Εξελίξεις στην αντι-μικροβιακή αντοχή

Gram-θετικοί κόκκοι

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Gram-θετικά παθογόνα με τις σημαντικότερες θεραπευτικές προκλήσεις σήμερα

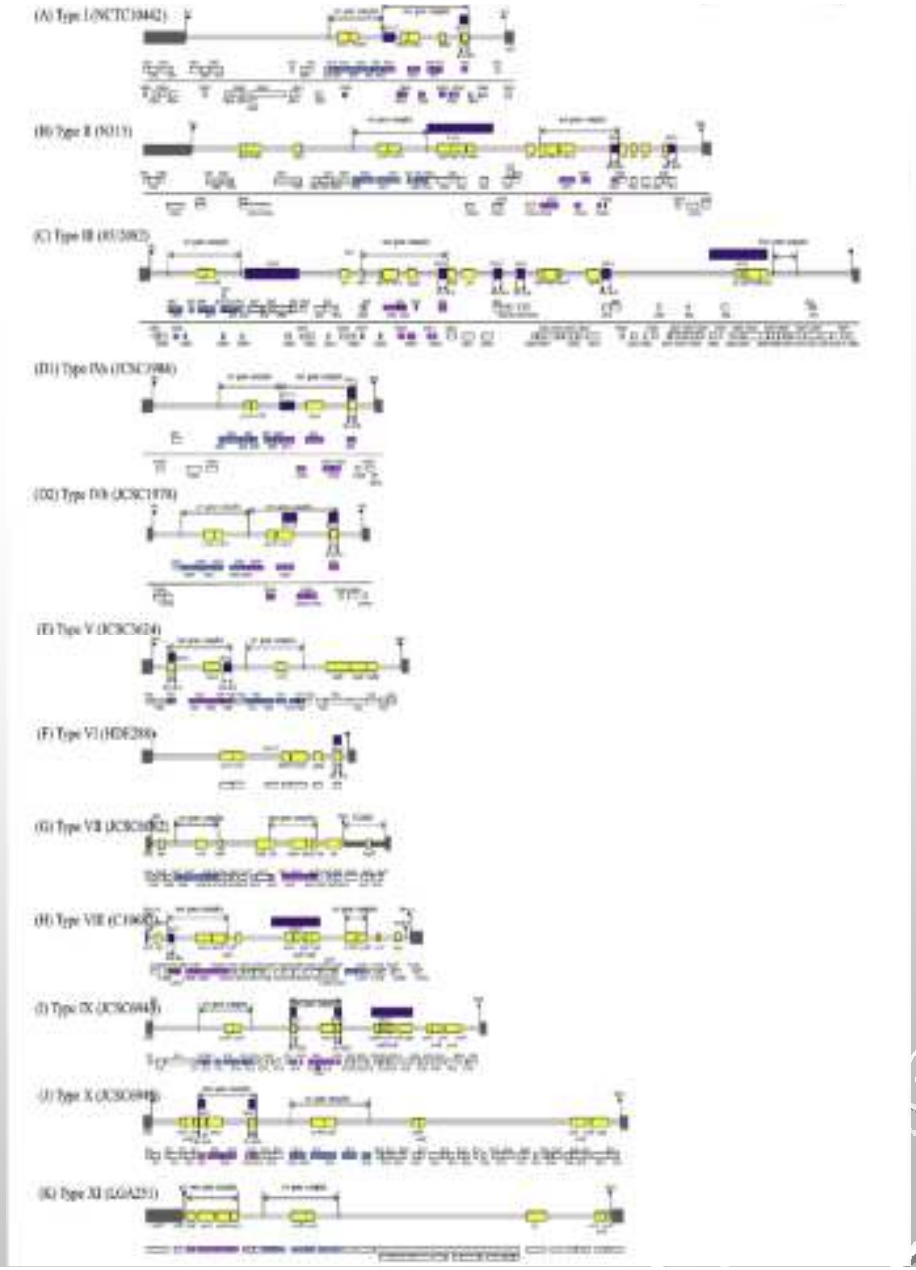
	CDC	PHAC*
• *Staphylococcus aureus*	serious threat	high priority
• *Enterococcus faecium*	serious threat	medium-high priority
• *Streptococcus pneumoniae*	serious threat	medium-low priority

