Newly approved antibiotic therapies

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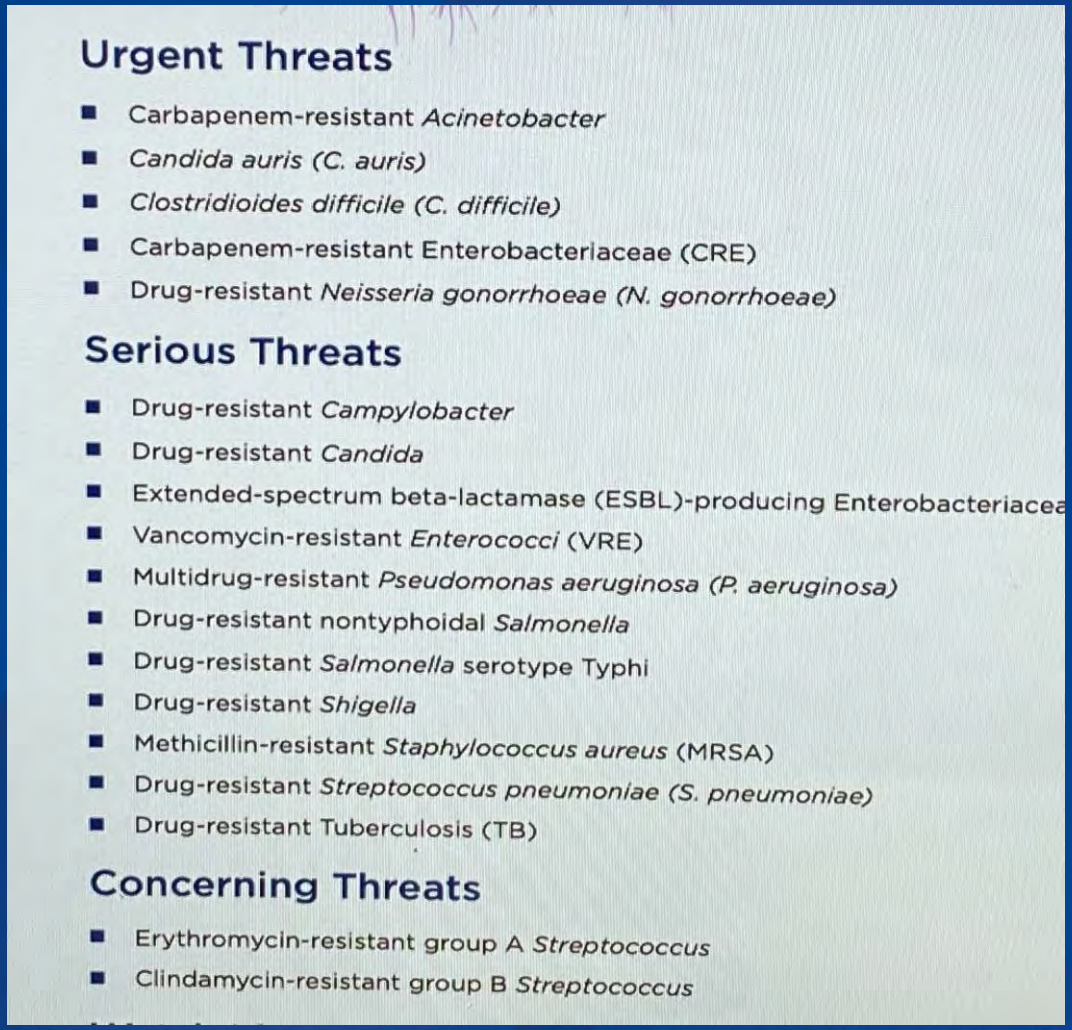
Disclosures:

- I am a consultant for MDStewardship, Inc.

Objectives:

- Recall common MDR isolates and how these could be identified
- Recall where new antibiotics could be useful against MDR isolates

CDC Antibiotic Resistant Threats



Urgent Threats

- Carbapenem-resistant *Acinetobacter*
- *Candida auris (C. auris)*
- *Clostridioides difficile (C. difficile)*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae (N. gonorrhoeae)*

Serious Threats

- Drug-resistant *Campylobacter*
- Drug-resistant *Candida*
- Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriacea
- Vancomycin-resistant *Enterococci* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa (P. aeruginosa)*
- Drug-resistant nontyphoidal *Salmonella*
- Drug-resistant *Salmonella* serotype Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae (S. pneumoniae)*
- Drug-resistant Tuberculosis (TB)

Concerning Threats

- Erythromycin-resistant group A *Streptococcus*
- Clindamycin-resistant group B *Streptococcus*

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Discussing today

- ESBL producing Enterobacterales
- Carbapenem-resistant Enterobacterales (CRE)
- MDR Pseudomonas aeruginosa

What are we talking about?

