FUTURE ANTIBIOTICS IN THE PIPELINE

Ravina Kullar, PharmD, MPH, FIDSA
Infectious Diseases Pharmacist & Epidemiologist
May 7, 2023

Objectives

- Discuss the burden of antimicrobial resistance (AMR)
- Provide an overview of antibiotics in Phase 3 development
- Summarize clinical trial results of 3 antibiotics in Phase 3 development


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THE WEEK AHEAD
IN THE KNOW

MONDAY
BALLOON BOY'S DAD OFF TO JAIL

Richard Heene begins his 90-day sentence for the Oct. 15 hoax.

TUESDAY
ELECTION DAY

Miami voters will head to the polls in a special election to fill two seats that have been vacant for two months – one in District 1, which covers most of Allapattah, and one in District 5, which runs from Overtown to Liberty City.

AMERICAN IDOL

The hit show starts its ninth season with the traditional audition round, which will run on Tuesdays and Wednesdays at 8 p.m. on FOX through Feb. 3.

GLOBAL TRADE NUMBERS

The Commerce Department will release international trade figures for November. They are expected to be down for

FIRST OF TWO PARTS

WHEN DRUGS STOP WORKING

The most lethal infectious diseases on the planet are mutating at an alarming rate worldwide. The reason: Overuse and misuse of the drugs that were supposed to save us.

A 'TIME BOMB':

BY MARISE MALOU

HEALTH

A Nevada woman dies of a superbug resistant to every available antibiotic in the US

By HELEN BRANSWELL @HelenBranswell / JANUARY 12, 2017


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24 January 2013 Last updated at 13:18

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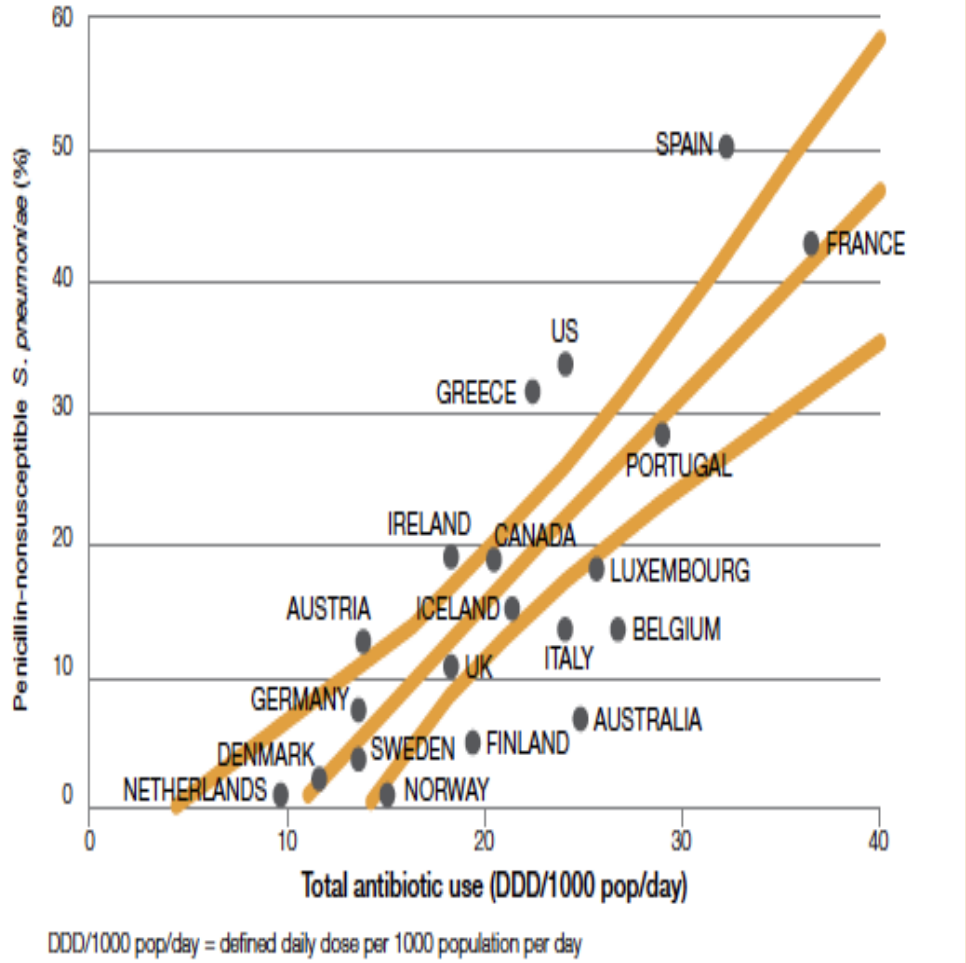
Antibiotic 'apocalypse' warning

By James Gallagher
Health and science reporter, BBC News

Antibiotic Use is Correlated with AMR



Relationship between total antibiotic consumption and *Streptococcus pneumoniae* resistance to penicillin in 20 industrialised countries.

Source: WHO country data, 2000-03

http://apps.who.int/medicinedocs/en/d/Js7920e/1.html

Ⓝ Novel class or target

QIDP-designated

not QIDP

	Drug name	Development phase	Company	Expected activity against ESKAPE pathogens?	Expected activity against CDC urgent or WHO critical threat pathogen?	Potential indication(s)	
+	**Benapenem**	Phase 3	Sihuan Pharmaceutical Co. Ltd.	Yes: *K. pneumoniae*, *Enterobacter* spp.	Yes: ESBL	8 12 19 23	CA-PNA, cUTI including pyelo, IAI, STI
+	**Cefepime + taniborbactam**	Phase 3	Venatorx Pharmaceuticals Inc./Global Antibiotic Research and Development Partnership (GARDP) (Everest Medicines II Ltd. Licensee)	Yes: *K. pneumoniae*, *P. aeruginosa*, *Enterobacter* spp. Possibly: *S. aureus*	Yes: CRE, CRPA	11	cUTI including acute pyelo
+	**Cefilavancin**	Phase 3	R-Pharm	Yes: *S. aureus*	No	2	ABSSSI

https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2014/antibiotics-currently-in-clinical-development

