectrum of activity: similar to trimethoprim
  - Gram positive
    - *Staphylococcus aureus* (MSSA and MRSA)
    - Coagulase negative staphylococci
    - Various streptococcal species
    - *Enterococcus*
  - Gram negative
    - *Neisseria gonorrheae, Haemophilus influenza, Moraxella catarrhalis, Enterobacteriaceae*
  - Atypical
    - *Chlamydia trachomatis, Chlamydia pneumoniae, Mycoplasma* species*, Legionella pneumophila*

Revive-1

- Study Design:
  - Phase 3, multicenter, double-blind, randomized trial comparing iclaprim with vancomycin for ABSSSI due to gram positive organisms
- Intervention:
  - Iclaprim 80mg IV (500mL NS) over 120 minutes q12h
  - Vancomycin 15mg/kg IV over 120 minutes q12h (trough levels at dose 5)
  - Duration: 5-14 days
  - Excluded patients with diabetic foot ulcers and uncomplicated SSTI
- Outcomes:
  - Primary: compare the early clinical response at 48-72 hrs
  - Secondary:
    - Clinical cure rate at test of cure
    - Safety and tolerability

Table 4. Clinical Responses for Primary Endpoint and Secondary Analyses in the Intent-to-Treat Population by Treatment

Clinical Response	Iclaprim (n = 298)	Vancomycin (n = 300)	Treatment Difference (%; 95% Confidence Interval)
Primary endpoint			
ECR at ETP in intent-to-treat	241 (80.9%)	243 (81.0%)	–0.13 (–6.42, 6.17)
Secondary analyses			
ECR at ETP among major cutaneous abscess	35/40 (87.5)	49/55 (89.1)	–1.59 (–14.74, 11.56)
ECR at ETP among cellulitis/erysipelas	54/76 (71.1)	68/87 (78.2)	–7.11 (–20.50, 6.28)
ECR at ETP among wound infections	152/182 (83.5)	126/158 (79.7)	3.77 (–4.50, 12.04)
ECR at ETP among methicillin-resistant *Staphylococcus aureus* infected	59/73 (80.8%)	50/61 (82.0%)	–1.15 (–17.94, 15.80)
ECR at ETP among methicillin-susceptible *S. aureus* infected	81/97 (84.4%)	88/104 (85.4%)	–1.06 (–14.94, 12.85)
ECR at ETP among *Streptococci pyogenes* infected	20/25 (80.0%)	18/25 (72.0%)	8.00 (–32.98, 33.86)
ECR at ETP among diabetics	16/20 (80.0%)	26/35 (74%)	5.71 (–21.94, 32.74)
ECR at ETP among mild renal impairment (CrCl of 60–89 mL/min)	24/30 (80%)	35/44 (80%)	0.45 (–22.43, 23.52)
ECR at ETP among moderate and severe renal impairment (CrCl of <60 mL/min)	5/6 (83%)	9/12 (75%)	8.00 (–46.02, 52.44)
ECR at ETP in per-protocol	228 (84.8%)	232 (86.2%)	–1.49 (–7.44, 4.46)
Clinical cure at TOC	248 (83.2%)	262 (87.3%)	–4.11 (–9.78, 1.56)
Modified clinical cure[a] at TOC	227 (76.2%)	240 (80.0%)	–3.83 (–10.45, 2.80)

Abbreviations: CrCl, creatinine clearance; ECR, early clinical response; ETP, early time point; TOC, test-of-cure.

[a] Modified clinical cure defined as a ≥90% reduction in lesion size compared to baseline, no increase in lesion size since ETP, and no requirement for additional antibiotics (except aztreonam or metronidazole) or unplanned significant surgical procedures after ETP.

Iclaprim – Potential niche?

- Other clinical trials on clinicaltrials.gov
  - Iclaprim vs vancomycin for ABSSSI – Revive-2: completed
  - Iclaprim vs vancomycin for HAP, VAP, or HCAP: terminated
  - Iclaprim vs linezolid in cSSTI-Assist-1: completed
  - Iclaprim vs linezolid in cSSTI-Assist-2: completed
- Thoughts
  - No information on vancomycin target attainment
  - Why was the pneumonia study was canceled?
  - Good option for complicated vancomycin dosing
  - Unclear clinical utility other than for MRSA

Lefamulin

- Pleuromutilin
- Mechanism of action: binds to the 23s of the 50s subunit at the peptidyl transferase center inhibiting peptide bond formation and inhibiting protein synthesis
  - https://www.youtube.com/watch?v=gFG8yWYV3ew