- Multi-drug resistant (MDR) organisms:
  - Resistant to a > 2 antimicrobial classes

<u>2024 isolates</u>

- *E. coli*
  N=473/11,832 (4%)
- *K. pneumoniae*
  N=184/2,058 (9%)
- *P. aeruginosa*
  N=89/986 (9%)

ESBL-producing Enterobacterales

- Any Gm-negative organism has potential to harbor ESBL genes
  - Most prevalent in:
    - *E coli*
    - *K. pneumoniae*
    - *K. oxytoca*
    - *P. mirabilis*

Case from Omaha

- 64 yo with abd. pain; s/p stent placement in biliary system. Developed fever, UQ pain and U/S showed pericolic fluid collection. Collection was tapped by IR, culture shows *K. pneumoniae* with ESBL enzyme Susceptibilities are

Drug	*K. pneumoniae* MIC (mg/L)	Interpretation
Ampicillin	32	Resistant
Cefazolin (non-urine)	≥32	Resistant
Cefepime	2	Resistant
Ceftriaxone	≤ 0.25	Resistant
Ertapenem	≤ 0.12	Sensitive
Gentamicin	< 1	Sensitive
Levofloxacin	< 0.12	Sensitive
Piperacillin-tazobactam	≥128	Resistant
TMP-SMZ	≥ 16/304	Resistant

Evaluating culture results

- CTX-M enzyme are the most common ESBL in the U.S.
- Usually identified in rapid diagnostic testing (Biofire) blood ID (BCID2)
- Isolate is resistant (MIC $\geq$ 2mg/L) to ceftriaxone – proxy for ESBL production

Preferred Anbx in ESBL cUTI

- TMP-SMX
- Quinolones
- Carbapenems –resistance or toxicities preclude other agents
- Alternatives:
- aminoglycosides

Preferred Anbx for ESBL outside the urinary system

- Carbapenems

- If hypoalbuminemic (Alb < 2.5 g/dl) use meropenem or imipenem-cilastatin

AmpC producing β-lactamases

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AmpC β-lactamase producing Enterobacterales

- AmpC β-lactamases are enzymes produced at basal levels in Enterobacterales & glucose non-fermenting Gm-negative organisms
- Increased AmpC production:
  - Inducible chromosomal gene expression
  - Stable chromosomal gene de-repression
  - Constitutively expressed AmpC genes on plasmids

Which organisms are AmpC production?