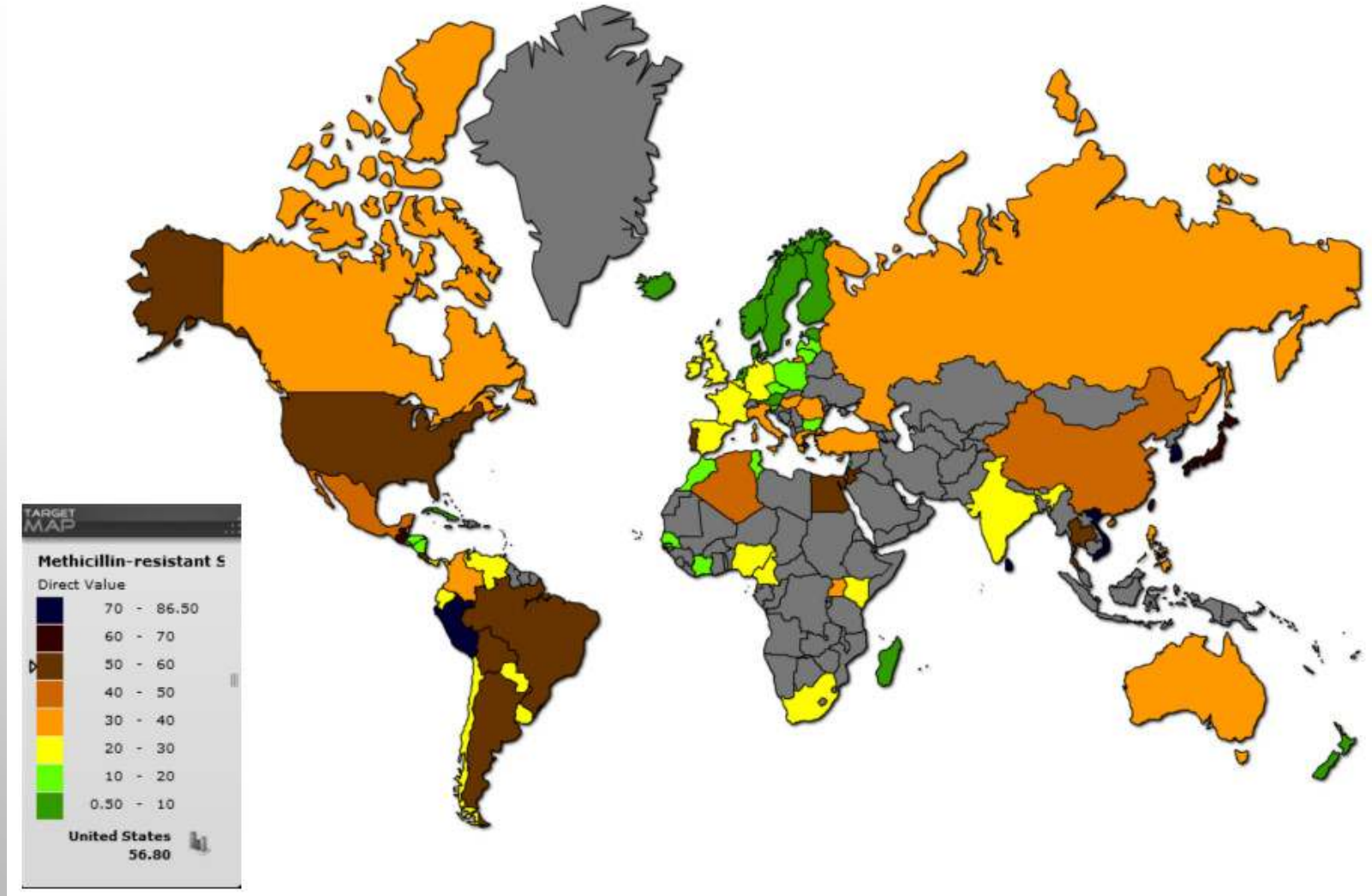
*PHAC: Public Health Agency of Canada

Σταθμοί στην αντοχή των Gram-θετικών κόκκων

- 1946: στελέχη *Staphylococcus aureus* με αντοχή σε φυσική πενικιλλίνη (παραγωγή πενικιλλινάσης)
- 1961: πρώτο στέλεχος *Staphylococcus aureus* με αντοχή στα β-λακταμικά (MRSA) σε νοσοκομείο σε UK (*mecA,* SCC*mec*)
- 1961-1967: σποραδικές επιδημίες από HA-MRSA, 1968-1995 ενδημικό νοσοκομειακό παθογόνο
- 1967: απομόνωση στελέχους πνευμονιοκόκκου οροτύπου 4 με $MIC_{penicillin}$: 0.5 μg/ml από φάρυγγα τρίχρονου αγοριού στη Ν. Γουινέα; 1977: επιδημία στη Ν. Αφρική με στέλεχος με MIC 2-8 μg/ml
- 1980: ευρεία χρήση βανκομυκίνης και ανάδυση VISA/ GISA
- 1981: πρώτη εμφάνιση CA-MRSA, 1982 επιδημία σε χρήστες στο Detroit, Michigan, 1980-1990 επιδημίες
- 1988: πρώτη απομόνωση VRE στη Γαλλία, 1989 εμφάνιση VRE σε UK
- 1990-: ευρεία διασπορά CA-MRSA
- 2005 : πρώτη απομόνωση LA-MRSA σε άνθρωπο/ ανάλογα στελέχη από μαστίτιδα αγελάδων αναφέρονται από το 1975 (*mecC,* SCC*mec* XI)

SCC*mec* types




TARGET MAP
Methicillin-resistant S
Direct Value
70 - 86.50
60 - 70
50 - 60
40 - 50
30 - 40
20 - 30
10 - 20
0.50 - 10
United States
56.80

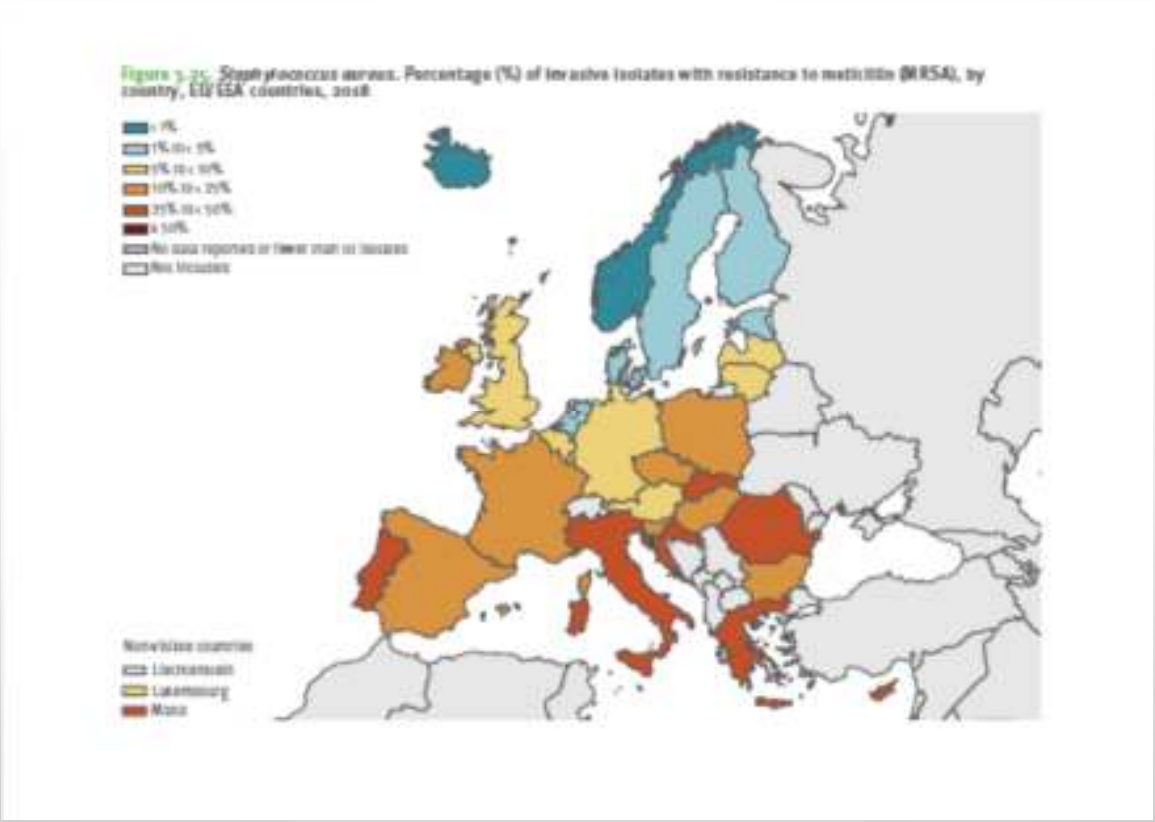
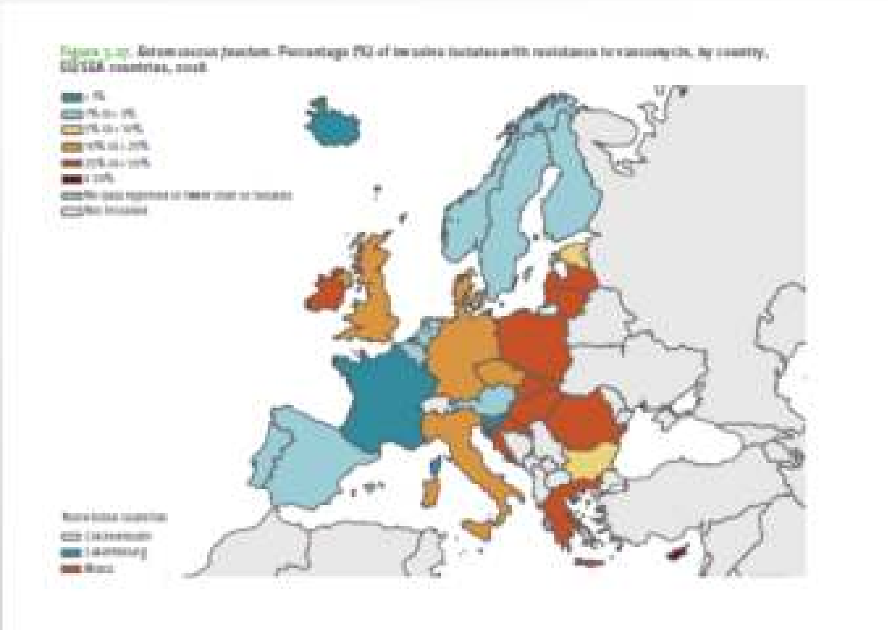


