Epidemiology and Management of Carbapenem-Resistant *Acinetobacter baumannii* (CRAB)

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Disclosures

- Consultant: Shionogoi, Merck, Qpex, Allecra, Venatorx, AbbVie, Spero, Entasis
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Objectives

- Prevalence and impact
- Mechanisms of resistance
- Approaches to treatment
- What the future holds

CDC: Drug-Resistant Gram-Negative Bacterial Infection Threats

Urgent and Serious GNR Threats

Carbapenem-resistant Acinetobacter (urgent)

Carbapenem-resistant Enterobacteriaceae (urgent)

ESBL-producing Enterobacteriaceae (serious)

Multidrug-resistant *Pseudomonas aeruginosa* (serious)

WHO Priority Pathogens List For R&D of New Antibiotics

Priority 1: Critical

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae*, carbapenem-resistant, 3rd generation ceph-resistant

Acinetobacter baumannii – Carbapenem-Resistant

ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES, 2019, CDC.GOV

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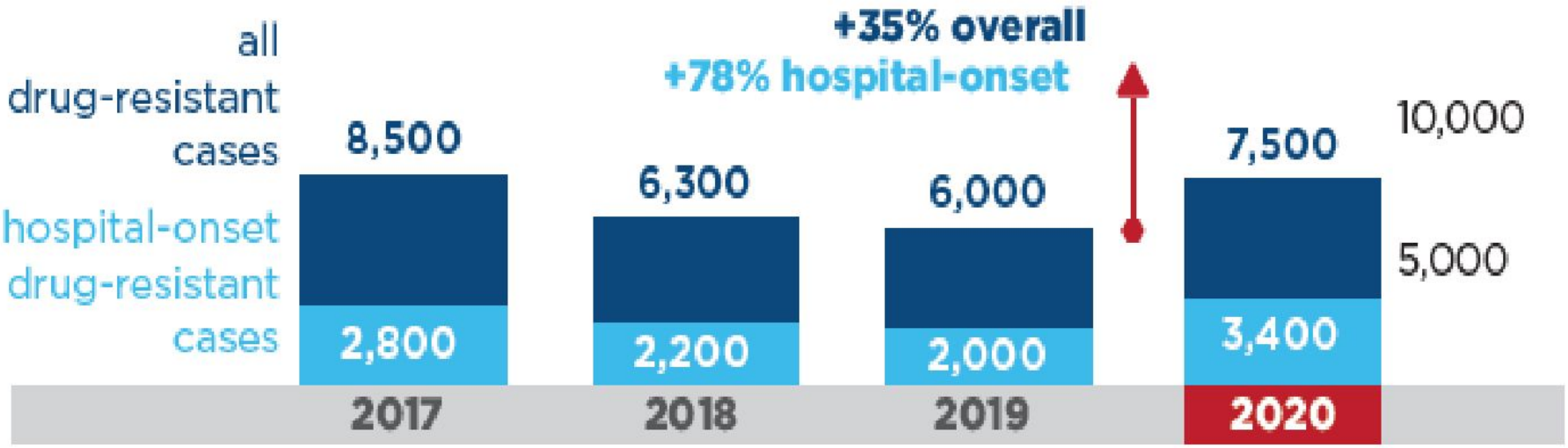
The rates of hospital-onset carbapenem-resistant *Acinetobacter* cases decreased 2012-2017, began to plateau, then increased 78% in 2020.



Data from 2018–2020 are preliminary.