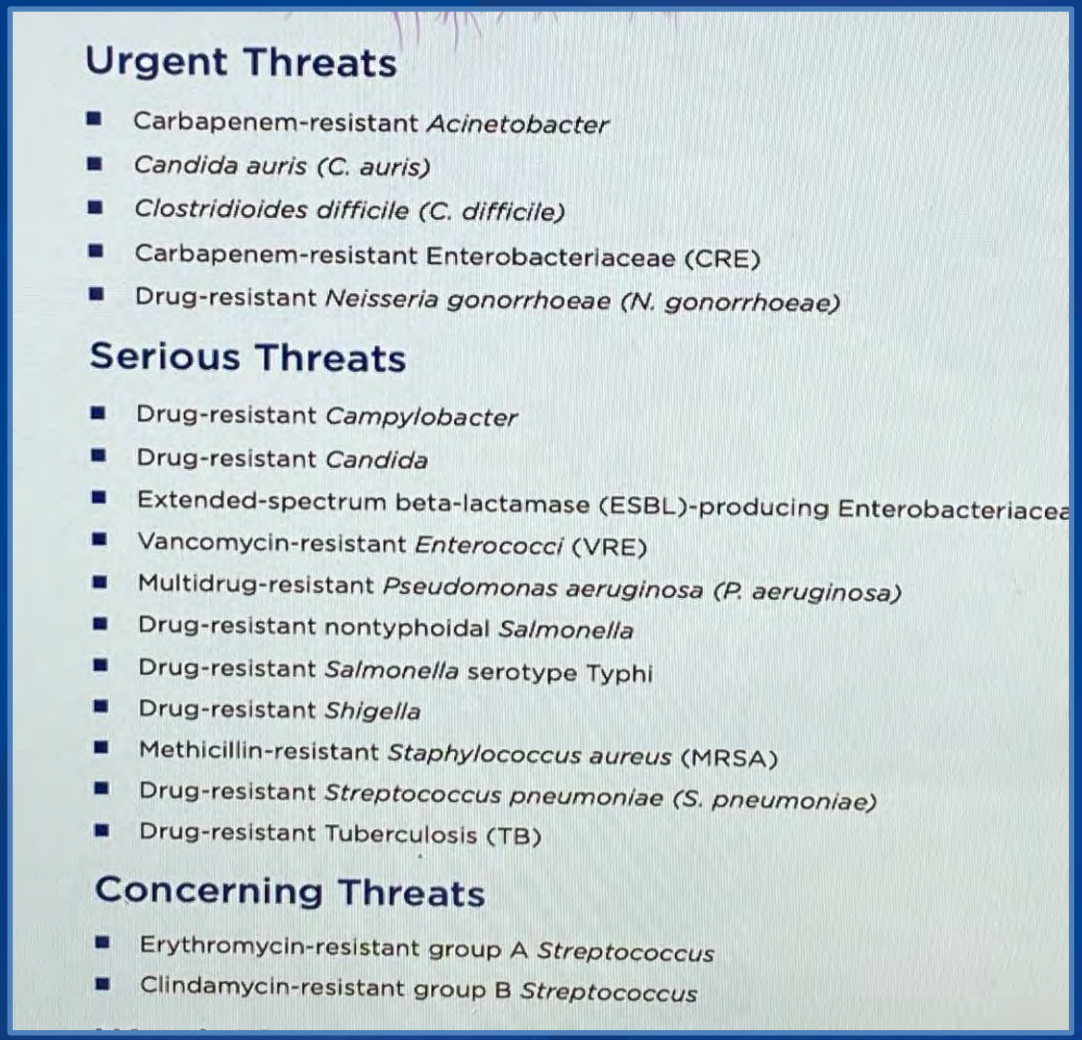
- *Enterobacter cloacae* complex
- *Klebsiella aerogenes*
- *Citrobacter freundii*

- Treatment – cefepime, quinolones, TMP-SMX, aminoglycosides, tetracyclines

Common β-lactams for inducing ampC genes

- Aminopenicillins
- 1st generation cephalosporins
- Cephamycins
- Imipenem

CDC Antibiotic Resistant Threats



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Ambler β–lactamase classification

Ambler classification	Characteristics	Examples	Effective Inhibitors
Class A (serine β-lactamase)	Penicillinases Carbapenemases	TEM, SHV, CTX-M, **KPC**	Tazobactam, vaborbactam, avibactam, relebactam
Class B (metallo-β-lactamase)	Contain metal ion (Zn) carbapenemases inhibited by aztreonam	**IMP, VIM, NDM**	
Class C (serine β-lactamase)	Cephalosporinases Resistant to clavulanic acid; intrinsic in certain species of Gram-negative	AmpC	Vaborbactam, avibactam, relebactam
Class D (serine β-lactamase)	Oxacillinases; carbapenemase	**OXA**	Avibactam

Sheu C-C, et al. *Front Microb* 30 Jan 2019 doi.org/10.3389/fmicb.2019.00080

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Carbapenem-resistant Enterobacterales (CRE)

Klebsiella pneumoniae Carbapenemase (KPC)	OXA-48-like carbapenemase	New Delhi metallo b–lactamase (NDM-1)
• 2001 – initially reported in N.C. • Most predominant MDR isolate in US	• Concerning in Europe (France, Spain, Belgium)	• Concerning in India, southeast Asia • Sporadic cases in US

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What should be used for KPC isolate outside of urinary system?

Ceft-Avi	Mero-vabor	Imip-cilas-releb
>95% activity	>95% activity	>95% activity
Clinical cure & 30-day mortality 61% & 19% (n=105)	Clinical cure & 30-day mortality 85% & 12% (n=26)	
20% had recurrent CRE infx with resistance*	0% had recurrent CRE infx with resistance*	

Ackley R, et al. *Antimicrob Agents Chemother* Apr 21 2020;64(5):e02313-19. doi:10.1128/AAC.02313-19

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Newer options – FDA approved