Gram Positive	Gram Negative	Atypicals	Anaerobes
Staphylococcal aureus (MSSA, MRSA, VRSA)	*Haemophilus* sp.	*Mycoplasma pneumoniae*	*Propionibacterium acnes*
Coagulase negative *Staphylococcus aureus*	*Moraxella catarrhalis*	*Chlamydia* pneumoniae	*Peptocstreptococcus* sp
Streptococcus pneumoniae	*Neisseria* sp.	*Legionella pneumophilia*	*Prevotella* sp
Enterococcus faecium (VRE)			*Clostridium perfringens*

HTTPS://WWW.NABRIVA.COM/PIPELINE-RESEARCH
COLD SPRING HARB PERSPECT MED 2017;7:A027110
SCI REP 2016;6:39004

Lefamulin Clinical Trial

- Study design: double-blind, parallel group, multicenter phase 2 study for use of lefamulin in ABSSSI
- Interventions:
  - Lefamulin 100mg IV q12h
  - Lefamulin 150mg IV q12h
  - Vancomycin 1g (adjusted to institution guidelines) IV q12h
  - Duration: 5-14 days
- Outcomes:
  - Primary: clinical success at test of cure
  - Secondary:
    - Microbiological outcome
    - Safety

Antimicrob Agents Chemother. 2013;57(5):2087-2094

Lefamulin

- Baseline characteristics were similar except:
  - Vancomycin group had slightly fewer patients with fever (n=3 vs 5 and 7)
  - Lefamulin 100mg had more patients with a lower extremity infection while vancomycin had more patients with upper extremity infections
  - Lefamulin 150mg had more patients with diabetes mellitus and higher weight
- Micro:
  - 151/155 patients had a gram positive infection
    - 90.8% with *Staphylococcus aureus* with 69.1% being MRSA

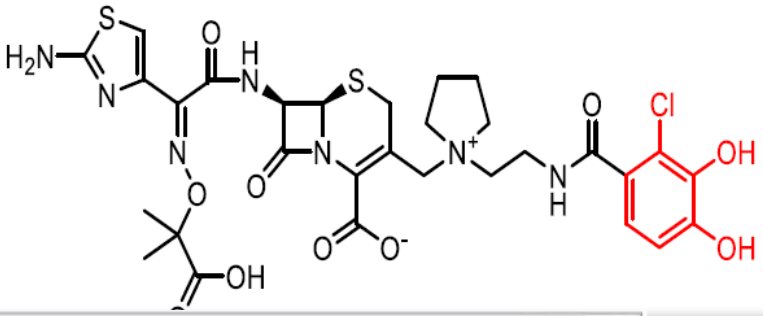
	# of Patients	Success	Failure	95% CI
Lefamulin 100mg	60	54 (90)	6 (10)	79.5, 96.2
Lefamulin 150mg	54	48 (88.9)	11.1)	77.4, 95.8
Vancomycin 1g	51	47 (92.2)	4 (7.8)	81.1, 97.8