https://www.cdc.gov/drugresistance/covid19.html

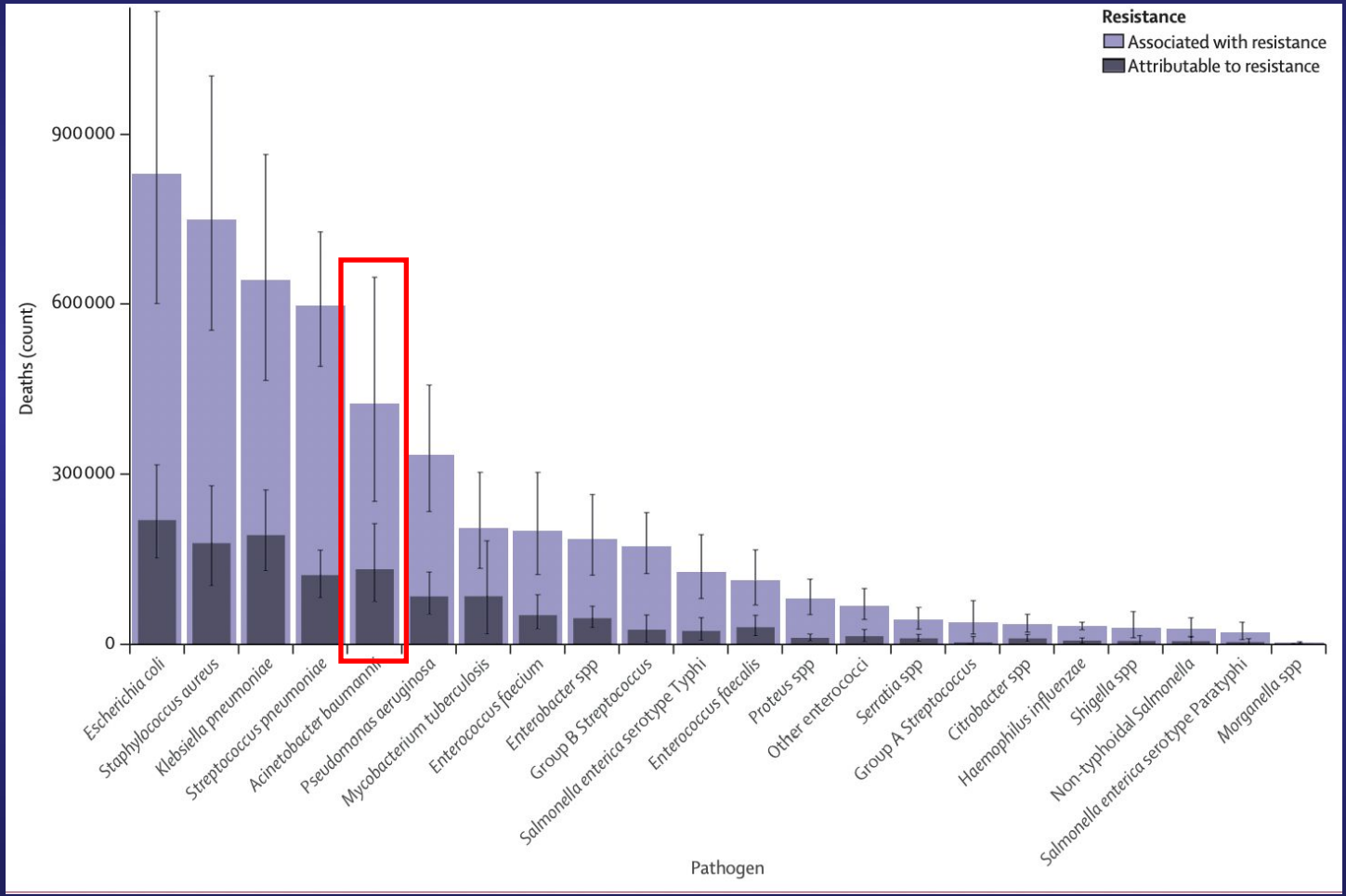
Gram-negative Pathogens: Change in Rates from 2019-2020

	CRAB	CRE	ESBL	MDR *PA*
Overall	35% increase		10% increase	
Hospital -onset	78% increase	35% increase	32% increase	32% increase

https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf

Gram-Negative Bacteria

- 4 out of top 6 pathogens leading to death from AMR were Gram-negative



- Carbapenem-resistant *A. baumannii* is the fourth leading cause of death attributable to antimicrobial resistance globally

Murray CJ,. *The Lancet*. 2022;399(10325)

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Carbapenem-Resistant *A. baumannii* (CRAB)

- Mechanisms of resistance to antimicrobials multiple, diverse; carbapenem resistance often driven by carbapenemases
  - Porin mutations
  - Altered PBPs
  - Metallo-beta-lactamases, serine carbapenemases (OXA)
    - OXA-23-like, OXA-24/40-like, OXA-51-like, OXA-58-like
- Carbapenem resistance seen in multiple geographic locales worldwide
- Problem pathogen in ICU patients (particularly in burn units), elderly and combat injuries from middle east
- Can cause hospital outbreaks