Figure 3.25. Staphylococcus aureus. Percentage (%) of invasive isolates with resistance to meticillin (MRSA), by country, EU/EEA countries, 2018
< 1%
1% to < 5%
5% to < 10%
10% to < 25%
25% to < 50%
≥ 50%
No data reported or fewer than 10 isolates
Non-EU/EEA countries
Liechtenstein
Luxembourg
Malta

Enterococcus faecium και αντοχή σε γλυκοπεπτίδια EARS-net 2018



Επιδημιολογία των VRE στην Ελλάδα

- Κυρίως είναι στελέχη *Enterococcus faecium*
- Κυριότερο γονίδιο *vanA*
- Πολυκεντρική μελέτη του 2007 από διάφορα ελληνικά νοσοκομεία έδειξε επικράτηση του CC17 (ST16, ST16, ST203, ST412)
- Σημαντική η επιδημιολογική επιτήρηση (εμφανίζονται νέα στελέχη, αλλαγή από *vanA* σε *vanB*)*

- Vancomycin-resistant *Enterococcus faecium* sequence type 796 - rapid international dissemination of a new epidemic clone. Antimicrob Resist Infect Control 2018 22;7:44.

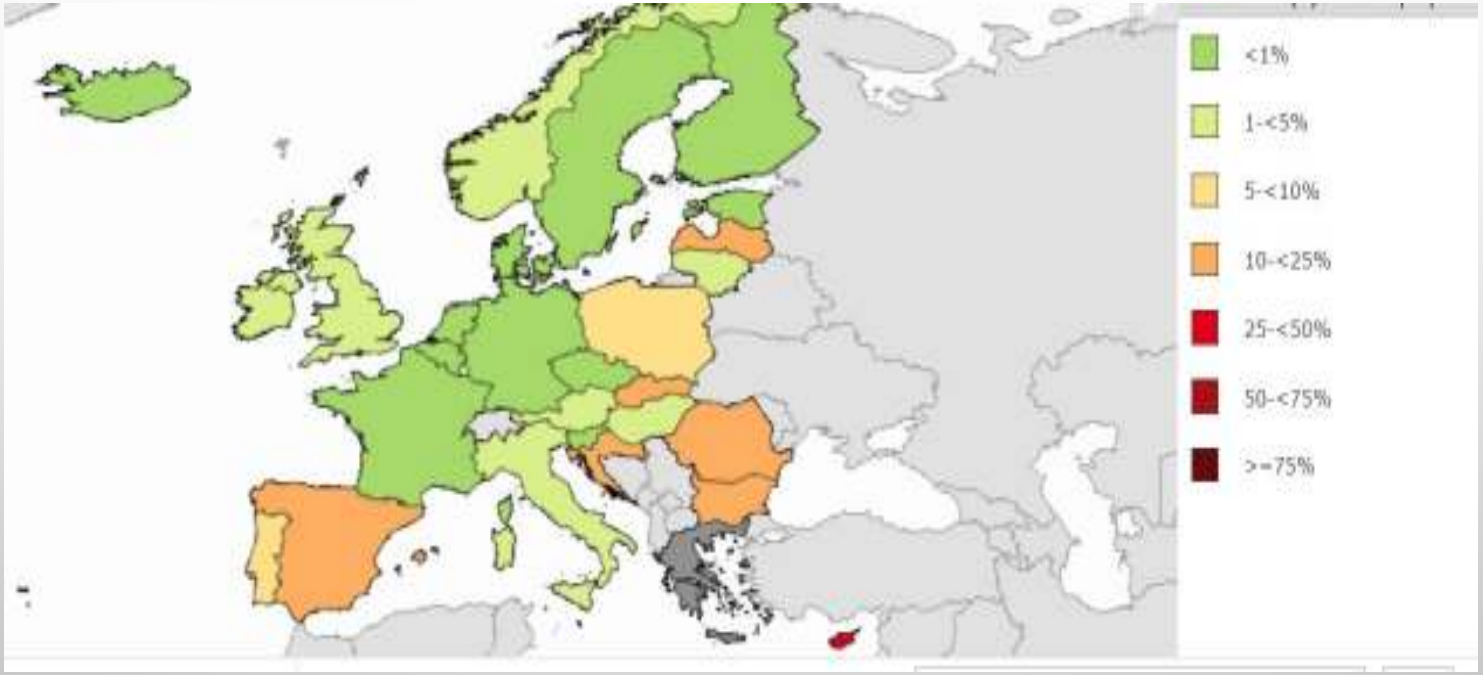
Αυστραλία/ Νέα Ζηλανδία

Πνευμονιόκοκκοι και β-λακτάμες

- πρώτη εμφάνιση το 1969, ορότυπος 4 από φορεία στο φάρυγγα ενός τρίχρονου αγοριού στη Ν. Γουινέα ($MIC_{penicillin}$: 0.5 mg/L, Susceptible: E, Chl, Te)
- 1977 επιδημία στη Ν. Αφρική από στέλεχος με $MIC_{penicillin}$: 2-8 mg/L, Resistant : Chl, E, Te)
- διασπορά σε όλο τον κόσμο MDR πνευμονιόκοκκοι
- σημαντική η συμβολή των πολυ-σακχαριδικών εμβολίων στον περιορισμό της αντι-μικροβιακής αντοχής μέσω περιορισμού του αποικισμού

  (PCV7: 6B, 9V, 14, 19F, 23F ενώ το PCV13 : 6B, 9V, 14, 19F, 23F και 19A)

Streptococcus pneumoniae
Αντοχή σε πενικιλλίνη (EARS-NET 2017)



Συμμετοχή: 9 Ευρωπαικές χώρες,
Περίοδος: από 11/2010 έως 8-2011
Ρινικά επιχρίσματα υγιών ατόμων (4-90 ετών)

Table 6 Distribution of antimicrobial resistance by serotype. Only serotypes represented by more than 10 isolates are reported. Correlation between frequency of serotypes in study population and in MDR fraction is given in the last column