Drug name	Development phase	Company	Expected activity against ESKAPE pathogens?	Expected activity against CDC urgent or WHO critical threat pathogen?	Potential indication(s)	
EMROK/EMROK O	Phase 3	Wockhardt Ltd.	Yes: *S. aureus*	No	2, 14, 18, 28	ABSSSI, DFI, HA-PNA, concurrent bacteremia
Exblifep (cefepime + enmetazobactam)	Phase 3	Allecra Therapeutics GmbH	Yes: *K. pneumoniae*, *Enterobacter* spp.	Yes: ESBL	9, 12, 18, 27	cIAI, cUTI including pyelo, HA-PNA, VA-PNA
Gepotidacin (GSK2140944)	Phase 3	GlaxoSmithKline PLC	Yes: *S. aureus*	Yes: Drug-resistant *N. gonorrhoeae* Possibly: ESBL	25, 26	uUTI, uncompl urogenical gonorrhea
Ridinilazole	Phase 3	Summit Therapeutics Inc.	No	Yes: *C. difficile*	6	CDI

https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2014/antibiotics-currently-in-clinical-development

	Drug name	Development phase	Company	Expected activity against ESKAPE pathogens?	Expected activity against CDC urgent or WHO critical threat pathogen?	Potential indication(s)	
+	Sulbactam + durlobactam	Phase 3	Entasis Therapeutics Inc.	Yes: *A. baumannii*	Yes: CRAB	4, 11, 18, 27	Bacteremia, cUTI incl acute pyelo, HA-PNA, VA-PNA
+	T-4288 (solithromycin)	Phase 3	Toyama Chemical Co. Ltd.	Yes: *E. faecium*	Yes: Drug-resistant *N. gonorrhoeae*	8, 26	CA-PNA, uncompl urogenital gonorrhea
+	Tebipenem/tebipenem pivoxil hydrobromide	Phase 3	Spero Therapeutics Inc.	Yes: *K. pneumoniae*, *Enterobacter* spp.	Yes: ESBL Possibly: *C. difficile*	3, 8, 10, 14	Acute pyelo, CA-PNA, cUTI, DFI
+	WCK 5222 (cefepime + zidebactam)	Phase 3	Wockhardt Ltd.	Yes: *K. pneumoniae*, *Enterobacter* spp. Possibly: *S. aureus*, *P. aeruginosa*	Yes: CRE Possibly: CRPA	10, 18, 27	cUTI, HA-PNA, VA-PNA

https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2014/antibiotics-currently-in-clinical-development

Drug name	Development phase	Company	Expected activity against ESKAPE pathogens?	Expected activity against CDC urgent or WHO critical threat pathogen?	Potential indication(s)
Zevtera (ceftobiprole)	Phase 3	Basilea Pharmaceutica International Ltd.	Yes: *S. aureus*, *K. pneumoniae*, *Enterobacter* spp. Possibly: *P. aeruginosa*	No	2, 8, 18, 22
Zoliflodacin (ETX0914)	Phase 3	Entasis Therapeutics Inc./Global Antibiotic Research and Development Partnership (GARDP)	Yes: *S. aureus*	Yes: Drug-resistant *N. gonorrhoeae*	24

ABSSSI, CA-PNA, HA-PNA, SAB

Uncomplicated gonorrhea

https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2014/antibiotics-currently-in-clinical-development

Sulbactam + Durlobactam

- Sulbactam
  - β-lactam widely used as a BLI in combination.
  - Has intrinsic activity against *A. baumannii*, including Class A β-lactamase producers (binds to PBP1 & PBP3)
- Durlobactam
  - β-lactamase inhibitor
  - Has broader activity against Class A, C and D β-lactamases.
  - Binds to PBP2
  - Restores the activity of sulbactam in *A. baumannii*
    - An in vitro study of SUL-DUR several *A. baumannii* isolates reported drug resistance low
  - Bacterial spectrum: Inhibitory activity against CRAB ABC
- Route & dosage: 3 h iv infusion q6h x 7 days up to 14 days.
- **4/17/23: FDA Advisory Committee voted unanimously that overall benefit-risk is favorable for the use of SUL-DUR for treatment of HABP and VABP caused by susceptible strains of ABC in adults**

Findlay J, et al. J Global Antimicrobial Resistance; 2022 (30): 445–450

CRAB=Carbapenem-resistant *Acinetobacter baumannii* ; ABC=*A. baumannii-calcoaceticus* complex

Sulbactam + Durlobactam

- ATTACK Trial:
  - Adult patients with ABC HAP, VAP or bacteremia
  - Part A-randomized, controlled portion of the study; durlobactam (1 mg) + sulbactam (1 g) combination (q6h iv infusion) or colistin (2.5 mg/kg) (q12h iv infusion), x 7 days, with patients in both arms receiving background therapy with imipenem + cilastatin (500 mg, q6h iv infusion)
  - Part B-efficacy of SUL-DUR as a single intervention for ABC-infected patients who did not qualify for Part A because the baseline pathogen was known to be resistant to colistin as well as subjects with cUTIs and acute pyelonephritis or surgical or post-traumatic wound infections (patients also received imi-cil).

https://clinicaltrials.gov/ct2/show/results/NCT03894046

Demographics and Baseline Characteristics Reflective of Patients in Real World

Characteristics	Part A		Part B
	SUL-DUR (N = 64)	Colistin (N = 64)	SUL-DUR (N = 28)
Age (years), Median (Min, Max)	**62** (25, 91)	**66** (19, 98)	**59** (18, 80)
Male, %	**72%**	**77%**	**75%**
Region			
United States	**2%**	**0%**	**0%**
Rest of World	**98%**	**100%**	**100%**
APACHE II score, Mean (SD)	**16.4** (5.11)	**17.2** (5.21)	**18.0** (5.03)
10 – 19	**67%**	**58%**	**65%**
20 – 30	**23%**	**30%**	**32%**
Creatinine clearance (mL/min), %			
< 90	**39%**	**40%**	**25%**
≥ 90	**61%**	**59%**	**75%**
Infection type, %			
Bacteremia	**3%**	**2%**	**61%**
HABP	**38%**	**48%**	**14%**
VABP	**59%**	**47%**	**25%**
Mechanical ventilation at baseline, %	**73%**	**78%**	**29%**
Monomicrobial infection, %	**58%**	**70%**	**82%**
Polymicrobial infection, %	**42%**	**30%**	**18%**

https://www.fda.gov/media/167158/download

Antibiotic Susceptibility of Baseline *Acinetobacter* Isolates (m-MITT Population, Parts A & B)