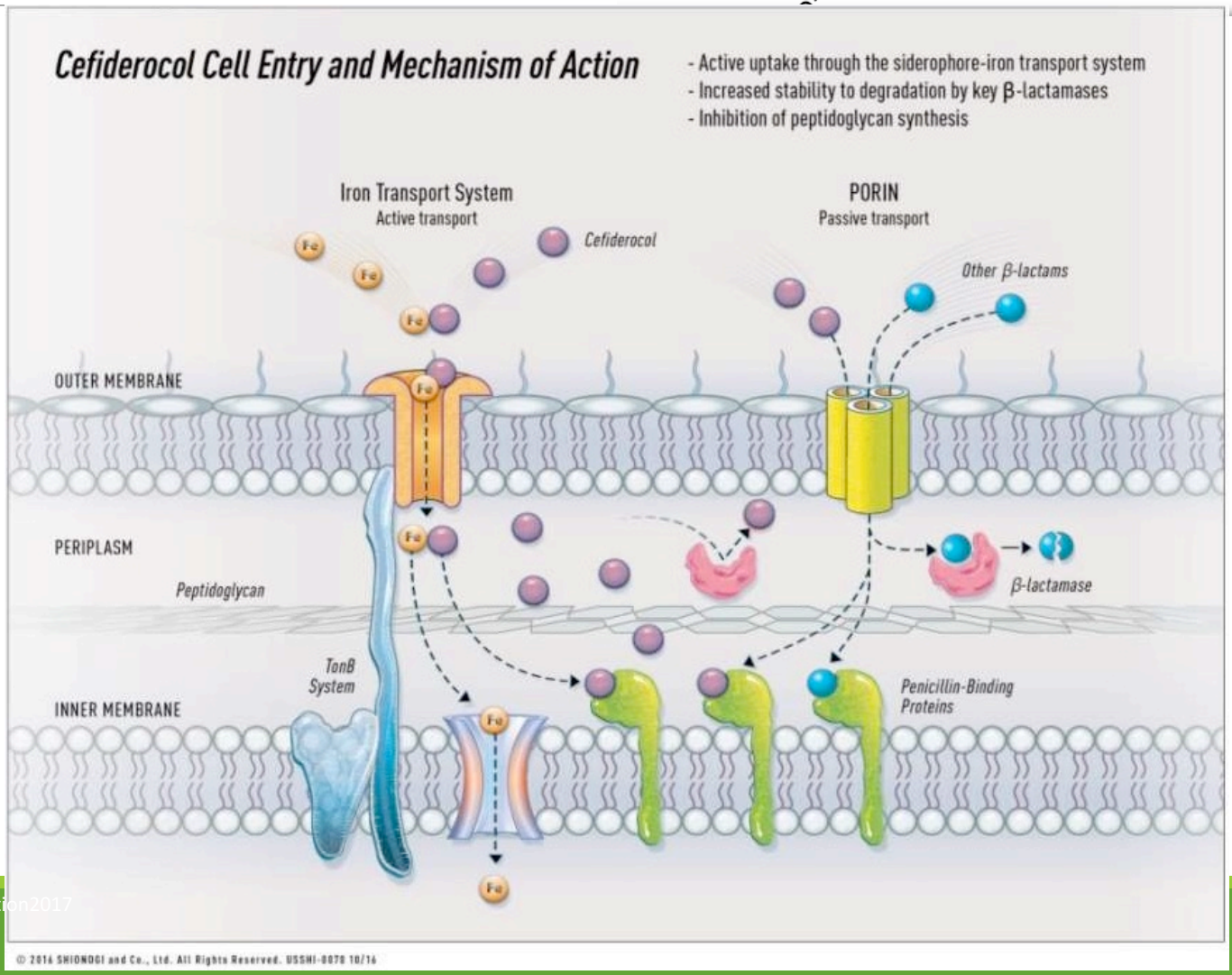
Antimicrob Agents Chemother. 2013;57(5):2087-2094

Potential niche?

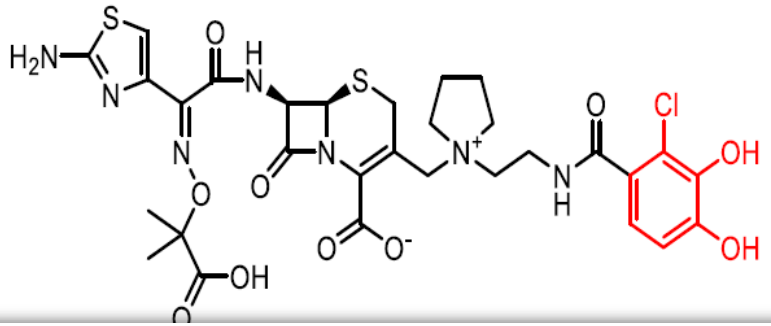
- Other trials on clincialtrials.gov
  - Lefamulin vs moxifloxacin for CAP – completed
  - Lefamulin vs moxifloxacin w/ or wo/ linezolid for CAP – completed
- Manufacturer website mentions possible use for ABSSSI, STIs, VABP, HABP, OM, and PJI
- Thoughts:
  - No information on vancomycin target attainment
  - Excited for this new mechanism of action
  - Great drug for CAP given spectrum of activity and high barrier to resistance
  - Could be good for Aspiration pneumonia, STIs, MRSA infections, obesity
  - Does not cover Enterobacteriaceae, *B. fragilis,* or *E. faecalis* so can spare gut flora – CDI implications?