serotypes	N (%)	Ceftaldine (%)	Clarithromycin (%)	Clindamycin (%)	Penicillin (%)	Tetracyclin (%)	Trimethoprim/ sulfamethoxazole (%)	MDR fraction N (%)	p value
11A	60 (6.4)	8.3	6.7	5.3	5.0	0.0	10.0	5 (8.3)	0.090
23A	58 (6.2)	0.0	10.0	1.90	1.7	15	24.1	2 (3.4)	0.007*
19A	52 (5.5)	67.3	53.8	5.0	67.3	**55.8**	**30.8**	32 (61.5)	< 0.001*
9	50 (5.3)	0.0	0.0	0.0	0.0	0.0	2.0	0 (0.0)	0.001*
6C/D	44 (4.7)	6.8	20.5	2.73	27.3	25.0	0.0	11 (25.0)	0.001*
23B	39 (4.2)	12.8	0.0	0.0	30.8	0.0	38.5	11 (28.2)	0.003
19F	37 (3.9)	32.4	16.8	48.6	37.8	54.1	18.9	14 (37.8)	0.001*
23F	37 (3.9)	13.5	16.2	10.8	16.2	10.8	16.2	6 (16.2)	0.934
15B/C	35 (3.7)	2.9	8.6	0.0	22.9	11.4	31.4	3 (8.6)	0.255
35B	34 (3.6)	38.2	8.8	5.9	38.2	2.9	5.9	3 (8.8)	0.283
35F	33 (3.5)	6.1	3.0	3.0	0.0	0.0	0.0	1 (3.0)	0.050
23F	32 (3.4)	0.0	0.0	0.0	0.0	0.0	0.0	0 (0.0)	0.017*
6A	28 (3.0)	35.3	35.3	10.7	39.3	10.7	25.0	10 (35.7)	0.019*
10A	28 (3.0)	7.1	10.7	7.1	7.1	10.7	10.7	2 (7.1)	0.243
6B	25 (2.7)	24.0	32.0	28.0	20.0	28.0	24.0	8 (32.0)	0.081
15A	24 (2.6)	58.3	**62.5**	**62.5**	62.5	50	8.3	15 (62.5)	< 0.001*
13	23 (2.5)	8.7	4.3	4.3	8.7	4.3	0.0	1 (4.3)	0.173
24F	21 (2.2)	28.6	28.6	28.6	28.6	28.6	19.0	6 (28.6)	0.260
18C	20 (2.1)	0.0	0.0	0.0	0.0	0.0	10.0	0 (0.0)	0.070
14F	19 (2.0)	0.0	15.8	15.8	0.0	15.8	42.1	1 (5.3)	0.283
37	17 (1.8)	0.0	0.0	0.0	0.0	0.0	5.9	0 (0.0)	0.117
7F	17 (1.8)	0.0	0.0	0.0	0.0	0.0	0.0	0 (0.0)	0.117
5 N	17 (1.8)	0.0	0.0	0.0	0.0	0.0	0.0	0 (0.0)	0.117
14	16 (1.7)	**81.3**	31.3	25.0	**81.3**	18.8	43.8	8 (50.0)	0.001*
33F	15 (1.6)	0.0	33.3	33.3	0.0	26.7	6.7	1 (6.7)	0.462
21	13 (1.4)	0.0	0.0	0.0	7.7	0.0	0.0	0 (0.0)	0.201
31	13 (1.4)	0.0	0.0	0.0	0.0	0.0	0.0	0 (0.0)	0.201
34	13 (1.4)	61.5	0.0	0.0	30.8	0.0	23.1	0 (0.0)	0.201

*p < 0.05 is significant; MDR = Multidrug resistance; in bold serotypes presenting the most MDR isolates; underlined: highly resistance

Int J Antimicrob Agents 2007 Jul;30(1):87-92.

Nationwide surveillance of Streptococcus pneumoniae in Greece: patterns of resistance and serotype epidemiology.

This nationwide study assessed the antimicrobial susceptibility and seroprevalence of Streptococcus pneumoniae **in paediatric carriage** isolates and in **clinical isolates from adult pneumococcal disease** in Greece during the years **2004-2006.**

Among 780 isolates recovered from the nasopharynx of children <6 years old attending day-care centres, non-susceptibility rates to penicillin was 34.7%, 25.1% cefuroxime, 1.0% ceftriaxone, 33.5% erythromycin, 26.4% tetracycline and 44.2% trimethoprim/sulfamethoxazole

Among 89 adult clinical isolates, the respective rates were 48.3% to penicillin , 46.1% to cefuroxime, 5.6% to ceftriaxone, 48.3% to erythromycin, 32.6% to tetracycline and 40.4% to trimethoprim/sulfamethoxazole .

The emerging problem of linezolid-resistant enterococci

Bi R et al. J Glob Antimicrob Resist 2018

- First report of a linezolid-resistant vancomycin-resistant *Enterococcus faecium* strain in Greece. Bersos Z, Maniati M, Kontos F, Petinaki E, Maniatis AN. J Antimicrob Chemother. 2004 ;53(4):685-6

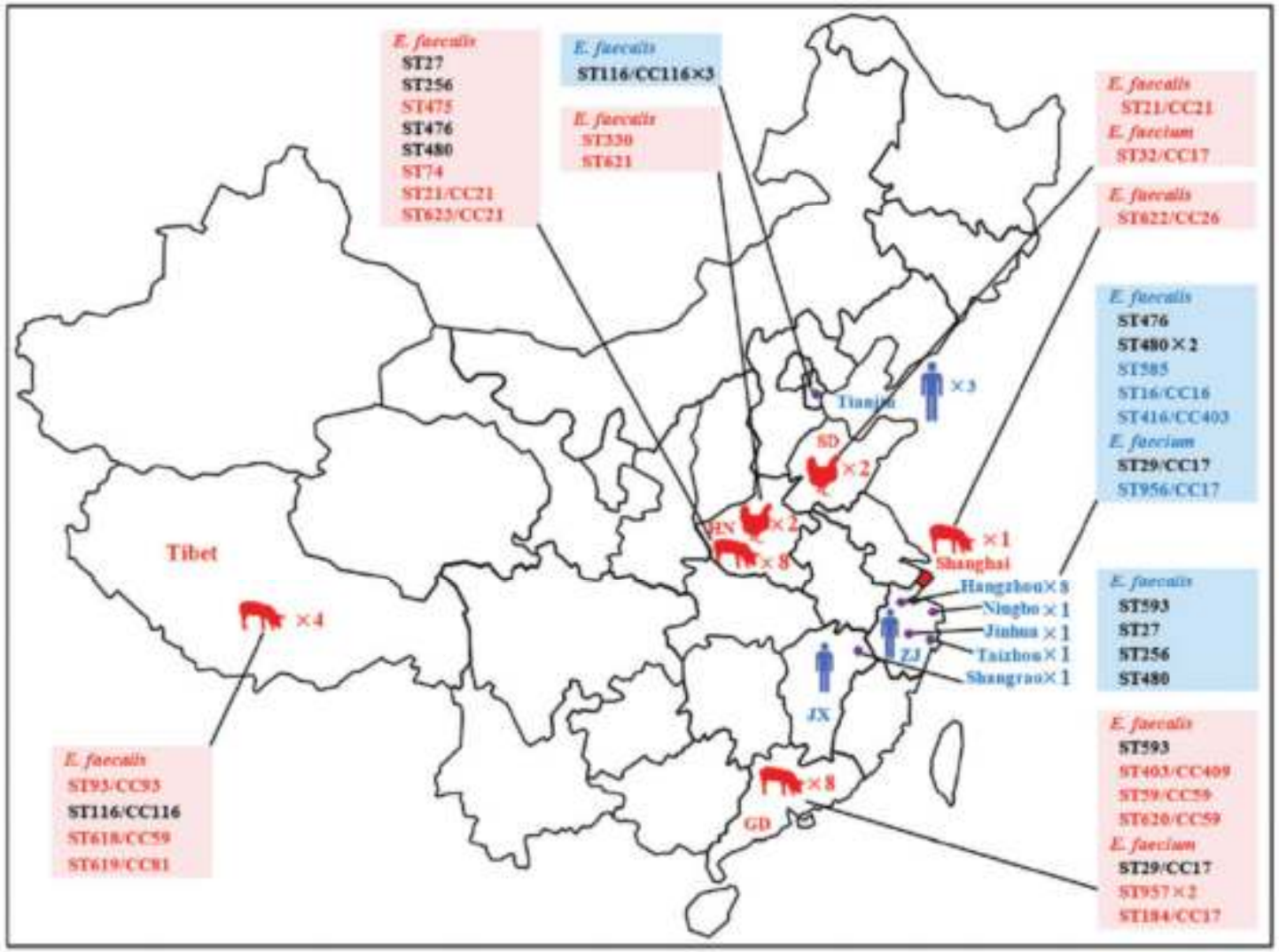
- Linezolid-resistant enterococci in Greece: epidemiological characteristics. Spiliopoulou I, Damani A, Chini V, Zerva L, Kolonitsiou F, Anastassiou ED, Petinaki E. Chemotherapy. 2011;57(3):181-5.