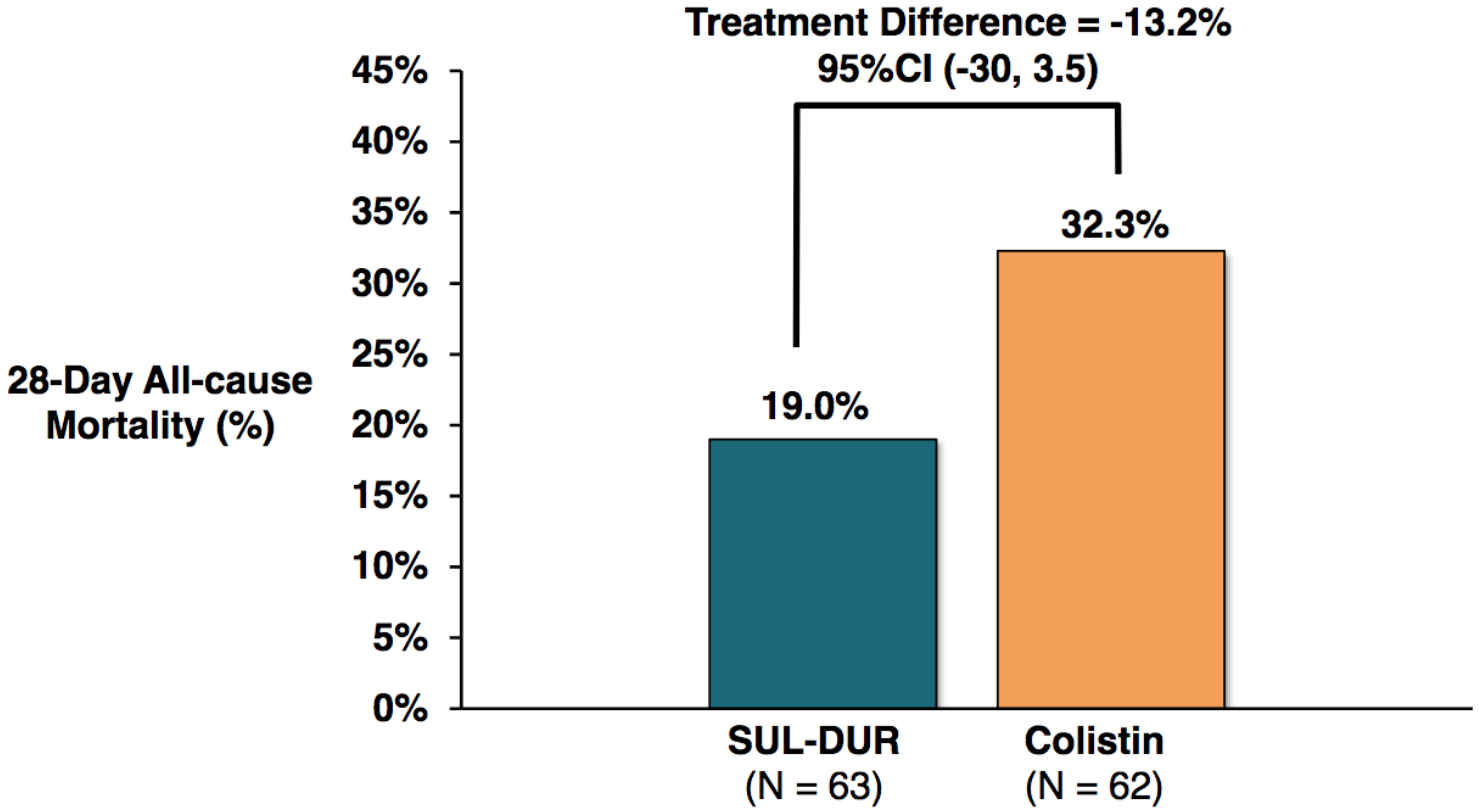
Category	*Acinetobacter* baseline isolates, N (%)	SUL-DUR MIC (μg/mL)		
		Range	MIC_{50}	MIC_{90}
All	175 (100%)	0.25 - 16	2	4
Carbapenem resistant	168 (96%)	0.5 - 16	2	4
Colistin-non-susceptible	30 (17%)	1 - 8	2	4
Multidrug resistant*	168 (96%)	0.5 - 16	2	4
Extensively drug resistant*	148 (85%)	0.5 - 16	2	4
Pan drug resistant	26 (15%)	1 - 8	2	4

175 baseline *Acinetobacter* isolates from m-MITT patients were available for testing at the central laboratory
*As defined by Magiorakos *et al.*, *Clin. Microb. Infect.* 2012 18:268-81

https://www.fda.gov/media/167158/download

Primary Endpoint Achieved

SUL-DUR Non-inferior to Colistin for 28-Day All-Cause Mortality (ACM)

