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A look at some useful antibiotics currently not available/recently approved for use in Belgium

Rakan Nasreddine, MD

Séminaire Diagnostic et Surveillance des Maladies Infectieuses

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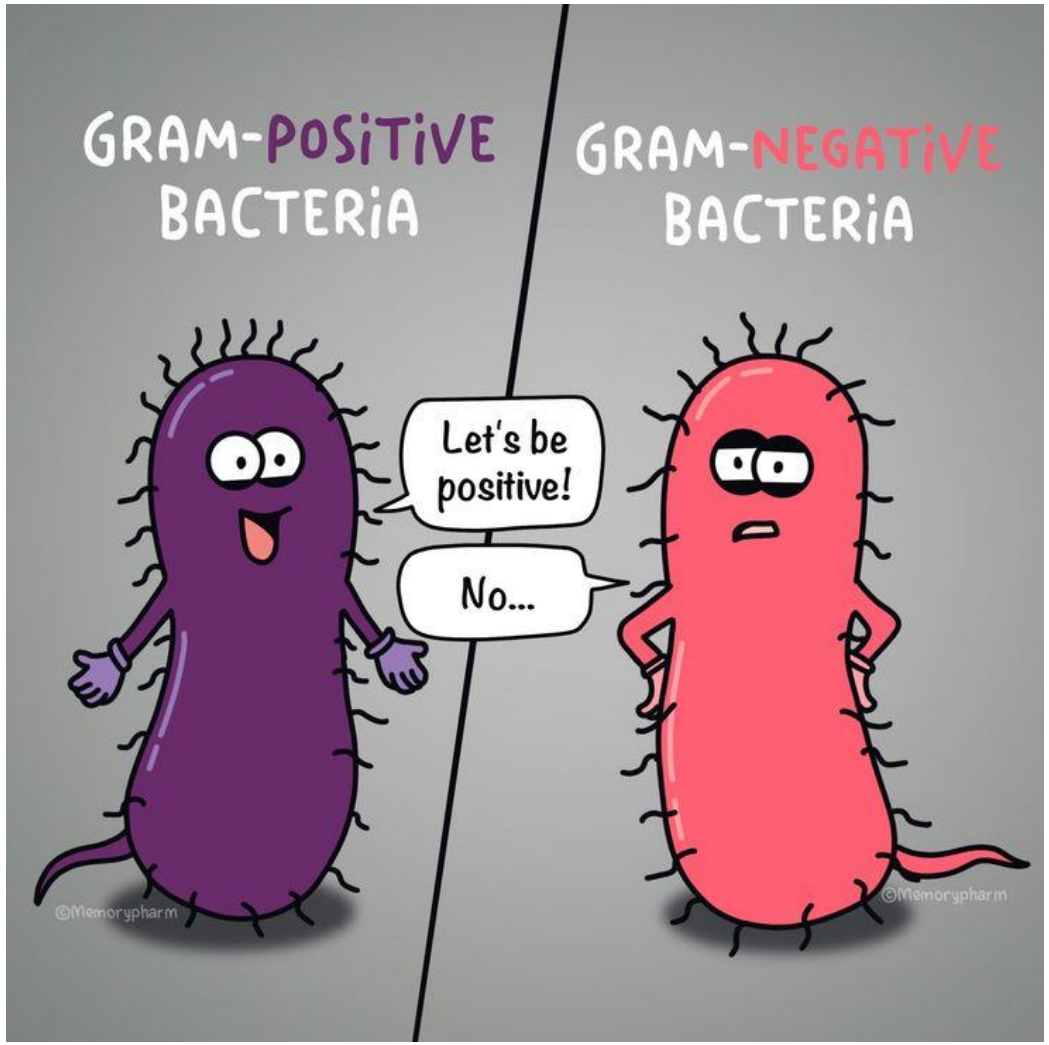
Disclosures

- No conflicts of interest to declare


GRAM-POSITIVE BACTERIA
GRAM-NEGATIVE BACTERIA
Let's be positive!
No...
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Gram-positive bacteria

Table 1. General features of nine Food and Drug Administration (FDA)- or European Medicines Agency (EMA)- approved antibiotic drugs with Gram-positive activity discussed in this paper.