Μετάλλαξη G2576T 23SrRNA, CC17

- Detection in Greece of a clinical *Enterococcus faecium* carrying the novel oxazolidinone resistance *poxtA*. Papagiannitsis CC, Tsilipounidaki K, Malli E, Petinaki E. J Antimicrob Chemother. 2019 ; 74(8):2461-2462

  ST117, CC17

- First detection of an *optrA*- positive linezolid-resistant ST16 *Enterococcus faecalis* from human in Greece. Tsilipounidaki K, Gerontopoulos A, Papagiannitsis C, Petinaki E. New Microbes New Infect. 2019;29:10051


E. faecalis
ST27
ST256
ST475
ST476
ST480
ST74
ST21/CC21
ST623/CC21
E. faecalis
ST116/CC116×3
E. faecalis
ST330
ST621
E. faecalis
ST21/CC21
E. faecium
ST32/CC17
E. faecalis
ST622/CC26
E. faecalis
ST476
ST480×2
ST585
ST16/CC16
ST416/CC403
E. faecium
ST29/CC17
ST956/CC17
Tianjin
×3
SD
×2
HN
×2
×8
Tibet
×4
Shanghai
×1
Hangzhou×8
Ningbo×1
Jinhua×1
Taizhou×1
Shangrao×1
ZJ
JX
GD
×8
E. faecalis
ST593
ST27
ST256
ST480
E. faecalis
ST593
ST403/CC409
ST59/CC59
ST620/CC59
E. faecium
ST29/CC17
ST957×2
ST184/CC17
E. faecalis
ST93/CC93
ST116/CC116
ST618/CC59
ST619/CC81

Dissemination of two international linezolid-resistant *Staphylococcus epidermidis* clones in Greek hospitals

A. Liakopoulos[1], I. Spiliopoulou[2], A. Damani[1], M. Kanellopoulou[1], S. Schoina[2], E. Papafragas[3], M. Marangos[4], F. Fligou[5], E. Zakynthinos[6], D. Makris[6], E. Protonotariou[7], F. Tsiapara[7], K. Filos[5], E. Diza[7], E. D. Anastassiou[2] and E. Petinaki[1]*

Table 1. MICs of linezolid in correlation with molecular characteristics of linezolid-resistant *S. epidermidis*

			Mutation and location of mutation			
Hospital[a]	No. of isolates	MIC of linezolid (mg/L)	C2534T	G2576T	T2504A	ST
A	2	8–10	*rlD*, *rlF*	—	—	ST22
A	3	16–24	*rlD*, *rlF*	*rlA*, *rlD*, *rlE*, *rlF*	—	ST2
A	2	1024	*rlD*, *rlF*	—	*rlA*, *rlD*, *rlE*, *rlF*	ST22
B	10	1024	*rlD*, *rlF*	—	*rlA*, *rlD*, *rlE*, *rlF*	ST22
C	4	16–24	*rlD*, *rlF*	*rlA*, *rlD*, *rlE*, *rlF*	—	ST2
C	1	8	*rlD*, *rlF*	—	—	ST22
D	4	64	*rlD*, *rlF*	*rlA*, *rlB*, *rlD*, *rlE*, *rlF*	—	ST2

[a]A, Sismanoglion General Hospital of Athens; B, University Hospital of Patras; C, University Hospital of Larissa; D, University Hospital AHEPA.

J Antimicrob Chemother 2010; **65**: 1070–1077

- In vitro activity of daptomycin against Gram-positive cocci: the first multicenter study in Greece

  Int J Antimicrob Agents. 2008 ;32(6):525-8

Activity of vancomycin, linezolid and daptomycin against staphylococci and enterococci isolated in Greek hospitals during a 5-year period (2008-2012)

Diagn Microbiol Infect Dis. 2015 ;83(4):386-8 (see Table)

Glycopeptide and daptomycin susceptibility and vancomycin heteroresistance of methicillin-resistant Staphylococcus aureus (MRSA) clinical isolates from a Greek university hospital

Int J Antimicrob Agents. 2011; 38(5):451-2

hVISA $MIC_{DAPTO} 1.5\ mg/L$

CLSI, EUCAST : <=1mg/L staphylococci

CLSI, IE : <=4mg/L enterococcii

e 1

ution of MIC_{50} and MIC_{90} among studied isolates.

	Number	Vancomycin		Linezolid		Daptomycin		Number	Vancomycin		Linezolid		Daptomycin	
		MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}		MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
		MSSA							MRSA					
08	354	1	2	1.5	1.5	0.25	0.5	338	2	2	1.5	2	0.25	1
09	331	1	2	1.5	1.5	0.25	0.5	340	1	2	1.5	1.5	0.25	0.75
10	396	1	1.5	1.5	1.5	0.25	0.5	710	1.5	2	1.5	2	0.5	1
11	283	1	1.5	1.5	1.5	0.25	0.38	369	1	2	1	1.5	0.5	1
12	320	0.5	1	1.5	1.5	0.25	0.38	310	1	2	1.5	1.5	0.25	0.75
tal	1684	1	2	1.5	1.5	0.25	0.38	2067	1	2	1.5	1.5	0.25	1
		MS-CNS							MR-CNS					
08	18	1	2	0.5	1	0.25	0.5	98	2	3	1	2	0.25	1
09	34	1.5	2	0.5	1	0.25	0.5	173	2	2	1	2	0.5	0.75
10	34	1.5	2	0.5	1	0.25	0.5	117	2	4	1	2	0.5	0.75
11	62	1.5	2	1	1	0.25	0.5	306	1	3	1	4	0.5	0.75
12	25	1	2	1	2	0.25	0.5	109	1.5	2	1	4	0.5	0.75
tal	238	1.5	2	1	2	0.25	0.5	802	2	3	1	2	0.38	0.5
		VSE							VRE					
08	300	2	2	2	2	1	2	50	256	256	1	2	1	2
09	311	1	2	2	2	0.5	1	39	256	256	1	2	1.5	2
10	361	1	2	2	2	0.75	1.5	84	256	256	1.5	3	1.5	2
11	582	1	2	2	2	0.5	1.5	95	256	256	1.5	2	1.5	3
12	264	1	2	2	2	1	2	43	256	256	2	2	1.5	4
tal	1818	1	2	2	2	0.5	2	311	256	256	1.5	2	1.5	2

Table 1. Summary of novel antibiotics against Gram-positive bacteria approved by FDA and/or EMA during the last decade.