Landman, JAC, 2007; Ahmed et al, Journal of Pure and Applied Microbiology, 2016, 1675-1682; https://arpsp.cdc.gov/story/cra-urgent-public-health-threat

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Role of Sulbactam

- SUL competitively and irreversibly binds to PBPs at high doses against *A. baumannii*[1]
  - Not interchangeable with other β-lactamase inhibitors
- Retains activity against some strains that produce OXA-23 [2]
- Ampicillin/SUL MICs = surrogates for SUL activity if susceptible (≤8/4 mg/L), but not when resistant[2]
  - Ampicillin/SUL 3 g q6hr over 1 hr: >90% probability of achieving 40% *f*T > MIC for isolates with MICs ≤16 mg/L
  - 6-12 g SUL per day can result in adequate exposure for MICs 16-32 mg/L
- SUL being developed in combination with durlobactam[6]

1. Wang. Infect Drug Resist. 2021;14:3971. 2. Abdul-Matakabbir. Infect Dis Ther. 2021;10:2177. 3. Lenhard. Antimicrob Agents Chemother. 2017;61:e01268-16. 4. Betrosian. Scan J Infect Dis. 2007;39:38. 5. Jaruatanasirikul. Eur J Pharm Sci. 2019;136:104940. 6. NCT03894046.

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CRAB Often Resistant To Other Antibiotics

PERCENT OF GERMS THAT TESTED NON-SUSCEPTIBLE (NOT SENSITIVE) TO OTHER TYPES OF ANTIBIOTICS

Select Antibiotics	2013	2014	2015	2016	2017
Any fluoroquinolone	98%	93%	97%	92%	89%
Any extended-spectrum β-lactam	80%	75%	81%	79%	75%
Ampicillin/sulbactam	62%	62%	59%	64%	61%
Trimethoprim/ sulfamethoxazole	84%	74%	81%	77%	66%

ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES, 2019, CDC.GOV

New(er) Approved Therapies – B-lactam/B-lactam Inhibitor Combinations

Agent	MoA	Approved Indications	In Vitro Activity	Treatment Niche
Ceftolozane/ tazobactam	Novel cephalosp β-lactam inhibito	ith zole	▪ E: TEM ▪ P: A	***Pseudomonas aeruginosa*, including XDR rains**
Ceftazidime/ avibactam	Cephalosporin/ novel β-lactamase inhibitor	▪ py ▪	ain rD loss	▪ **CRE – KPC, OXA-48** ▪ ***P. aeruginosa***
Meropenem/ vaborbactam	Carbapenem/ novel β-lactam inhibitor			▪ **CRE- KPC**
Imipenem/ relebactam	Carbapen novel β-lactamase inhibitor	ding ephritis AI HABP/VABP	▪ E: certain ▪ P: AmpC	**CRE-KPC *P. aeruginosa* including some XDR strains**

*E, *Enterobacteriaceae*; P, *P. aeruginosa*

Ceftolozane/tazobactam [package insert]. November 2016. Ceftazidime/avibactam [package insert]. February 2018. Meropenem/vaborbactam [package insert]. April 2018. Imipenem/relebactam [package insert]. July 2019.

New BLI Agents…Don't Help

- Carbapenem-resistant largely mediated by carbapenemases
  - Primarily Class D Oxacillinases
  - Growing reports of class B NDM-1 enzymes
- These enzymes readily hydrolyze cephalosporins and carbapenems
- Neither tazobactam, avibactam, vaborbactam, nor relebactam inhibit these enzymes….