	Cephalosporins	**Lipopeptides**	**Lipoglycopeptides**			**Oxazolidinones**		**Fluoroquinolones**	**Tetracyclines**
	Ceftaroline	**Daptomycin**	**Telavancin**	**Dalbavancin**	**Oritavancin**	**Linezolid**	**Tedizolid**	**Delafloxacin**	**Omadacycline**
In vitro activity	MSSA, MRSA, CoNS, streptococci, some *Enterococcus faecalis* isolates	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB*	MSSA, MRSA, CoNS, streptococci, *E. faecalis*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB*
No activity	*Enterococcus faecium*, VRE *vanA, vanB*		VRE *vanA*	VRE *vanA*				*E. faecium*, VRE *vanA, vanB*	
Drug target	Cell wall synthesis	Cell wall synthesis	Cell wall synthesis	Cell wall synthesis	Cell wall synthesis	Protein synthesis	Protein synthesis	DNA replication	Protein synthesis

Bloem et al. J Clin Med. 2021

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Daptomycin (Cubicin®)

- Lipopeptide antimicrobial with activity against gram-positive organisms

- The spectrum of activity includes:
  - *Staphylococcus* spp
  - *Enterococcus* spp
  - *Streptococcus spp*
  - *Corynebacterium* spp
  - *Leuconostoc* spp
  - *Cutibacterium acnes*

- Daptomycin is approved by the FDA and the EMA for use in:
  - Complicated skin and soft tissue infections (adult dose: 4 mg/kg IV every 24 hours)
  - *S. aureus* bacteremia associated with either complicated skin and soft tissue infections or right-sided endocarditis (adult dose: 6 mg/kg IV every 24 hours)

- There has been increasing clinical experience with off-label use of daptomycin for a wider spectrum of infection syndromes:
  - Left-sided and prosthetic valve endocarditis
  - Bone and joint infections including prosthetic material
  - Complicated urinary tract infections

- The efficacy of daptomycin seems to be dose-dependent

- 61 patients with staphylococcal prosthetic valve IE treated with daptomycin containing regimens had significant lower 30-day mortality than those without daptomycin (6.5% vs. 38%, $p < 0.001$)[1]
  - This study also reported that the group of NVIE patients receiving a standard dose of daptomycin (4–6 mg/kg/day) showed a two times higher mortality risk (odds ratio 2.2, 95% CI 1.91–4.56, p = 0.02) compared to the group receiving a higher dose of daptomycin (>8 mg/kg/day).

- One systematic review and meta-analysis on daptomycin use in VRE bacteremia showed a significantly higher 30-day mortality for daptomycin standard dose (OR 1.61; 95% CI 1.08 - 2.40, p = 0.01) compared to linezolid[2]

- The European Cubicin® Outcomes Registry and Experience (EU-CORE) study[3]
  - 638 patients with osteomyelitis
  - Clinical cure rate was 85% in patients who received a dose of 10 mg/kg/day
  - 85% for 6–8 mg/kg/day
  - 71% for 4–6 mg/kg/day

[1]Wang et al. BMJ Open. 2014
[2]Balli et al. Antimicrob Agents Chemother. 2014
[3]Malizos et al. Eur J Clin Microbiol Infect Dis. 2016

- The most important severe adverse effects of daptomycin include:
  - Muscle toxicity (myopathy/rhabdomyolysis; 2-14%)[1]
    - Administration of daptomycin with concomitant statin therapy has been variably reported to increase the risk of myopathy
  - Eosinophilic pneumonia (1-5%)[2]

- Daptomycin may be used for:
  - Targeted treatment against gram-positive infections for situations in which standard therapy is not possible due to bacterial resistance or intolerance to other antibiotic agents (vancomycin)
  - Empiric treatment of serious infection in patients known to be colonized with a resistant gram-positive organism

[1]Dare RK et al. Clin Infect Dis. 2018
[2]Soldevila-Boixader et al. Antibiotics (Basel). 2021

Gram-negative bacteria

ESBL and AmpC	KPC	OXA	MBL	Carbapenem Nonsusceptible *A. baumanii*	Carbapenem Nonsusceptible *P. aeruginosa*
				Plazomicin →	Aminoglycoside approved for cUTI
				Eravacycline →	Tetracycline approved for cIAI
				Temocillin	
				Cefiderocol	
				Ceftazidime/avibactam	
				Ceftolozane/tazobactam	
				Meropenem/vaborbactam	