Drug	Approval Time	Antibiotic Class	Company	Spectrum Against Organisms	Indication	Dose [1]	Comments/Warnings [2]
Ceftaroline (Teflaro/Zinforo)	FDA: October 2010 EMA: August 2012	Cephalosporin	Allergan Pharmaceutical Industries Ltd. (US/Canada); Takeda Pharmaceutical Company Ltd. (Japan); Pfizer (globally except US/Canada/Japan)	ABSSSI: MRSA, MSSA, *S. pyogenes*, *S. agalactiae* CABP: MSSA, *S. pneumoniae*, *H. influenzae*	FDA: CABP and ABSSSI EMA: CABP and cSSSI	[3] IV: 600 mg over 5 to 60 min every 12 h [13]	• Serious anaphylactic reactions have been reported with beta-lactam antibiotics • Direct Coombs' test seroconversion has been reported; if anaemia develops during or after therapy, consider drug-induced haemolytic anaemia and ceftaroline
Ceftobiprole (Zevtera/Mabelio)	EMA: October 2013	Cephalosporin	Basilea Pharmaceutica Ltd.	MRSA, ampicillin-susceptible enterococci and penicillin-resistant pneumococci	EMA: HAP (excluding VAP) and CABP	IV: 500 mg over 2 h every 8 h [14]	• Serious anaphylactic reactions have been reported in patients receiving beta-lactam antibiotics
Telavancin (Vibativ)	FDA: September 2009	Lipoglycopeptide	Theravance Biopharma Antibiotics, Inc.,	MRSA, vancomycin-intermediate *S. aureus* and penicillin-resistant *S. pneumoniae*	FDA: cSSSI, HAP (including VAP)	IV: 10 mg/kg over 60 min every 24 h for 7–14 days (cSSSI) and 7–21 days (HAP/VAP) [15]	• Decreased efficacy with moderate/severe pre-existing renal impairment • Interferes with some coagulation tests e.g., prothrombin time, international normalised ratio • QTc prolongation • Serious and potentially fatal hypersensitivity reactions • Infusion-related reactions
Dalbavancin (Dalvance/ Xydalba)	FDA: May 2014	Lipoglycopeptide	Durata Therapeutics (acquired by Actavis in 2014)	MRSA, *S. pyogenes*, *S. agalactiae* and *E. faecalis* strains susceptible to vancomycin	FDA: ABSSSI	IV: 1000 mg over 30 min followed one week later by 500 mg over 30 min [16]	• Serious anaphylactic and skin reactions have been reported with glycopeptides • Rapid IV glycopeptide infusion can cause upper body flushing, urticaria, pruritis and/or rash • ALT elevations have been reported
Oritavancin (Orbactiv)	FDA: August 2014 EMA: March 2015	Glycopeptide	Melinta Therapeutics Inc.	MSSA, MRSA, VRE and vancomycin-intermediate and vancomycin-resistant staphylococci	FDA: ABSSSI EMA: ABSSSI	IV: 1200 mg single dose over 3 h [17]	• Co-administration with warfarin may increase warfarin exposure and increase bleeding risk • Oritavancin administration may artificially prolong aPTT for up to 48 h and prolong PT/INR for up to 24 h • Hypersensitivity and infusion related reactions including pruritus, urticaria and flushing have been reported • [4] A higher incidence of osteomyelitis reported in the oritavancin treated ABSSSI arm than vancomycin-treated arm

Cephalosporins[1]	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
	S ≤	R >	ATU		S ≥	R <	ATU	
Cefaclor[2]	Note[1]	Note[1]			Note[A]	Note[A]		1/A. Susceptibility of staphylococci to cephalosporins is inferred from the cefoxitin susceptibility except for ceftolme, ceftazidime, ceftazidime-avibactam, ceftibuten and ceftolozane-tazobactam, which do not have breakpoints and should not be used for staphylococcal infections. For agents given orally, care to achieve sufficient exposure at the site of the infection should be exercised. If cefotaxime and ceftriaxone are reported for methicillin-susceptible staphylococci, these should be reported "Susceptible, increased exposure" (I). Some methicillin-resistant *S. aureus* are susceptible to ceftaroline and ceftobiprole, **see Notes 6/D and 7/F.** 2. See table of dosages. 3. *S. aureus* and *S. lugdunensis* with cefoxitin MIC values =4 mg/L and *S. saprophyticus* with cefoxitin MIC values =8 mg/L are methicillin resistant, mostly due to the presence of the *mecA* or *mecC* gene. Disk diffusion reliably predicts methicillin resistance. 4. For staphylococci other than *S. aureus*, *S. lugdunensis* and *S. saprophyticus*, the cefoxitin MIC is a poorer predictor of methicillin resistance than the disk diffusion test. 5/D. Methicillin-susceptible isolates can be reported susceptible to ceftaroline without further testing. 6/E. Resistant isolates are rare. 7/F. Methicillin-susceptible isolates can be reported susceptible to ceftobiprole without further testing. 8. If coagulase-negative staphylococci are not identified to species level, use zone diameter breakpoints S≥25, R<25 mm. C. Cefoxitin screen for methicillin resistance in *S. pseudintermedius* and *S. schleiferi* is less predictive of the presence of *mecA* than in other staphylococci. Use the oxacillin 1 µg disk with zone diameter breakpoints S≥20, R<20 mm to screen for methicillin resistance.
Cefadroxil	Note[1]	Note[1]			Note[A]	Note[A]		
Cefalexin	Note[1]	Note[1]			Note[A]	Note[A]		
Cefazolin	Note[1]	Note[1]			Note[A]	Note[A]		
Cefepime	Note[1]	Note[1]			Note[A]	Note[A]		
Cefixime	-	-			-	-		
Cefotaxime[2]	Note[1]	Note[1]			Note[A]	Note[A]		
Cefoxitin (screen only), *S. aureus* and coagulase-negative staphylococci other than *S. epidermidis*	Note[3,4]	Note[3,4]		30	22[A,3]	22[A,3]		
Cefoxitin (screen only), *S. epidermidis*	Note[4]	Note[4]		30	25[A,3]	25[A,3]	25-27	
Cefoxitin (screen only), *S. pseudintermedius* and *S. schleiferi*	NA	NA			Note[C]	Note[C]		
Cefpodoxime	Note[1]	Note[1]			Note[A]	Note[A]		
Ceftaroline, *S. aureus* (indications other than pneumonia)	1[5]	2[A,5]	1	5	22[5]	17[A,5]	18-20	
Ceftaroline, *S. aureus* (pneumonia)	1[5]	1[5]	1	5	22[5]	22[5]	18-20	
Ceftazidime	-	-			-	-		
Ceftazidime-avibactam	-	-			-	-		
Ceftibuten	-	-			-	-		
Ceftobiprole, *S. aureus*	2[7]	2[7]	2	5	17[7]	17[7]	16-17	
Ceftolozane-tazobactam	-	-			-	-		
Ceftriaxone[2]	Note[1]	Note[1]			Note[A]	Note[A]		
Cefuroxime iv	Note[1]	Note[1]			Note[A]	Note[A]		
Cefuroxime oral	Note[1]	Note[1]			Note[A]	Note[A]		

Carbapenems[1]	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
	S ≤	R >	ATU		S ≥	R <	ATU	
Ertapenem	Note[1]	Note[1]			Note[A]	Note[A]		1/A. Susceptibility of staphylococci to carbapenems is inferred from the cefoxitin susceptibility.
Imipenem	Note[1]	Note[1]			Note[A]	Note[A]		
Imipenem-relebactam	Note[1]	Note[1]			Note[A]	Note[A]		
Meropenem	Note[1]	Note[1]			Note[A]	Note[A]		
Meropenem-vaborbactam	Note[1]	Note[1]			Note[A]	Note[A]		

In Vitro Activity Of Ceftaroline And Comparators Against *Staphylococcus aureus* Isolates: Results From 6 Years Of The ATLAS Program (2012 to 2017)

Infect Drug Resist 2019;12:3349-3358

A total of 226 centers from five geographical regions (Europe, Asia-Pacific, South America, Africa-West Asia, and the United States) participated in the ATLAS program.