Wang et.al. Antimicrob Agents Chemother. 2014;58(3):1774-8.; Yoshizumi A et.al.J Infect Chemother. 2015;21(2):148-51

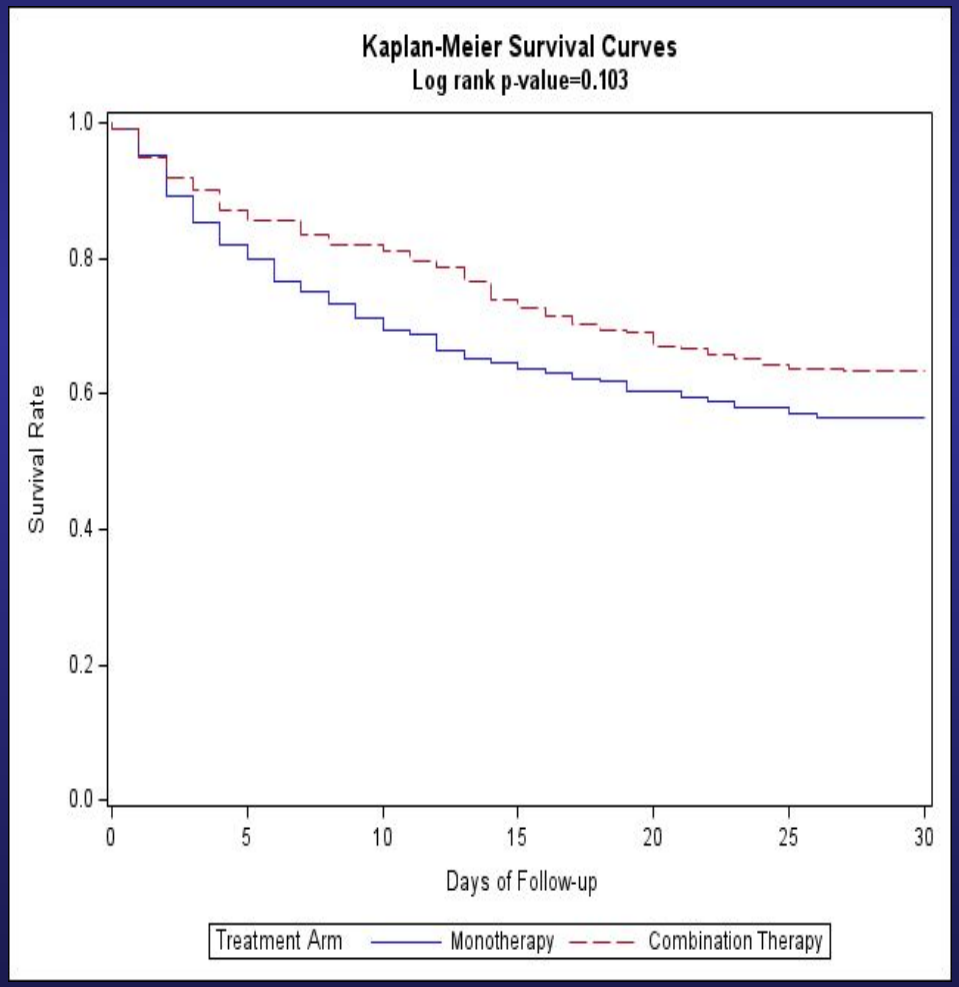
Are Polymyxins Still the Mainstay of CRAB Treatment?

- These drugs have lots of issues
  - PK concerns (poly B more straightforward)
  - Nephrotoxicity in the 30 – 50% range
  - Particular concerns in pneumonia

- The inability to safely achieve therapeutic targets often leads to combination therapy
  - Evidence to support is lacking
  - ACTIVE second agent might be the key
    - Extrapolate from the CRE experience

OVERCOME: Colistin alone vs Colistin + Meropenem

Primary outcome: 28-day mortality



	Colistin + Placebo (%)	Colistin + Meropenem (%)	P value
Overall	92/213 (43)	77/210 (37)	0.17
Pneumonia	69/152 (45)	59/146 (40)	0.39
BSI	23/61 (38)	18/64 (28)	0.25
A. baumannii	76/165 (46)	69/164 (42)	0.47
P. aeruginosa	10/23 (43)	5/20 (25)	0.21
CRE	11/34 (32)	6/35 (17)	0.14

Kaye et al, NEJM Evidence, 2022

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Tetracyclines: Important Rx Considerations for CRAB