Cefiderocol





Cefiderocol



- Spectrum of activity
  - No activity against gram positive organisms
  - Covers gram negative bacteria including CREs and MDR non-fermenters
    - Stable to serine (KPC, OXA, etc.) and metallo β-lactamases (VIM, IMP, NDM, L1, etc.)
    - Potent activity against *Acinetobacter baumannii, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Stentotrophomonas maltophilia*
  - MIC testing should be done in iron depleted medium
- Clinical trials on clinicaltrials.gov
  - cUTI vs imipenem/cilastatin – completed
  - Severe infection caused by CRE vs best available therapy – recruiting
  - Nosocomial pneumonia caused by gram negative pathogens vs meropenem and linezolid - recruiting

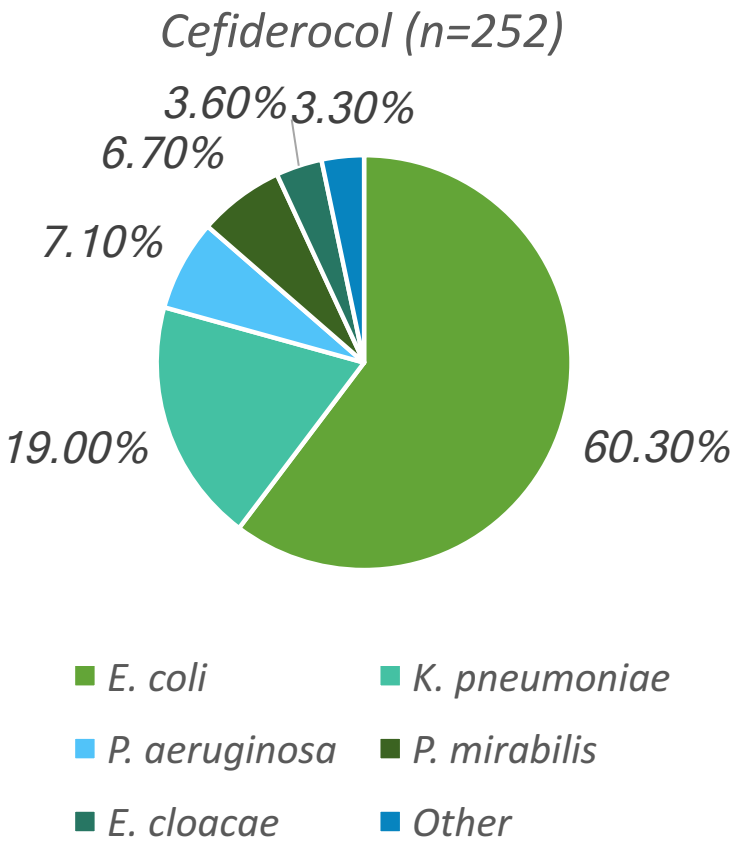
Cefiderocol Clinical Trials

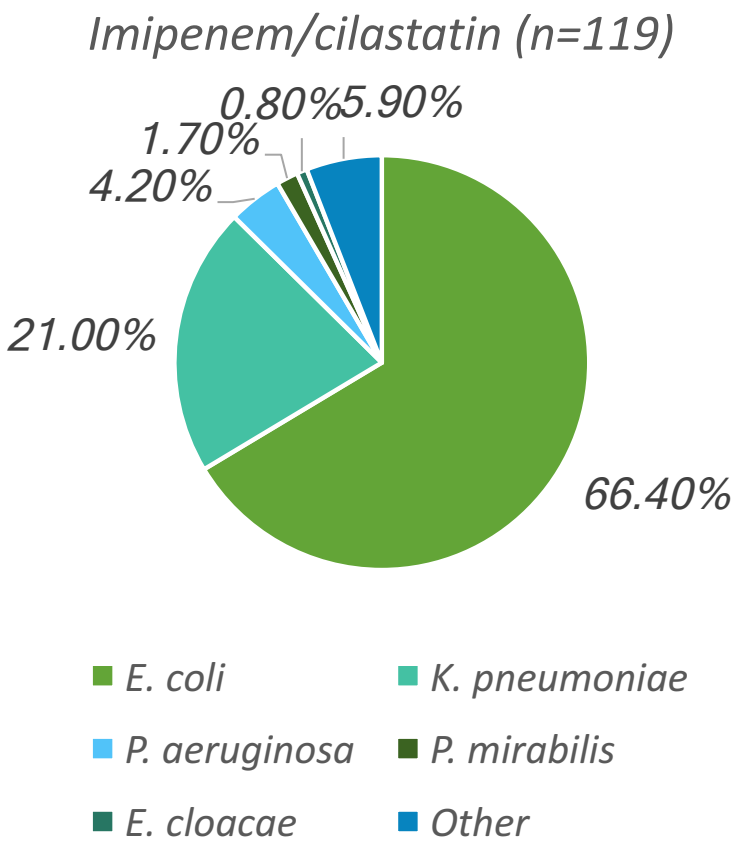
- Study Design:
  - Phase 3, multicenter, double-blind, randomized, non-inferiority trial to evaluate cefiderocol for treatment of cUTI w/ or w/o pyelonephritis
- Intervention:
  - Cefiderocol 2g IV tid
  - Imipenem/cilastatin 2g IV tid
  - Duration: 7-14 days
  - Excluded diabetic foot infections
- Outcomes:
  - Primary: composite clinical and microbiological response at TOC in MITT population
  - Secondary:
    - Microbiological response at TOC in MITT population