Table 1 In Vitro Activity Of Ceftaroline Tested Against Isolates Of *Staphylococcus aureus*

Organism (No. Of Isolates Tested)	Ceftaroline MIC (mg/L)			CLSI MIC Interpretation			EUCAST MIC Interpretation		
	MIC_{50}	MIC_{90}	MIC Range	% Susceptible	% SDD	% Resistant	% Susceptible	% SDD	% Resistant
S. aureus (61,045)	0.5	1	0.015–64	93.7	5.9	0.4	93.7	5.9	0.4
MRSA (35,837)	0.5	2	0.015–64	89.3	10.0	0.7	89.3	10.0	0.7
MSSA (25,208)	0.25	0.25	0.015–2	>99.9	<0.1	0	>99.9	<0.1	0

Abbreviations: MIC, minimal inhibitory concentration; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; SDD, susceptible-dose dependent; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

CEFTAROLINE RESISTANCE BY CLONE-SPECIFIC POLYMORPHISM IN PENICILLIN-BINDING PROTEIN 2A OF METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS

Antimicrob Agents Chemother 2018;62(9).

A total of 281 nonduplicated *Staphylococcus aureus* blood isolates were collected from January to May 2017 from eight hospitals in **South Korea** to investigate the epidemiological traits of ceftaroline resistance in methicillin-resistant *S. aureus* (MRSA). Cefoxitin-disk diffusion tests and the *mecA* gene PCR revealed that 56.6% (159/281) of the *S. aureus* isolates were MRSA, and most belonged to ST5 (50.3%, 80/281) and ST72 (41.5%, 66/281). Of the MRSA isolates, 44.0% (70/159) were nonsusceptible to ceftaroline (MIC ≥ 2 mg/liter), whereas all of the methicillin-susceptible *S. aureus* isolates were susceptible to the drug.

Eight amino acid substitutions in penicillin-binding protein 2a (PBP2a), including four (L357I, E447K, I563T, and S649A) in the penicillin-binding domain (PBD) and four (N104K, V117I, N146K, and A228V) in the non-PBD (nPBD) of PBP2a, were associated with ceftaroline resistance. The accumulation of substitutions in PBP2a resulted in the elevation of ceftaroline MICs: one substitution at 1 to 2 mg/liter, two or three substitutions at 2 to 4 mg/liter, and five substitutions at 4 or 16 mg/liter. Ceftaroline resistance in MRSA might be the result of clone-specific PBP2a polymorphism, along with substitutions both in PBD and nPBD, and the elevated ceftaroline MICs were associated with the substitution sites and accumulation of substitutions.

Nationwide surveillance of resistance rates od Staphylococcus aureus clinical isolates from Greek hospitals

2012-2013 Infect Dis (Lond). 2016 ; 48(4):287-292

A total of 1005 isolates (39% MRSA) were studied.

Susceptibility rates were: erythromycin 66.5%, clindamycin 79.2%, SXT 98.9%, rifampicin 97.3%, fusidic acid 67%, moxifloxacin 78.8%, vancomycin 99.9%, ceftaroline 92.9% and linezolid, tigecycline and daptomycin 100%.

Characterization of methicillin-resistant Staphylococcus aureus displaying increased MICs of ceftaroline

4 Staphylococcus aureus MIC 4 μg/ml, Αθήνα 2008

J Antimicrob Chemother 2012; 67(6):1321–4.

Streptococcus pneumoniae

Expert Rules and Intrinsic Resistance Tables

EUCAST Clinical Breakpoint Tables v. 10.0, valid from 2020-01-01

Cephalosporins[1]	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
	S ≤	R >	ATU		S ≥	R <	ATU	
Cefaclor	0.001	0.5		30	50	28		1/A. The oxacillin 1 µg disk screen test or a benzylpenicillin MIC test shall be used to exclude beta-lactam resistance mechanisms. When the screen is negative (oxacillin inhibition zone ≥20 mm, or benzylpenicillin MIC ≤0.06 mg/L) all beta-lactam agents for which clinical breakpoints are available, including those with "Note" can be reported susceptible without further testing, except for cefaclor, which if reported, should be reported as "susceptible, increased exposure" (I). When the screen is positive (inhibition zone <20 mm, or benzylpenicillin MIC >0.06 mg/L), **see flow chart below**.
Cefadroxil	-	-			-	-		
Cefalexin	-	-			-	-		
Cefazolin	-	-			-	-		
Cefepime	1	2			Note[A]	Note[A]		
Cefixime	-	-			-	-		
Cefotaxime	0.5	2			Note[A]	Note[A]		
Cefoxitin	NA	NA			NA	NA		
Cefpodoxime	0.25	0.5			Note[A]	Note[A]		
Ceftaroline	0.25	0.25			Note[A]	Note[A]		
Ceftazidime								
Ceftazidime-avibactam	-	-			-	-		
Ceftibuten	-	-			-	-		
Ceftobiprole	0.5	0.5			Note[A]	Note[A]		
Ceftolozane-tazobactam	-	-			-	-		
Ceftriaxone	0.5	2			Note[A]	Note[A]		
Cefuroxime iv	0.5	1			Note[A]	Note[A]		
Cefuroxime oral	0.25	0.5			Note[A]	Note[A]		

***In Vitro* Activities of Ceftaroline and Comparators against Streptococcus pneumoniae Isolates from U.S. Hospitals: Results from Seven Years of the AWARE Surveillance Program (2010 to 2016)** Antimicrob Agents Chemother 2018 ;62(2).

TABLE 3 Susceptibilities of *S. pneumoniae* isolates over time to ceftaroline and comparators in the AWARE program (2010 to 2016)

	% susceptible[b] (no. tested)							
Antibiotic[a]	All years (8,768)	2010 (919)	2011 (1,755)	2012 (1,202)	2013 (1,333)	2014 (1,150)	2015 (1,237)	2016 (1,172)
Ceftaroline	>99.9	100.0	100.0	100.0	100.0	99.9	100.0	100.0
Ceftriaxone[c]	93.1	90.4	88.4	91.4	92.6	94.3	98.1	97.7
Penicillin[d]	91.3	86.1	84.8	90.0	92.3	94.1	96.6	96.8
Amox-clav	88.1	84.0	80.6	86.5	87.9	89.8	95.0	95.2
Meropenem	79.2	77.9	74.9	79.1	80.4	82.4		82.1
Clindamycin	82.1	77.9	78.1	81.3	82.5	83.5	87.0	85.0
Erythromycin	54.8	58.4	55.0	56.4	53.1	52.3	55.7	53.4
Levofloxacin	98.8	99.1	98.8	99.2	98.9	97.7	99.4	98.8
Linezolid	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Tetracycline	77.1	75.2	74.3	75.5	76.7	77.6	80.1	81.4
Tigecycline	99.9	100.0	99.9	100.0	99.9	100.0	99.8	99.5
TMX	68.1	65.9	64.4	66.1	67.0	69.5	73.5	71.3

[a]Abbreviations: Amox-clav, amoxicillin-clavulanic acid; TMX, trimethoprim-sulfamethoxazole.
[b]Percent susceptible according to CLSI criteria.
[c]Using non-meningitis breakpoints.
[d]Using parenteral non-meningitis breakpoints.

Table 1. Summary of novel antibiotics against Gram-positive bacteria approved by FDA and/or EMA during the last decade.