- Minocycline
  - Shows good activity against *A. baumannii* (including CRAB) ~75% susceptible; But breakpoint likely off (breakpoint is 4; recent data suggest that 0.5-1 is more accurate)
  - Clinical evidence limited, but encouraging
- Tigecycline
  - Serum and epithelial lining fluid concentrations suboptimal
  - Experience as monotherapy conflicting - resistance development, clinical failures
- Eravacycline
  - Potency advantage over tigecycline
    - Recent PK/PD data suggest that breakpoint is too high
  - More evidence needed; do not overreact to lower MICs

Cefiderocol: Activity against CRAB

	MIC (mg/L)			Resistance (%)		
Species/antibiotic	MIC range	MIC_{50}	MIC_{90}	S	I	R
A. baumannii (*n*=107)						
cefiderocol	≤0.03–2	0.06	0.5	NA	NA	NA
meropenem	8–>64	64	>64	0	0	100
ceftazidime	8–>64	>64	>64	0.9	5.6	93.5
cefepime	8–>16	>16	>16	5.6	7.5	86.9
ceftazidime/avibactam	0.25–>64	32	64	NA	NA	NA
ceftolozane/tazobactam	2–>64	32	>64	NA	NA	NA
aztreonam	8–>32	>32	>32	NA	NA	NA
amikacin	8–>64	>64	>64	6.5	5.6	87.9
ciprofloxacin	≤0.25–>4	>4	>4	2.8	0	97.2
colistin	≤0.5–>8	1	8	57.9	0	42.1
tigecycline	≤0.25–4	1	2	NA	NA	NA

Falagas et al. J Antimicrob Chemother. 2017 Jun 1;72(6):1704-1708

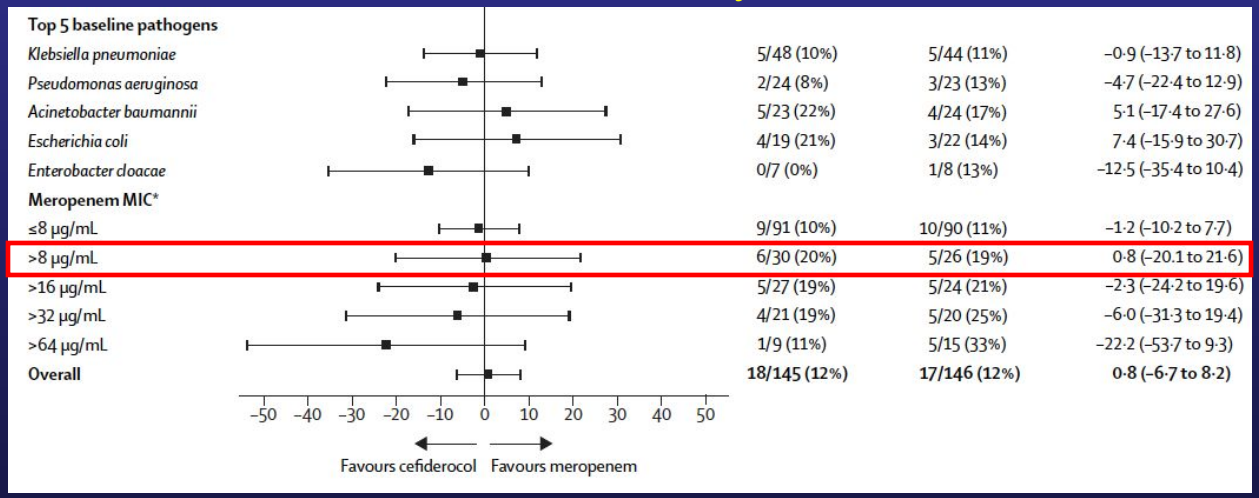
Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial

Lancet Infect Dis 2020

Richard G Wunderink, Yuko Matsunaga, Mari Ariyasu, Philippe Clevenbergh, Roger Echols, Keith S Kaye, Marin Kollef, Anju Menon, Jason M Pogue, Andrew F Shorr, Jean-Francois Timsit, Markus Zeitlinger, Tsutae D Nagata