Cefiderocol - Results

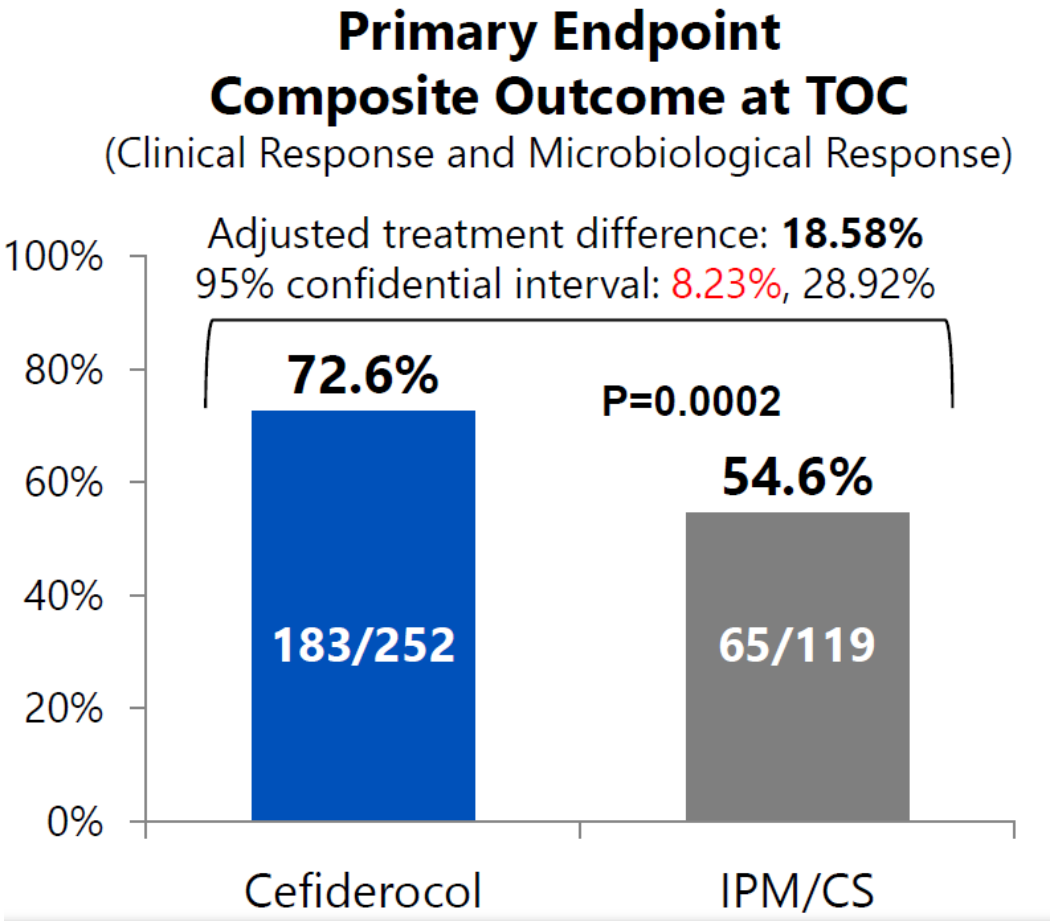
- Baseline demographics were similar except
  - The cefiderocol group had a few more cUTI w/ or w/o pyelonephritis (74.2% vs 70.6%)
  - The cefiderocol group hade fewer acute uncomplicated pyelonephritis (25.8% vs 29.8%)
  - The cefiderocol group had a few more patients with a history of neoplasms and chronic pyelonephritis
- Adverse effects
  - Similar but numerically more for the imipenem/cilastatin arm
  - The most common side effects in the cefiderocol arm were
    - Diarrhea (4.3%)
    - Hypertension (4.3%)
    - Constipation (3.3%)
    - Infusion site pain (3%)

Cefiderocol – Micro Results





Cefiderocol – Primary outcome

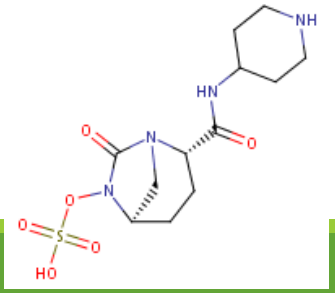


Cefiderocol – Potential Niche?