Yusuf et al. J Clin Med. 2021

Meropenem/Vaborbactam (Vaborem®)

- Combination antibiotic incorporating both a broad spectrum carbapenem and a novel beta-lactamase inhibitor[1]
  - Potently inhibits class A carbapenemases (including *K. pneumoniae* carbapenemases [KPC])
  - However, it shows limited activity against class B or D carbapenemases (ie, metallo-beta-lactamases and OXA-type enzymes)
  - If the isolate demonstrates inherent resistance to meropenem, then it is unlikely that meropenem/vaborbactam will have any clinical viable activity (ex. *Stenotrophomonas maltophilia*)

- Approved for use in adult patients with[2]:
  - cIAI
  - cUTI
  - HAP
  - VAP
  - Bacteremia that occurs in association with any of these infections, and infections due to aerobic gram-negative organisms where treatment options are limited

[1]Castanheira et al. Antimicrob Agents Chemother. 2017
[2]European Medicines Agency. 2018

- TANGO II study (comparison in HAP, VAP, cUTI, cIAI, and bacteremia)[1]
  - Higher clinical cure at day 28 in comparison with the best-available therapy (65.6% vs. 33.3%; p = 0.03)
  - Decreased mortality (15.6% vs. 33.3%; p = 0.02)

- In another study, meropenem/vaborbactam inhibited 99.0% of KPC-positive isolates of Enterobacteriaceae at ≤4 mg/L and compared to CAZ-AVI and tigecycline had superior in vitro activity[2]
  - Meropenem-vaborbactam at MIC90: 1 mg/L, was four times more potent than CAZ-AVI and at least 64-fold greater than meropenem alone

[1]Wunderink et al (TANGO II). Infect Dis Ther. 2018
[2]Hackel MA et al. Antimicrob Agents Chemother. 2017

- Main adverse reactions occurring in patients treated with this antibiotic are:
  - Headache, phlebitis/infusion-site reactions, mild nausea, vomiting, and diarrhea
  - It also carries warnings for hypersensitivity reactions, clostridiodes difficile-associated diarrhea, and seizures

- Scarce published data exists on real-life experience with meropenem/vaborbactam, which is extremely important to define its real position in clinical practice
  - Among its major advantages is the potent in vitro activity against KPC-producers and the low potential for resistance development
  - It represents an important player in the treatment of CRE mediated by KPC production

Vaborem [package insert]. 2020, Melinta Therapeutics, Inc.: Lincolnshire, IL, USA.

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Ceftolozane/Tazobactam (Zerbaxa®)

- Novel cephalosporin + beta-lactamase inhibitor (as compared to ceftazidime/avibactam which is a cephalosporin + novel beta-lactamase inhibitor)

- Approved for cUTI, cIAI, HAP, and VAP

- Potent activity against ESBL Enterobacterales and *P. aeruginosa*
  - A demonstrated in vitro susceptibility against *Burkholderia spp.* and *Stenotrophomonas maltophilia* isolates
  - Does not have reliable activity against carbapenemases and MDR *Acinetobacter spp.*
  - Very limited gram-positive activity

Karaiskos et al. Front Public Health. 2019

- ASPECT cIAI trial[1]:
  - Ceftolozane/tazobactam (plus metronidazole) was noninferior to meropenem in adult patients with cIAI (clinical cure rate 83% vs. 87%)
  - In patients with ESBL-producing Enterobacterales, clinical cure rates were 96% and 89% in the ceftolozane/tazobactam plus metronidazole vs. meropenem groups
  - The frequency of adverse events was similar in both treatment groups (44.0% vs 42.7%)

- ASPECT cUTI trial[2]:
  - Ceftolozane/tazobactam was non-inferior to high-dose levofloxacin for composite cure of cUTI: 306/398 (77%) vs 275/402 (68%) [treatment difference 95% CI 2·3–14·6]
  - Adverse event profiles were similar in the two treatment groups

- ASPECT NP trial[3]:
  - 24% of patients in the ceftolozane/tazobactam group vs. 25.3% in the meropenem group died
  - 54% patients in the ceftolozane/tazobactam group vs. 53% in the meropenem group were clinically cured

[1]Solomkin et al. Clin Infect Dis. 2015
[2]Wagenlehner et al. Lancet. 2015
[3]Kollef et al. Lancet Infect Dis. 2019