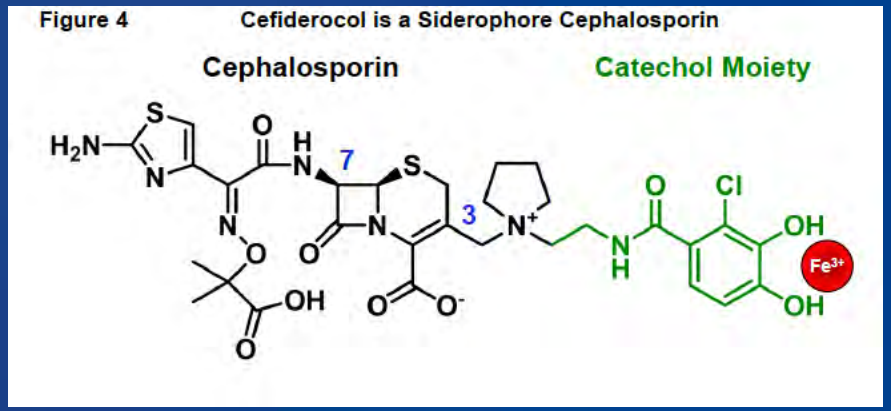
- Cefiderocol
- Aztreonam-avibactam

Cefiderocol

Siderophore cephalosporin

Binds to free iron & is actively transported into bacterial cells

Trojan horse



FDA filing. NDA #209445 Cefiderocol. Shiongi, Inc. accessed 2/17/20

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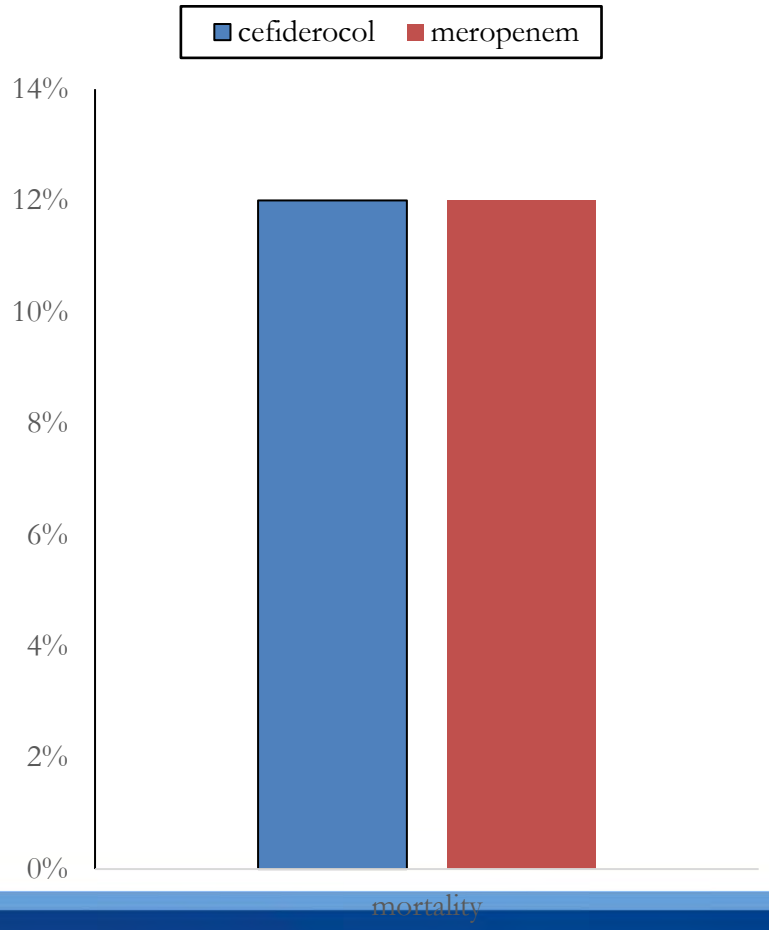
Cefiderocol vs. meropenem EI APEKS-NP study