- Novel mechanism of action
- Strictly gram negative agent with good stability to β-lactamases
  - MDROs
  - Empiric for risk factors for MDROs?
  - Neutropenic fever?
- Coverage against *S. maltophilia* could be a potential niche
- I'm curious why they chose imipenem as their comparator
- Concern for impact on patient's iron levels and microbiological testing

Imipenem/cilastatin/relebactam

- Bicyclic diazabicyclooctane β-lactamase inhibitor against class A and class C β-lactamases
- Mechanism of action:
  - Imipenem – binds to PBP to inhibit cell wall synthesis
  - Cilastatin – competitive inhibition of dehydropeptidase of renal tubules to prevent imipenem metabolism
  - Relebactam – β- lactamase inhibitor
    - Active against class A and C β- lactamases
    - PK/PD parameter: AUC:MIC
- Qualified Infectious Disease Product for HABP, VABP, cIAI, and cUTI



HTTP://INVESTORS.MERCK.COM/NEWS/PRESS-RELEASE-DETAILS/
ANTIMICROB AGENTS CHEMOTHER 2017.24:61(6).PII:E02209-16

Imipenem/cilastatin Review

Gram Positive Aerobic Bacteria	Gram Negative Aerobic Bacteria
Enterococcus faecalis	*Acinetobacter* sp.
Staphylococcus aureus	*Citrobacter* sp.
Staphylococcus epidermidis	***Enterobacter* sp.**
Streptococcus agalactiae	*Escherichia coli*
Streptococcus pneumoniae	*Gardnerella vaginalis*
Streptococcus pyogenes	*Haemophilus influenza*
	***Klebsiella* sp.**
	Morganella morganii
	Proteus vulgaris
	Providencia rettgeri
	Pseudomonas aeruginosa
	Serratia sp.

Primaxin™. [Package Insert]. Whitehouse Station, NJ:Merck &Co. 2017

Imipenem/cilastatin/relebactam Clinical Trial for cUTI

- Study Design:
  - Prospective, randomized, double-blind, multicenter, non-inferiority (with nested superiority), Phase 2b dose-ranging study to evaluate two dose of imipenem/cilastatin/relebactam vs imipenem/cilastatin for cUTI
- Intervention:
  - Imipenem/cilastatin 500mg IV + relebactam 250mg IV over 30 min q6h
  - Imipenem/cilastatin 500mg IV + relebactam 125mg IV over 30 min q6h
  - Imipenem/cilastatin 500mg IV + placebo IV over 30 min q6h
  - If adequate response at 96 hrs could switch to oral ciprofloxacin
- Outcomes:
  - Primary: Microbiological response at discontinuation of IV therapy
  - Secondary
    - Microbiological response at early follow up and late follow up
    - Microbiological response at discontinuation of IV therapy in imipenem-resistant pathogens
    - Clinical response at discontinuation of IV therapy, early follow up, and late follow up

Imipenem/cilastatin/relebactam Results

- Baseline demographics similar except
  - 250mg relebactam group had slightly fewer nephrolithiasis
  - 250mg relebactam group had slightly fewer patients with *K. pneumoniae*
  - Placebo group had slightly more patients with residual urine
  - Placebo group had fewer imipenem non-susceptible pathogens