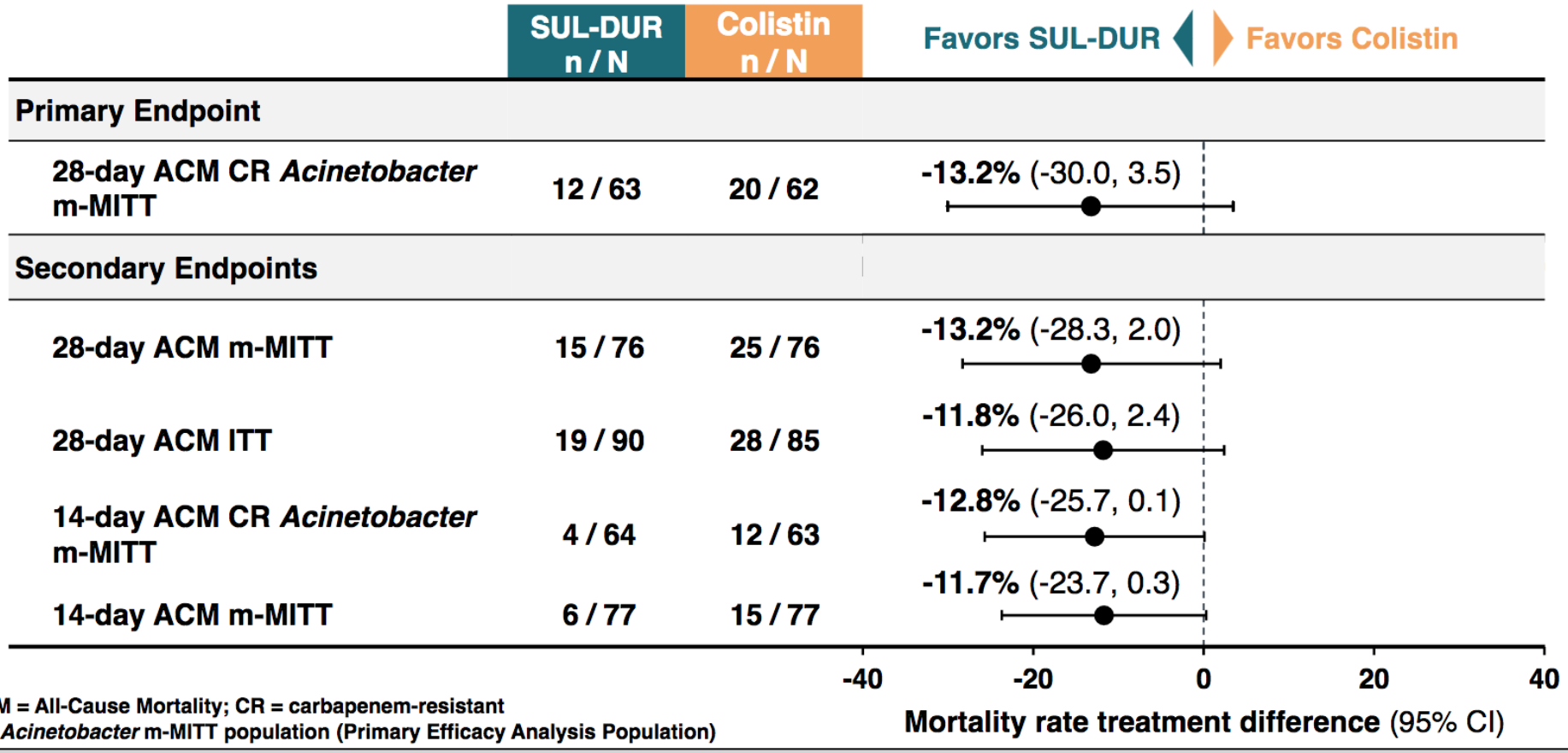


Participants with missing survival status treated as a death
Non-inferiority concluded if upper limit of 2-sided 95% CI < 20%
Carbapenem-resistant *Acinetobacter* m-MITT population (Primary Efficacy Analysis Population)

https://www.fda.gov/media/167158/download

CO-41

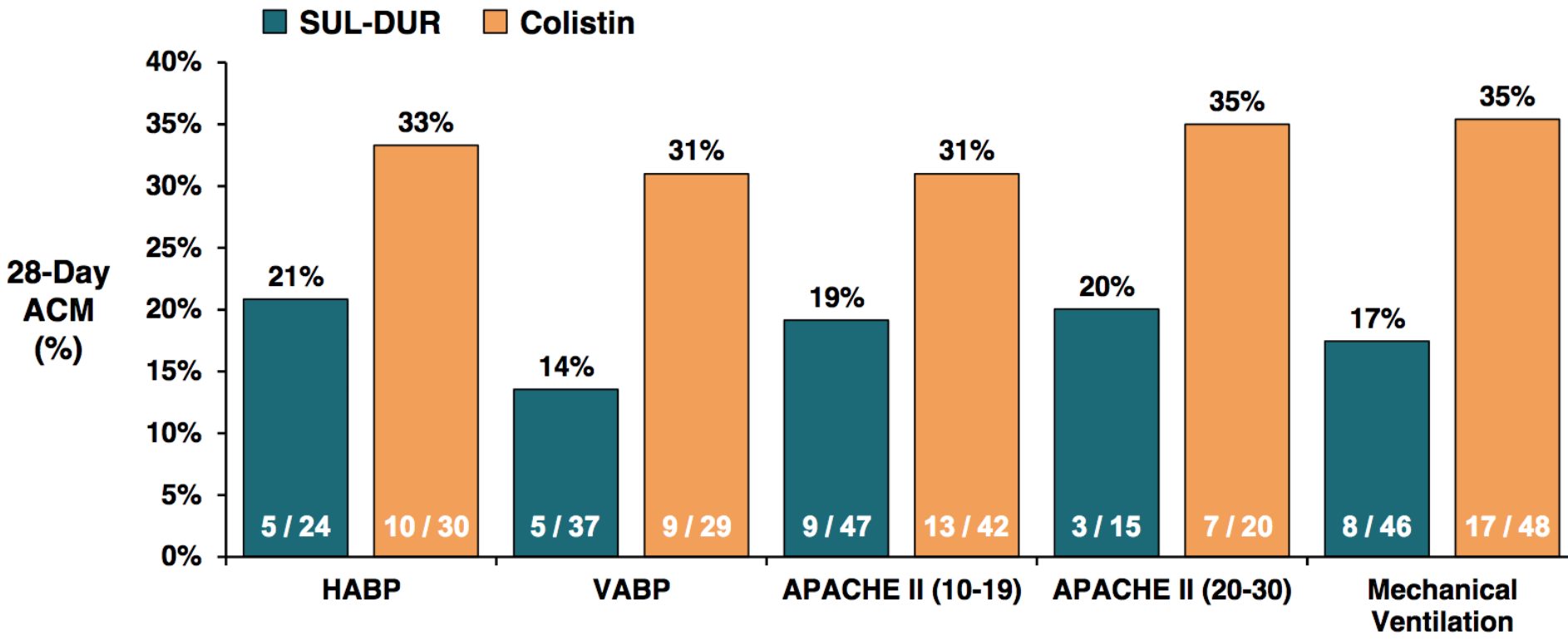
ACM Consistently Lower with SUL-DUR in All Prespecified Secondary Endpoints