	Cefiderocol (n=145)	Meropenem (n=147)	Treatment difference (95% CI)
Clinical cure			
All patients	94/145 (65%)	98/147 (67%)	−1·8 (−12·7 to 9·0)
HAP	33/59 (56%)	41/60 (68%)	−12·4 (−29·7 to 4·9)
VAP	39/59 (66%)	36/64 (56%)	9·9 (−7·3 to 27·0)
HCAP	22/27 (82%)	21/23 (91%)	−9·8 (−28·5 to 8·8)
Top five baseline pathogens			
Klebsiella pneumoniae	31/48 (65%)	29/44 (66%)	−1·3 (−20·8 to 18·1)
Pseudomonas aeruginosa	16/24 (67%)	17/24 (71%)	−4·2 (−30·4 to 22·0)
Acinetobacter baumannii	12/23 (52%)	14/24 (58%)	−6·2 (−34·5 to 22·2)
Escherichia coli	12/19 (63%)	13/22 (59%)	4·1 (−25·8 to 33·9)
Enterobacter cloacae	5/7 (71%)	4/8 (50%)	21·4 (NA)

All-Cause Mortality



Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial

Matteo Bassetti, Roger Echols, Yuko Matsunaga, Mari Ariyasu, Yohei Doi, Ricard Ferrer, Thomas P Lodise, Thierry Naas, Yoshihito Niki, David L Paterson, Simon Portsmouth, Julian Torre-Cisneros, Kiichiro Toyoizumi, Richard G Wunderink, Tsutae D Nagata

	Cefiderocol (n=101)	Best available therapy (n=49)
Acinetobacter spp*	21/42 (50%)	3/17 (18%)
Acinetobacter baumannii	19/39 (49%)	3/17 (18%)
Klebsiella pneumoniae	8/34 (24%)	4/16 (25%)
Without *Acinetobacter* spp	6/28 (21%)	4/15 (27%)
Pseudomonas aeruginosa	6/17 (35%)	2/12 (17%)
Without *Acinetobacter* spp	2/11 (18%)	2/11 (18%)
Escherichia coli	1/6 (17%)	0/3
Without *Acinetobacter* spp	0/3	0/1
Stenotrophomonas maltophilia	4/5 (80%)	NA
Without *Acinetobacter* spp	2/3 (67%)	NA

Data are n/N (%). NA=not available. *Includes *Acinetobacter baumannii* (for 39 patients assigned cefiderocol and 17 assigned best available therapy), *Acinetobacter nosocomialis* (for two patients assigned cefiderocol), and *Acinetobacter radioresistens* (for one patient assigned cefiderocol).

Table 6: **All-cause mortality at the end of study by most frequent baseline pathogen in the safety population**

2022 IDSA Guidance: CRAB

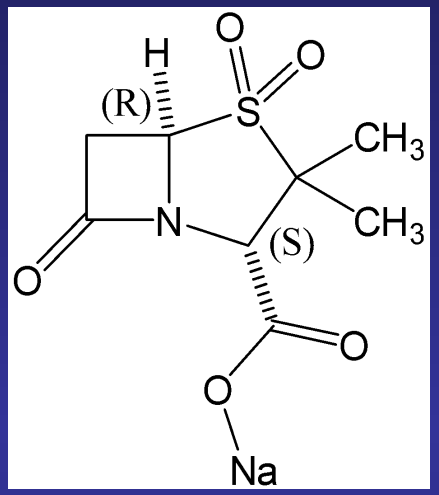
CRAB Infection	Preferred	Notes
Mild	▪ Single-agent: high-dose ampicillin/sulbactam (when pathogen is susceptible)	▪ Polymyxin B (colistin for cystitis), tetracycline (eg, minocycline or tigecycline) or cefiderocol monotherapy may be considered
Moderate to severe	▪ Combination of ≥2 active agents (even if a single agent demonstrates activity), including • High-dose ampicillin/sulbactam • Polymyxin B • Extended-infusion meropenem • Tetracycline (minocycline, tigecycline; little data for eravacycline)	▪ Nebulized antibiotics are not recommended for respiratory infections ▪ Meropenem plus polymyxin without third agent is not recommended ▪ Rifamycin is not recommended
Refractory to other antibiotics	▪ Cefiderocol as part of a combination regimen	▪ Also recommended if patient is intolerant of other treatment options

- If nonsusceptibility to ampicillin/sulbactam is demonstrated, high-dose ampicillin/sulbactam may remain an effective treatment; addition of a second active agent is recommended, including mild infection.