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Organism/antimicrobial agent/geographic region	%S by year (no. of isolates)							
	2012	2013	2014	2015	2016	2017	2018	%S
P. aeruginosa								
Western Europe	(765)	(870)	(1042)	(615)	(637)	(597)	(558)	(5084)
ceftolozane/tazobactam	92.8	93.3	92.9	95.8	95.1	94.5	96.2	94.1
piperacillin/tazobactam	71.9	73.2	77.2	79.5	77.7	79.6	80.3	76.7
ceftazidime	74.8	78.3	77.8	81.8	83.3	82.9	82.3	79.7
meropenem	77.3	74.4	81.2	81.1	77.9	79.9	82.8	79.0
levofloxacin	65.6	63.0	67.6	68.1	68.6	70.7	71.0	67.4
tobramycin	85.9	86.9	88.8	88.3	88.9	91.0	92.5	88.6
colistin	98.4	99.5	99.1	100.0	99.8	99.5	99.6	99.4
Enterobacterales								
Western Europe	(3664)	(3862)	(4746)	(2859)	(2936)	(3139)	(3060)	(24 266)
ceftolozane/tazobactam	94.3	93.2	95.1	95.1	94.8	94.4	94.4	94.5
piperacillin/tazobactam	85.7	84.2	86.4	85.7	85.3	84.1	84.6	85.2
ceftazidime	81.9	81.4	83.8	80.5	79.4	79.3	79.9	81.1
meropenem	98.5	98.0	98.7	98.4	97.9	97.9	98.3	98.3
levofloxacin	75.8	75.2	79.2	76.2	75.5	76.6	78.7	76.9
amikacin	95.9	96.8	98.1	97.3	97.3	96.6	97.5	97.1
colistin	80.0	79.8	81.3	79.5	83.1	84.1	84.9	81.7

Sader et al. J Antimicrob Chemother. 2020

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	P. aeruginosa			Enterobacterales			
		%S (EUCAST)			%S (EUCAST)		
Region/country	No.	C/T	MEM	No.	C/T	CAZ	MEM
Western Europe	5084	94.1	79.0	24 266	94.5	81.1	98.3
Austria	49	95.9	79.6	159	96.2	93.7	100.0
Belgium	147	82.3	53.4	879	93.3	74.4	99.5
Denmark	51	100.0	100.0	163	95.1	93.9	100.0
Finland	50	100.0	100.0	160	98.1	96.9	100.0
France	883	97.6	83.7	3574	95.7	82.5	99.8
Germany	838	95.7	77.7	4816	95.0	83.0	99.5
Ireland	288	99.3	86.1	2166	95.3	74.7	99.9
Italy	881	92.7	76.9	3881	86.0	67.1	91.1
Netherlands	49	91.8	57.1	159	97.5	88.7	100.0
Norway	50	98.0	94.0	152	95.4	89.5	100.0
Portugal	320	70.6	56.9	978	96.0	78.4	99.3
Spain	944	95.6	81.7	3264	96.4	87.6	99.5
Sweden	171	97.7	84.8	1522	98.6	93.6	99.9
Switzerland	44	97.7	95.5	156	98.1	90.4	99.4
UK	319	99.7	84.3	2237	98.3	86.7	99.7

Sader et al. J Antimicrob Chemother. 2020

- The side effect profile of ceftolozane/tazobactam does not differ greatly from other beta-lactam antibiotics and has generally been associated with relatively mild nausea, vomiting, and diarrhea
  - The drug also carries warnings for hypersensitivity reactions and *Clostridioides difficile*-associated diarrhea

- The main place in therapy of cetolozane/tazobactam would be the empirical or definitive treatment of infections where *Pseuodomonas aeruginosa* and/or ESBLs are suspected

Matlock et al. Intern Emerg Med. 2021

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Ertapenem (Invanz®)

	Meropenem	Ertapenem
Mechanism of action	Inhibits bacterial cell wall synthesis	
Spectrum of activity		Not active against Pseudomonas, Acinetobacter, and Enterococcus
Limitations of use		CNS infections, neutropenic fever, and septic shock
Adverse effects	Similar	
Administration	IV: 3x/day Adjust dose when CrCl <50	IV, IM: 1x/day Adjust dose when CrCl <30

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Thank You
For Your Attention