ACM = All-Cause Mortality; CR = carbapenem-resistant
CR *Acinetobacter* m-MITT population (Primary Efficacy Analysis Population)

https://www.fda.gov/media/167158/download

28-Day All-Cause Mortality Lower for SUL-DUR in Subgroup Analyses (Part A)

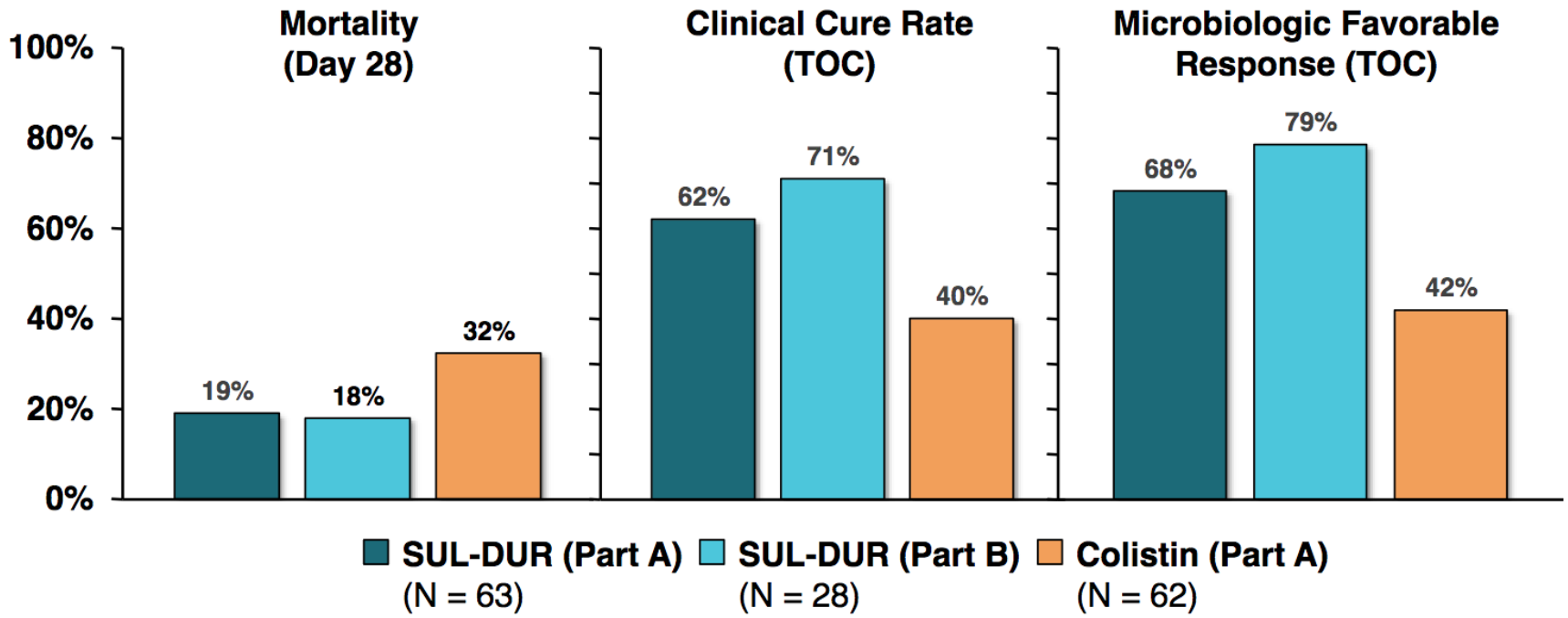


HABP = Hospital-acquired bacterial pneumonia; VABP = Ventilator-associated bacterial pneumonia
Carbapenem-resistant *Acinetobacter* m-MITT population (Primary Efficacy Analysis Population)
Note: APACHE II score was used first and when not available SOFA or qSOFA were used

https://www.fda.gov/media/167158/download

Part B (N = 28) Results Consistent with Part A

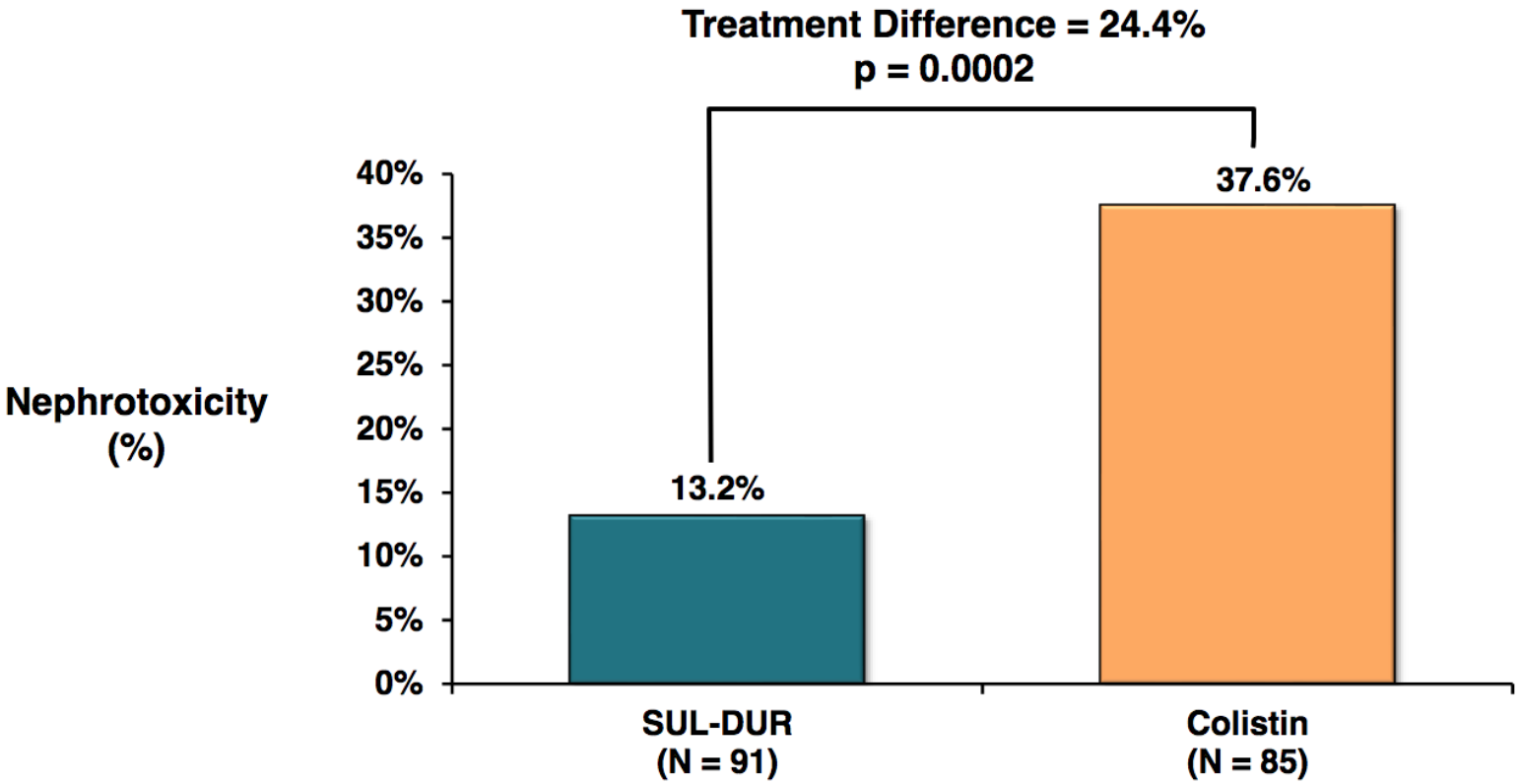
Part B: colistin-resistant or intolerant to colistin (61% with blood-stream infections)