idsociety.org/practice-guideline/amr-guidance-2.0/

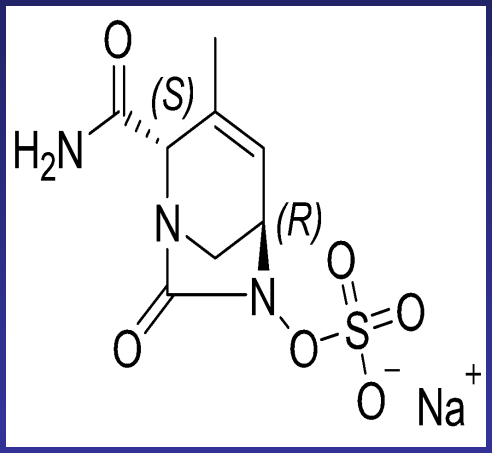
Sulbactam-Durlocbactam to the Rescue?

Sulbactam



- Penicillin derivative with intrinsic activity against ABC
- β-lactamase–mediated resistance is common (MIC_{90} 64 mg/L; N = 4252 global clinical isolates)

Durlobactam (ETX2514)

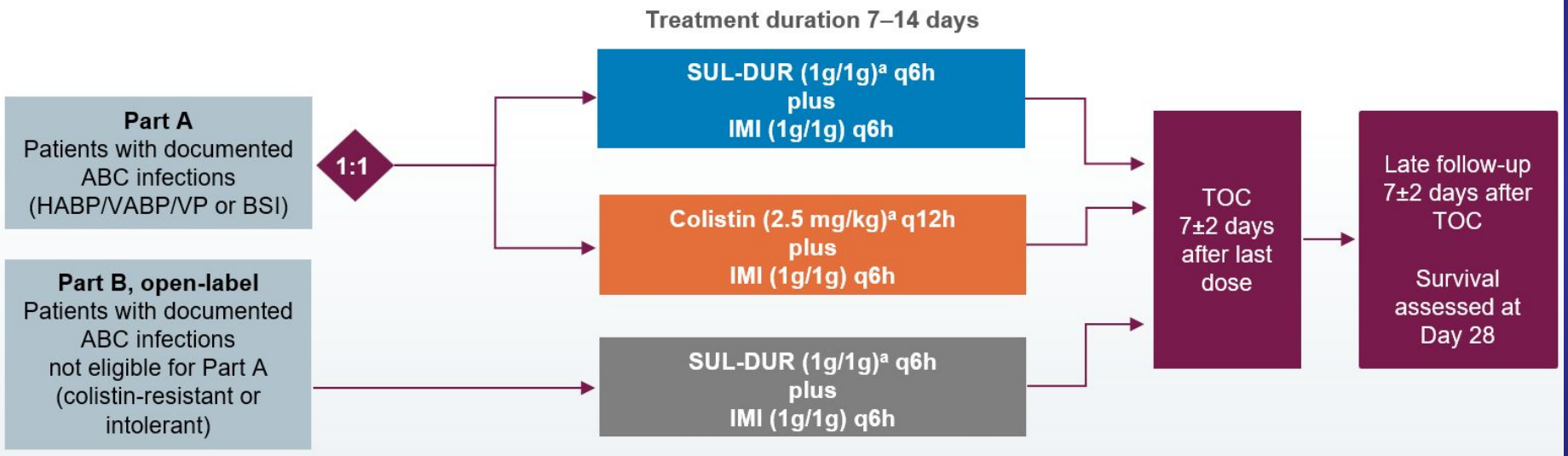


- Diazabicyclooctane β-lactamase inhibitor
- Potent inhibitor of class A, C, and D β-lactamases
- Restores sulbactam activity in vitro and in vivo

Antimicrobial Resistance Collaborators. *Lancet.* 2022;399:629-655;
Shapiro AB et al. *Front Microbiol*. 2021;12:709974;
Hackel M et al. Presented at ECCMID; April 23-26, 2022; Lisbon, Portugal. Abstract #01106.

ATTACK Study Design

- Phase 3, multinational, randomised, controlled, noninferiority trial conducted to evaluate the efficacy and safety of SUL-DUR versus colistin, both in combination with imipenem/cilastatin as background therapy, for patients with serious infections due to *A. baumannii*, including CRAB strains.