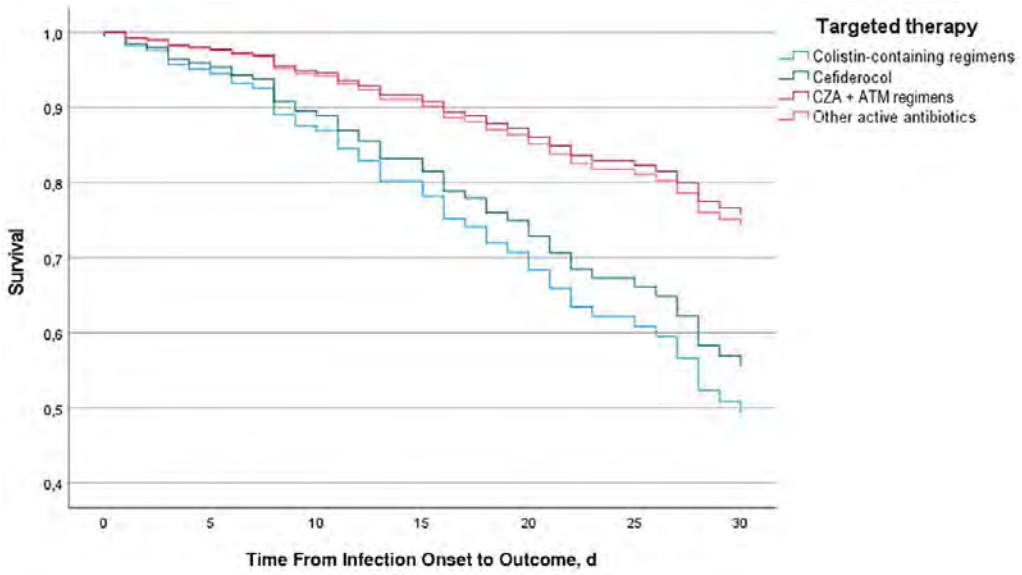
- R, DB, phase 3 trial with Gm-negative HAP/VAP
- Cefiderocol 2G q8h over 3h
- Meropenem 2G q8h over 3h
- Primary endpt: all cause mortality at D14



Wunderink RG, et al. *Lancet Inf Dis* 2021;21:213-25.

Preferred anbx outside urinary tract for CRE if NDM (MBL)?

Drug	Cefiderocol	Colistin-based	Other AA	Ceftaz-avib+aztre
Enrolled pts	(n=33)	(n=26)	(n=37)	(n=215)
Mortality (%)	33	50	13.5	22.3



Falcone M, et al. Clin Infect Dis. May 2024;78(5):1111-1119. doi:10.1093/cid/ciad725

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Aztreonam-avibactam

MBL-producing Enterobacterales (n=267)	Global 2012-2015	Antimicrobial agent	MIC90 (mg/L)	MIC range (mg/L)	% susceptible
		ATM-AVI	1	≤0.015 to 8	100
		ATM	>128	≤0.015 to 128	29
		Meropenem	>8	0.25 to >8	6.4
		Cefepime	>16	≤0.12 to >16	4.9
		Ceftazidime	>128	0.25 to >128	1.5
		Piperacillin-tazobactam	>128	0.5 to >128	6
		Amikacin	>32	0.5 to >32	57.7
		Tigecycline	4	0.06 to 8	89
		Levofloxacin	>4	≤0.03 to >16	29

Al Musawa, et al. Pharmacother 2024; Nov 4. DOI: 10.1002/phar.4629.

REVISIT trial

Variable	Aztre-avi	Mero+colistin
cIAI vs. VAP/HAP	298 vs 74	104 vs 36
Enterobacterales: (%) *E coli* *K pneumoniae* *E cloacae*	 83 12 3	 73 17 5
Tx duration (d)	7.8	8.5
cIAI clinical cure (toc)%	76	74
HAP clinical cure (%)	46	42
28-day mortality (%)	4	7

Carmeli Y, et al. *Lancet Infect Dis* 2025;25:218-30

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Case from Omaha

61 yo female, (116 kg; 5'10") admitted to CUMC-BMMC for ventral hernia repair; exploratory laparotomy in Sept 2022. In LTCF and developed fever. Urine culture was drawn and showed: *P. aeruginosa*

Drug	MIC	Interpretation
Amikacin	4	Sensitive
Cefepime	16	Resistant
Ciprofloxacin	1	Intermediate
Gentamicin	8	Intermediate
Levofloxacin	4	Resistant
Meropenem	>16	Resistant
Piperacillin-tazobactam		Resistant
Tobramycin	<1	Sensitive

MDR *Pseudomonas aeruginosa*

- MDR – not susceptible to 1 anbx in >2 antibiotic classes
- DTR – "difficult-to-treat"
- Interplay of multiple resistance mechanisms (OprD; cephalosporinase (ampC); efflux pumps; PBP mutation targets; bla_{oxa-10}

β-lactam activity MDR PA

Drug	Ceft-tazo	Ceftaz-avi	Imi-cil-rele	Cefid
DTR PA (%)	90	85	86	99

Good to get susceptibility data to help guideline treatment decisions

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Preferred anbx for MDR PA?

- PA not susceptible to carbapenems - use high-dose EI or newer b-lactam agent (alternative)

Summary for MDR Isolates

Agent	KPC-producer	NDM-producer	DTR-Pseudomonas
Ceftazidime-avibactam			
Ceftolozane-tazobactam			
Cefiderocol			
Aztreonam/avibactam			

Questions?

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