Carbapenem-resistant *Acinetobacter* m-MITT population (Primary Efficacy Analysis Population)
End of treatment was day of last dose; test of cure 7 ± 2 days after end of treatment, late follow-up 7 ± 2 days after test of cure

https://www.fda.gov/media/167158/download

SUL-DUR Achieved the Primary Safety Objective of Lower Nephrotoxicity than Colistin



Phase 3 Trial Part A
Based on modified RIFLE criteria
RIFLE = Risk, Injury, Failure, Loss, End Stage Kidney Disease

https://www.fda.gov/media/167158/download

Sulopenem

- Synthetic penem; sulopenem etzadroxil oral prodrug.
- Spectrum: Active against Enterobacterales, including ESBL-producers, but not CRE. Gram-positive activity is similar to carbapenems.
- Intended to provide the possibility of an oral switch early during treatment in stable patients, opening the option of earlier discharge from the hospital or of avoiding hospitalization.
- Cross-resistance with existing carbapenems has been reported
- Dosage:
  - uUTI in females: Sulopenem-etzadroxil/probenecid 500mg PO twice daily x 5 days.
  - cUTI and cIAI: Sulopenem 1000 mg iv QD X $\geq$5 days, followed by sulopenem-etzadroxil/probenecid 500 mg PO BID x 7–10 days.

Karlowsky JA, et al. *Antimicrob Agents Chemother* 2018; 63:e01832–18.

Sulopenem SURE-1 Phase 3 Study

- Study Design: Prospective, multicenter, double-blind, randomized study
- Study population: 1671 adult female patients with uUTI receiving sulopenem-etzadroxil 500 mg/probenecid 500 mg PO bid x 5 days vs. ciprofloxacin 250 mg PO bid x 3 days
- Primary end point (overall response): combined clinical & microbiologic response on day 12.
- Subsets of mMITT population:
  - mMITT-S: baseline pathogens susceptible to ciprofloxacin (MIC $\leq$1 µg/mL)
  - mMITT-R: baseline pathogens nonsusceptible to ciprofloxacin (MIC $\geq$2 µg/mL)

Dunne MW, et al. Clin Infect Dis; 2023: 76(1); 66–77

SURE-1 Results: Primary Efficacy

Time of End Point Assessment	Sulopenem etzadroxil/Probenecid n/N (%)	Ciprofloxacin n/N (%)	Absolute Difference (95% Confidence Interval)
Combined clinical and microbiologic response			
Day 5 (end of treatment)			
mMITT-R	95/147 (64.6)	42/139 (30.2)	34.4 (23.1 to 44.8)
mMITT-S	240/370 (64.9)	271/415 (65.3)	−0.4 (−7.1 to 6.2)
mMITT	335/517 (64.8)	313/554 (56.5)	8.3 (2.4 to 14.1)
Day 12 (test of cure: primary end point)			
mMITT-R	92/147 (62.6)	50/139 (36.0)	26.6 (15.1 to 37.4)
mMITT-S	247/370 (66.8)	326/415 (78.6)	−11.8 (−18.0 to −5.6)
mMITT	339/517 (65.6)	376/554 (67.9)	−2.3 (−7.9 to 3.3)
Day 28 (late follow-up)			
mMITT-R	100/147 (68.0)	62/139 (44.6)	23.4 (12.0 to 34.3)
mMITT-S	256/370 (69.2)	323/415 (77.8)	−8.6 (−14.8 to −2.5)
mMITT	356/517 (68.9)	385/554 (69.5)	−0.6 (−6.2 to 4.9)
Clinical response			
Day 5			
mMITT-R	99/147 (67.3)	83/139 (59.7)	7.6 (−3.5 to 18.7)
mMITT-S	256/370 (69.2)	290/415 (69.9)	−0.7 (−7.2 to 5.7)
mMITT	355/517 (68.7)	373/554 (67.3)	1.3 (−4.3 to 6.9)
Day 12			
mMITT-R	122/147 (83.0)	87/139 (62.6)	20.4 (10.2 to 30.4)
mMITT-S	300/370 (81.1)	349/415 (84.1)	−3.0 (−8.4 to 2.3)
mMITT	422/517 (81.6)	436/554 (78.7)	2.9 (−1.9 to 7.7)

Dunne MW, et al. Clin Infect Dis; 2023: 76(1); 66–77

SURE-1 … REASURRE

- In the mMITT-S population, sulopenem was not noninferior to ciprofloxacin, driven largely by a higher rate of ASB in those receiving sulopenem (12.7%) vs. cipro (3.9%)

- FDA: additional clinical data will be necessary to support approval of the medication for uUTI that are caused by "designated susceptible microorganisms proven or strongly suspected to be non-susceptible to a quinolone."
  - Called for Iterum to conduct an additional clinical study that uses a different drug for comparison; also recommended Iterum conduct a non-clinical study to determine optimal dosing.