This trial is registered at ClinicalTrials.gov: NCT03894046. Please see ECCMID abstract #02093 for Part B.

[a]SUL-DUR dosing was adjusted for renal function. Colistin dosing was adjusted to ideal body weight and renal function. A single colistin loading dose of 2.5 to 5 mg/kg given intravenously over 3 to 6 minutes (or according to standard of care) was administered on Day 1 for patients who had not received prior colistin therapy.

BSI, bloodstream infection; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; HABP, hospital-acquired bacterial pneumonia; IMI, imipenem/cilastatin; q×h, every × hours; TOC, test of cure; VABP, ventilator-associated bacterial pneumonia; VP, ventilated pneumonia.

Presented at 32nd ECCMID, 23–26 April 2022, Lisbon, Portugal

Sul-Dur Achieved Primary Endpoint and Key Secondary Endpoints, All In Patients with CRAB Infections

	Sul-Dur	Colistin	Difference (95% CI)
28-day Mortality CRAB (%)	19.0	32.3	-13.2 (-30.0-3.5)
Clinical Cure (%)	61.9	40.3	21.6 (2.9-40.3)
Nephrotoxicity (%)	13.2	37.6	-24.4 (p=0.0002)

Presented at 32nd ECCMID, 23–26 April 2022, Lisbon, Portugal

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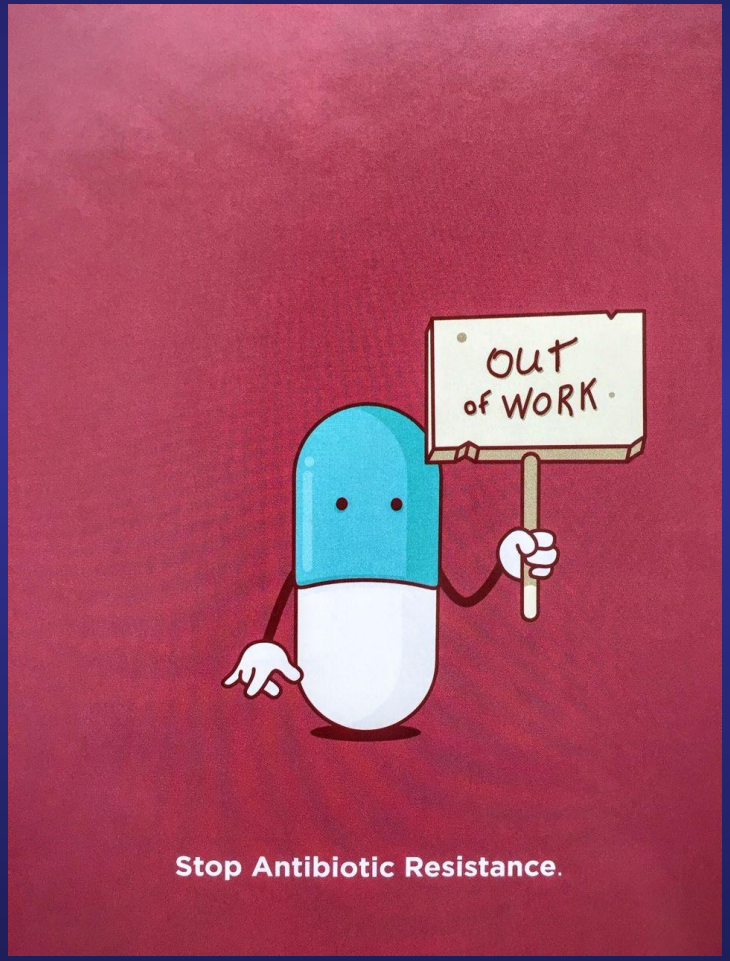
CRAB Treatment Summary

- When sulbactam is active, it should be used!
- We are still lacking good treatment options
  - Major unmet need
- Polymyxins should be avoided whenever possible
- Tetracyclines encouraging, but lack data and breakpoints are too high/doses are too low
- Cefiderocol should not be relied upon as a single agent
- So what do we do for CRAB (particularly when also resistant to sulbactam)?
  - ? cefiderocol + minocycline (or tigecycline)
- Sul-Dur holds promise for the future

Questions?



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