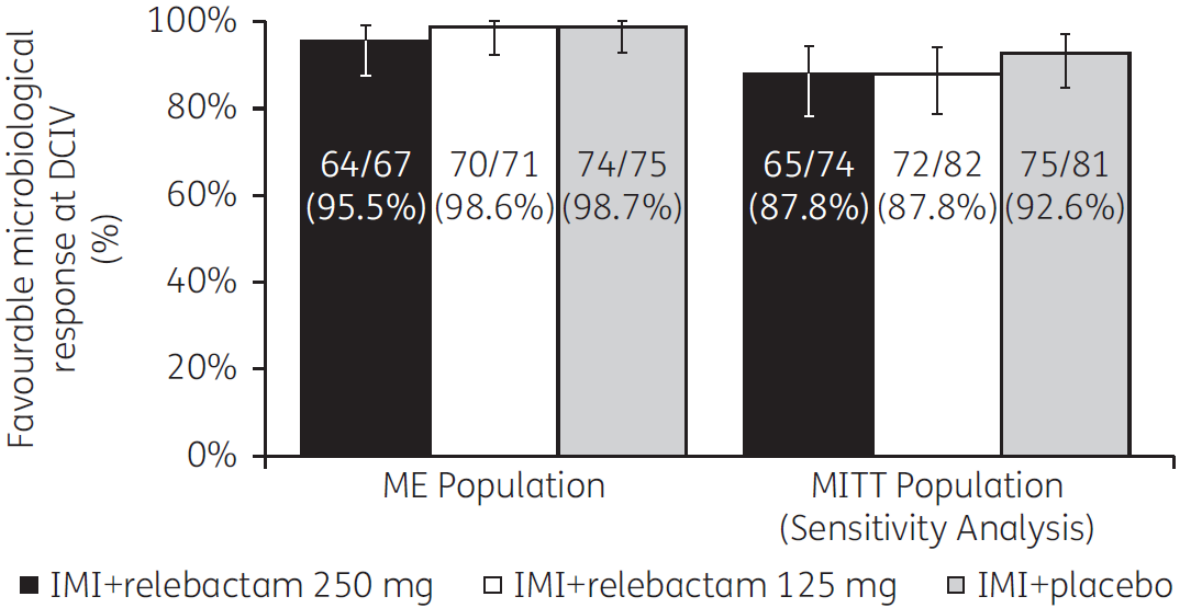
Imipenem/cilastatin/relebactam Micro

Table 3. *In vitro* susceptibility of baseline urine and/or blood pathogens (ME population at DCIV)

	Imipenem + relebactam				Imipenem			
Pathogens	**total**[a]	S (%)	I (%)	R (%)	**total**[a]	S (%)	I (%)	R (%)
All pathogens	247	93.9	2.0	4.0	248	89.9	3.2	6.9
Acinetobacter baumannii complex	4	0.0	0.0	100.0	4	0.0	0.0	100.0
Citrobacter freundii	3	100.0	0.0	0.0	3	100.0	0.0	0.0
Enterobacter aerogenes	1	100.0	0.0	0.0	1	100.0	0.0	0.0
Enterobacter cloacae	9	100.0	0.0	0.0	9	100.0	0.0	0.0
Escherichia coli	159	100.0	0.0	0.0	159	100.0	0.0	0.0
Klebsiella pneumoniae	34	100.0	0.0	0.0	43	97.1	2.9	0.0
Leclercia adecarboxylata	1	100.0	0.0	0.0	1	100.0	0.0	0.0
Morganella morganii	4	0.0	75.0	25.0	4	0.0	25.0	75.0
Myroides spp.	0	0.0	0.0	0.0	1	100.0	0.0	0.0
Pantoea spp.	1	100.0	0.0	0.0	1	100.0	0.0	0.0
Proteus mirabilis	11	54.5	9.1	36.4	11	45.5	9.1	45.5
Proteus vulgaris	2	100.0	0.0	0.0	2	50.0	50.0	0.0
Providencia rettgeri	2	50.0	50.0	0.0	2	50.0	50.0	0.0
Pseudomonas aeruginosa	16	93.8	0.0	6.3	16	50.0	18.8	31.3

I, intermediate; R, resistant; S, susceptible.
[a]Total number of baseline isolates with susceptibility data available.

Imipenem/cilastatin/relebactam Results



IMI+relebactam 250 mg vs IMI+placebo		IMI+relebactam 125 mg vs IMI+placebo	
ME population Difference (95% CI): -3.1 (-11.2–3.2)	MITT population Difference (95% CI): -4.8 (-15.1–4.9)	ME population Difference (95% CI): -0.1 (-6.4–5.9)	MITT population Difference (95% CI): -4.8 (-14.7–4.7)

J Antimicrob Chemoth. 2017:72:2616-2626

Imipenem/cilastatin/relebactam Clinical Trials cIAI

- Study Design:
  - Prospective, randomized, double-blind, multicenter, Phase 2 dose-ranging study to evaluate two dose of imipenem/cilastatin/relebactam vs imipenem/cilastatin for cIAI
- Intervention:
  - Imipenem/cilastatin + relebactam 250mg IV over 30 min q6h
  - Imipenem/cilastatin + relebactam 125mg IV over 30 min q6h
  - Imipenem/cilastatin + placebo IV over 30 min q6h
  - Duration 4-14 days
- Outcomes:
  - Primary: favorable clinical response at discontinuation of IV therapy

Imipenem/cilastatin/relebactam Results

- Baseline demographics were similar except
  - The placebo group had fewer preoperative and more postoperative enrollment times
  - APACHE2 scores were similar with most being ≤ 15
- Most common diagnoses:
  - Complicated appendicitis (52.5%)
  - Complicated cholecystitis (16.5%)
  - Perforated hollow viscus (11.4%)
- All comparisons of proportion of subjects with favorable clinical response were non-statistically significant