- REASSURE: Sulopenem vs. Augmentin for uUTI
  - Plan to resubmit NDA to FDA 2nd half of 2024

https://ir.iterumtx.com/press-releases/detail/99/iterum-announces-first-patient-dosed-in-reassure-a-phase-3

Sulopenem SURE-2 Phase 3 Study

- Study population: 1395 adult cUTI patients were randomized and parallelly assigned to receive either sulopenem iv QD x 5 days followed by sulopenem-etzadroxil/probenecid PO bid or ertapenem iv once daily x 5 days followed by either PO ciprofloxacin or amoxicillin-clavulanate bid, depending on the susceptibility of the baseline uropathogen.
- Conclusions: Sulopenem did not achieve statistical noninferiority to ertapenem, with a difference in outcome of 4.7% (95% CI: –10.3 to 1.0) using a non-inferiority margin of 10%.

Dunne MW, et al. *Clin Infect Dis.* 2023 Jan 6;76(1): 78-88.

Gepotidacin

- Novel topoisomerase inhibitor being developed for the treatment of uncomplicated urogenital gonorrhea & uUTI
- Route of administration & formulation: Intravenous/oral
- Cross-resistance: Some cross-resistance with FQs reported (potentially overlapping/close binding sites).
- Dose:
  - Uncomplicated urogenital gonorrhea: 3000 mg PO (four 750 mg tablets) at the study site, followed by 3000 mg PO (four 750 mg tablets) as an outpatient (EAGLE-1)
  - uUTI (tested in adult females only): 1500 mg PO (two 750 mg tablets) q12h for 5 days (EAGLE-2 & -3)

Watkins RR. *JAC*, 2023

EAGLE-2 & EAGLE-3 Results

- Halted early as met primary efficacy endpoint; EAGLE-3 demonstrated statistical superiority; New FDA endpoints (clinical + micro cure)
- ARDS %: gep>nitro

	EAGLE-2			EAGLE-3		
	gepotidacin 1500mg BID (n=320)	nitrofurantoin 100mg BID (n=287)	Treatment Difference[i] (95% CI)	gepotidacin 1500mg BID (n=277)	nitrofurantoin 100mg BID (n=264)	Treatment Difference[i] (95% CI)
Therapeutic success [ii]	162 **(50.6%)**	135 **(47.0%)**	**4.3%** (-3.6%, 12.1%)	162 **(58.5%)**	115 **(43.6%)**	**14.6%** (6.4%, 22.8%)
Clinical success[iii]	210 **(65.6%)**	187 **(65.2%)**	**1.2%** (-6.3%, 8.7%)	188 **(67.9%)**	167 **(63.3%)**	**4.4%** (-3.5%, 12.3%)
Microbiological success[iv]	232 **(72.5%)**	194 **(67.6%)**	**5.2%** (-2.1%, 12.5%)	200 **(72.2%)**	151 **(57.2%)**	**15.0%** (7.2%, 22.9%)

https://www.gsk.com/en-gb/media/press-releases/gepotidacin-s-positive-phase-iii-data-shows-potential-to-be-the-first-in-a-new-class-of-oral-antibiotics-for-uncomplicated-urinary-tract-infections/

RE-APPRAISAL OF NEW(ISH) ANTIBIOTICS

David Ha, PharmD, BCIDP

Stanford Medicine

Presented by: Ravina Kullar, PharmD, MPH, FIDSA

May 7, 2023

New(ish) Antibiotics

- Ceftazidime/Avibactam
- Meropenem/Vaborbactam
- Imipenem/Relebactam
- Ceftolozane/Tazobactam
- Cefiderocol
- Eravacycline
- Omadacycline

Which do you need?

- Depends on local epidemiology and resistance rates
  - Consult: ID clinicians, microbiology laboratory, and antibiogram to assess local applicability
  - High risk populations (e.g., immunocompromised, transplant, cystic fibrosis, patients with high antibiotic exposure, areas of endemic drug resistance)
- Will differ significantly between institutions
- **We will take an multi-drug resistant organism (MDRO)-based, rather than drug-based approach**

New(ish) Antibiotics

- MDROs of interest
  - Difficult-to-Treat Resistance *Pseudomonas aeruginosa* (DTR-PA)
  - Carbapenem-resistant Enterobacterales (CRE)
  - Carbapenem-resistant *Acinetobacter baumanii* (CRAB)
  - *Stenotrophomonas maltophila*
- Antibiotic "Menu"
  - Ceftazidime/Avibactam
  - Meropenem/ Vaborbactam
  - Imipenem/Relebactam
  - Ceftolozane/ Tazobactam
  - Cefiderocol
  - Eravacycline
  - Omadacycline

Difficult-to-Treat Resistance *Pseudomonas aeruginosa* (DTR-PA)

- DTR-PA = PA that is non-susceptible to pip/tazo, cephalosporins, carbapenems, and fluoroquinolones
- Severe, systemic infections:
  - Ceftolozane/tazobactam
  - Ceftazidime/avibactam (may reserve for CRE)
  - Imipenem/relebactam (may reserve for CRE)
  - Alternative: Cefiderocol (may reserve for select CRE or VIM carbapenemase-producing PA)
- Uncomplicated cystitis:
  - Added to above options: single dose aminoglycoside

Tamma et al. CID 2022. Pogue et al. CID 2020. Motsch et al. CID 2020. Stone et al. AAC 2018. Bassetti et al. Lancet ID 2021. Walkty et al. AAC 2014.

Carbapenem-Resistant Enterobacterales (CRE)

- Resistant to all carbapenems, not just ertapenem
  - Ertapenem-monoresistance may be treatable with non-ertapenem carbapenems, if susceptible
- Most commonly KPC in California
  - Less commonly metallo-beta lactamase (e.g., NDM, VIM, IMP), OXA, or non-carbapenemase-producing
  - Genotypic diagnostics enable assessment of CRE genotypes enabling better formulary decisions
- Discussion will focus on severe infections
  - Mild infections may be treated with non-beta lactams

Adelman et al. OFID 2021. CDPH HAI Program. https://www.cdph.ca.gov/Programs/CHCQ/HAI/Pages/CRE_InfectionPreventionStrategies.aspx

Carbapenem-Resistant Enterobacterales (CRE)

- KPC-producers
  - Meropenem/vaborbactam
    - Active against KPC 1, 2, and 3
    - Positive observational evidence
  - Ceftazidime/avibactam
    - Active against KPC 1 and 2 (not KPC 3)
    - Positive observational evidence, however, concerns regarding development of resistance on therapy (not seen with MEM/VAB)
  - Imipenem/relebactam
    - Active against KPC, however, limited clinical evidence
  - Cefiderocol
    - Active against KPC, consider reserving for other CRE/MDROs

Tamma et al. CID 2022. Ackley et al. AAC 2020. van Duin et al. CID 2018. Wunderink et al. Infect Dis Ther 2018. Motsch et al. CID 2020. Alosaimi et al. OFID 2020. Shields et al. AAC 2017. Karaiskos JAC 2021. Hakeam et al. IJID 2021. Alraddadi et al. BMC ID 2019.

Carbapenem-Resistant Enterobacterales (CRE)

- NDM-producers
  - Ceftazidime/avibactam + Aztreonam
    - Aztreonam active against NDM-producers while avibactam serves to protect aztreonam from other mechanisms (e.g., ESBL, ampC, OXA-48-like)
    - Favorable retrospective clinical evidence vs. polymyxin or tigecycline-based therapy
  - Cefiderocol
    - Favorable prospective clinical evidence vs. polymyxin-based therapy
    - No head-to-head data vs. ceftazidime/avibactam + aztreonam

Tamma et al. CID 2022. Falcone et al. CID 2021. Lodise et al. CID 2020. Bassetti et al. Lancet ID 2021.

Carbapenem-Resistant Enterobacterales (CRE)

- OXA-48-like producers
  - Active: Ceftazidime/avibactam or Cefiderocol
  - Not active: meropenem/vaborbactam, imipenem/relebactam
- Unknown CRE genotype or Negative genotype test
  - Ceftazidime/avibactam, Meropenem/vaborbactam, or Imipenem/relebactam
- Tetracycline derivatives
  - Beta lactams preferred but tetracycline derivatives can be considered as alternative therapy, avoid monotherapy in urinary or bloodstream infections

Tamma et al. CID 2022. de Jonge et al. AAC 2016. Spiliopoulou et al. AAC 2020. De la Calle et al. Int J Antimicrob Agents 2019.

Carbapenem-Resistant *Acinetobacter baumanii* (CRAB)

- Mild infections
  - Monotherapy with ampicillin/sulbactam preferred
- Moderate to Severe Infections
  - Combination therapy preferred
  - Should include ampicillin/sulbactam, if susceptible
    - High dose recommended by IDSA (27g/day continuous or divided q8H)
  - Other preferred agents, in combination:
    - Tetracycline derivatives (minocycline preferred, followed by tigecycline, limited data for eravacycline or omadacycline)
    - Polymyxin B
    - Cefiderocol (caution: increased mortality in CREDIBLE-CR)

Tamma et al. CID 2022. Makris et al. Indian J Crit Care Med 2018. Kaye et al. Paul et al. Lancet ID 2018. Sirijatuphat et al. AAC 2014. Durante-Mangoni et al. CID 2013. Aydemir et al. Epidemiol Infect 2013. Park et al. J Glob Antimicrob Resist 2019. Jung et al. Crit Care 2017

Stenotrophomonas maltophila

- Mild infections
  - Monotherapy with TMP/SMX preferred
  - Alternatives: minocycline, tigecycline, levofloxacin, cefiderocol
  - Avoid: ceftazidime (even if in vitro susceptible)
- Moderate to Severe Infections
  - Combination therapy preferred
  - Preferred: TMP/SMX + minocycline
  - Alternative #1: TMP/SMX monotherapy with addition of second agent if lack of clinical response
    - Second agent options: Minocycline (preferred), tigecycline, levofloxacin, cefiderocol
  - Alternative #2: Ceftazidime/avibactam + Aztreonam
  - Emerging evidence for eravacycline

Tamma et al. CID 2022. Muder et al. CID 1996. Sarzynski et al. OFID 2022. Mojica et al. mBio 2019. Hand et al. JAC 2016. Tekce et al. JAC 2012. Bassetti et al. Lancet ID 2021. Diarra et al. IDNow 2021. Carr et al. OFID 2020.

Summary

Drug	DTR-PA	CRE-KPC	CRE-NDM	CRE-OXA
Ceftazidime/ Avibactam	Preferred (Reserve)	Alternative (May develop resistance)	Preferred (combined with aztreonam)	Preferred
Meropenem/ Vaborbactam	Not active	Preferred	Not active	
Imipenem/ Relebactam	Preferred (Reserve)	Alternative (Limited clinical evidence)		
Ceftolozane/ Tazobactam	Preferred	Not active		
Cefiderocol	Alternative (Reserve)	Alternative (Reserve)	Preferred	Preferred
Eravacycline, Omadacycline, Tigecycline	Not active	Alternative (if no beta lactam options)		

Summary (continued)

	Preferred	Alternative
CRAB		
Mild	• Ampicillin/sulbactam	
Moderate to Severe	• Ampicillin/sulbactam (high dose) + minocycline	• Ampicillin/sulbactam (high dose) + one of: tigecycline or polymyxin B
Stenotrophomonas maltophila		
Mild	• TMP/SMX	• Minocycline, tigecycline, levofloxacin, or cefiderocol
Moderate to Severe	• TMP/SMX + minocycline	• TMP/SMX + tigecycline • TMP/SMX + levofloxacin • TMP/SMX + cefiderocol