Imipenem/cilastatin/relebactam Micro

TABLE 6 Proportion of subjects in the ME population with favorable clinical response at DCIV by baseline pathogen[a]

	Result for treatment group						REL vs placebo comparison, % difference (95% CI)[b]	
	250 mg REL + IMI (n = 81)		125 mg REL + IMI (n = 86)		Placebo + IMI (n = 83)			
Pathogen	n/m	%	n/m	%	n/m	%	250 mg REL + IMI	125 mg REL + IMI
Gram-positive aerobic cocci	32/32	100	32/33	97.0	33/34	97.1	2.9 (−8.1 to 15.1)	−0.1 (−12.9 to 12.4)
Enterococcus faecalis	7/7	100	5/5	100	5/5	100	0.0 (−37.4 to 45.6)	0.0 (−46.1 to 46.1)
Streptococcus anginosus	5/5	100	6/6	100	7/7	100	0.0 (−45.6 to 37.4)	0.0 (−41.0 to 37.3)
Streptococcus constellatus	2/2	100	5/6	83.3	6/6	100	0.0	−16.7 (−57.9 to 28.5)
Gram-negative aerobic bacilli	73/75	97.3	73/73	100	68/72	94.4	2.9 (−4.4 to 11.2)	5.6 (0.4 to 13.5)
Enterobacter cloacae	7/7	100	4/4	100	4/4	100	0.0 (−37.6 to 51.4)	0.0 (−52.3 to 52.3)
Escherichia coli	53/55	96.4	56/56	100	47/51	92.2	4.2 (−5.7 to 15.4)	7.8 (1.1 to 18.6)
Klebsiella pneumoniae	10/10	100	12/12	100	10/12	83.3	16.7 (−14.4 to 45.5)	16.7 (−10.6 to 45.4)
Proteus mirabilis	8/8	100	4/4	100	6/6	100	0.0 (−34.1 to 40.8)	0.0 (−51.6 to 41.6)
Pseudomonas aeruginosa	11/11	100	13/13	100	10/12	83.3	16.7 (−12.4 to 45.5)	16.7 (−9.0 to 45.4)
Gram-negative anaerobic bacilli	22/24	91.7	30/30	100	26/27	96.3	−4.6 (−23.0 to 11.4)	3.7 (−8.1 to 18.5)
Bacteroides fragilis	11/11	100	8/8	100	12/12	100	0.0 (−26.7 to 25.1)	0.0 (−33.6 to 25.2)
Bacteroides thetaiotaomicron	6/6	100	6/6	100	6/7	85.7	14.3 (−29.9 to 52.8)	14.3 (−29.9 to 52.8)

[a] The most common pathogens (those with at least 15 unique baseline isolates) are shown. CI, confidence interval; IMI, imipenem-cilastatin; n/m, number of subjects with pathogen and favorable clinical response/number of subjects with pathogen and clinical response assessment. Subjects with an indeterminate or missing response are excluded from the analysis.

[b] The 95% confidence intervals are based on the unconditional asymptotic Miettinen and Nurminen method without stratification.

Potential niche?

- Trials on clinicaltrials.gov:
  - Imipenem/cilastatin/relebactam in Japanese patients with cIAI or cUTI – recruiting
  - Imipenem/cilastatin/relebactam vs colistimethate + imipenem/cilastatin for imipenem resistant bacteria – completed
  - PK in pediatric study – recruiting
  - Imipenem/cilastatin/relebactam vs piperacillin/tazobactam for bacterial pneumonia – recruiting
- Thoughts:
  - Last line therapy mostly for MDR *Pseudomonas aeruginosa* with susceptibility results
  - Still worried about side effects of imipenem
  - Likely dose will be imipenem/cilastatin 500mg + relebactam 250mg IV q6h

Where does relebactam fit in?

	ESBL producer	Amp-C producer	Carbapenamase
Ampicillin-sulbactam	R	R	R
Piperacillin-tazobactam	V	R	R
Ceftazidime-avibactam	S	S	V
Ceftolozane-tazobactam	S	S	V
Aztreonam-avibactam	S	S	V
Meropenem-vaborbactam	V	S	V
Imipenem/cilastatin-relebactam	**V**	**S**	**V**

R = resistant
S = sensitive
V = variable

Mayo Clin Proc 2015;90(3):395-403
Unpublished information request from The Medicines Company
Antimicrob Agents Chemother. 2017;61:e02209-16

Questions?

New Bugs? New Drugs!

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