Drug	Approval Time	Antibiotic Class	Company	Spectrum Against Organisms	Indication	Dose [1]	Comments/Warnings [2]
Ceftaroline (Teflaro/Zinforo)	FDA: October 2010 EMA: August 2012	Cephalosporin	Allergan Pharmaceutical Industries Ltd. (US/Canada); Takeda Pharmaceutical Company Ltd. (Japan); Pfizer (globally except US/Canada/Japan)	ABSSSI: MRSA, MSSA, *S. pyogenes*, *S. agalactiae* CABP: MSSA, *S. pneumoniae*, *H. influenzae*	FDA: CABP and ABSSSI EMA: CABP and cSSSI	[3] *IV*: 600 mg over 5 to 60 min every 12 h [13]	• Serious anaphylactic reactions have been reported with beta-lactam antibiotics • Direct Coombs' test seroconversion has been reported; if anaemia develops during or after therapy, consider drug-induced haemolytic anaemia and ceftaroline
Ceftobiprole (Zevtera/Mabelio)	EMA: October 2013	Cephalosporin	Basilea Pharmaceutica Ltd.	MRSA, ampicillin-susceptible enterococci and penicillin-resistant pneumococci	EMA: HAP (excluding VAP) and CABP	*IV*: 500 mg over 2 h every 8 h [14]	• Serious anaphylactic reactions have been reported in patients receiving beta-lactam antibiotics
Telavancin (Vibativ)	FDA: September 2009	Lipoglycopeptide	Theravance Biopharma Antibiotics, Inc.,	MRSA, vancomycin-intermediate *S. aureus* and penicillin-resistant *S. pneumoniae*	FDA: cSSSI, HAP (including VAP)	*IV*: 10 mg/kg over 60 min every 24 h for 7–14 days (cSSSI) and 7–21 days (HAP/VAP) [15]	• Decreased efficacy with moderate/severe pre-existing renal impairment • Interferes with some coagulation tests e.g., prothrombin time, international normalised ratio • QTc prolongation • Serious and potentially fatal hypersensitivity reactions • Infusion-related reactions
Dalbavancin (Dalvance/ Xydalba)	FDA: May 2014	Lipoglycopeptide	Durata Therapeutics (acquired by Actavis in 2014)	MRSA, *S. pyogenes*, *S. agalactiae* and *E. faecalis* strains susceptible to vancomycin	FDA: ABSSSI	*IV*: 1000 mg over 30 min followed one week later by 500 mg over 30 min [16]	• Serious anaphylactic and skin reactions have been reported with glycopeptides • Rapid IV glycopeptide infusion can cause upper body flushing, urticaria, pruritis and/or rash • ALT elevations have been reported
Oritavancin (Orbactiv)	FDA: August 2014 EMA: March 2015	Glycopeptide	Melinta Therapeutics Inc.	MSSA, MRSA, VRE and vancomycin-intermediate and vancomycin-resistant staphylococci	FDA: ABSSSI EMA: ABSSSI	*IV*: 1200 mg single dose over 3 h [17]	• Co-administration with warfarin may increase warfarin exposure and increase bleeding risk • Oritavancin administration may artificially prolong aPTT for up to 48 h and prolong PT/INR for up to 24 h • Hypersensitivity and infusion related reactions including pruritus, urticaria and flushing have been reported • [4] A higher incidence of osteomyelitis reported in the oritavancin treated ABSSSI arm than vancomycin-treated arm

Staphylococcus spp.

EUCAST Clinical Breakpoint Tables v. 10.0, valid from 2020-01-01

Expert Rules and Intrinsic Resistance Tables

Glycopeptides and lipoglycopeptides[1]	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
Dalbavancin[3]	0.125[3,4]	0.125[3]			Note[A]	Note[A]		1. Glycopeptide MICs are method dependent and should be determined by broth microdilution (ISO standard 20776-1). *S. aureus* with vancomycin MIC values of 2 mg/L are on the border of the wild-type distribution and there may be an impaired clinical response. ~~The resistant breakpoint has been reduced to 2 mg/L to avoid reporting "GISA" isolates in the I category as serious infections with "GISA" isolates are not treatable with increased doses of vancomycin or teicoplanin.~~
Oritavancin[3], *S. aureus*	0.125[3,4]	0.125[3]			Note[A]	Note[A]		
Teicoplanin[3], *S. aureus*	2	2			Note[A]	Note[A]		
Teicoplanin, Coagulase-negative staphylococci	4	4			Note[A]	Note[A]		
Telavancin[3], MRSA	0.125[3,5]	0.125[3]			Note[A]	Note[A]		2. Non-susceptible isolates are rare or not yet reported. The identification and antimicrobial susceptibility test result on any such isolate must be confirmed and the isolate sent to a reference laboratory.
Vancomycin[3], *S. aureus*	2	2			Note[A]	Note[A]		3. MICs must be determined in the presence of polysorbate-80 (0.002% in the medium for broth dilution methods; agar dilution methods have not been validated). Follow the manufacturer's instructions for commercial systems.
Vancomycin[3], Coagulase-negative staphylococci	4	4			Note[A]	Note[A]		4. *S. aureus* isolates susceptible to vancomycin can be reported susceptible to dalbavancin and oritavancin.
								5. MRSA isolates susceptible to vancomycin can be reported susceptible to telavancin.
								A. Disk diffusion is unreliable and cannot distinguish between wild type isolates and those with non-vanA-mediated glycopeptide resistance.

Enterococcus spp.

EUCAST Clinical Breakpoint Tables v. 10.0, valid from 2020-01-01

Expert Rules and Intrinsic Resistance Tables

Glycopeptides and lipoglycopeptides	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
Dalbavancin	IE	IE			IE	IE		A. Vancomycin susceptible enterococci exhibit sharp zone edges and do not exhibit colonies in the inhibition zone. Examine zone edges with transmitted light (plate held up to light). If the zone edge is fuzzy, colonies grow within the zone or if you are uncertain, then perform confirmatory testing with PCR or report resistant (**see pictures below**) even if the zone diameter is ≥ 12 mm. Isolates must not be reported susceptible before 24 h incubation.
Oritavancin	IE	IE			IE	IE		
Teicoplanin	2	2		30	16	16		
Telavancin	IE	IE			IE	IE		
Vancomycin	4	4		5	12[A]	12[A]		

Activity of dalbavancin and comparator agents against Gram-positive cocci from clinical infections in the USA and Europe 2015-16

J Antimicrob Chemother 2018; 73(10):2748-2756.

Objectives:

To evaluate the activity of dalbavancin against GPC isolated from a variety of infection types in the USA and Europe.

Methods:

A total of 14 319 *Staphylococcus aureus*, 1992 CoNS, 3269 β-haemolytic streptococci (BHS), 2071 *Enterococcus faecalis*, 936 *Enterococcus faecium*, 71 *Enterococcus gallinarum/casseliflavus* and other Enterococcus spp., 3487 *Streptococcus pneumoniae* and 1063 viridans group streptococci (VGS) causing clinical infections were consecutively collected (2015-16) and tested for susceptibility by broth microdilution methods.

Results:

All S. aureus (36.4% MRSA) isolates were susceptible to dalbavancin, teicoplanin and vancomycin, while daptomycin and linezolid showed susceptibility rates of >99.9% (according to CLSI criteria). Dalbavancin MIC results were at least 16-fold lower than these comparators against all *S. aureus*. **Dalbavancin was the most potent agent against CoNS** [62.2%/59.6% methicillin-resistant (CLSI/EUCAST)], followed by daptomycin, linezolid and vancomycin. **All vancomycin-susceptible *E. faecalis*** isolates were inhibited by dalbavancin at ≤0.25 mg/L (FDA susceptible breakpoint). **Dalbavancin was very active against BHS (MIC90 0.03 mg/L) and the most active agent against *S. pneumoniae* and VGS** (highest MIC 0.25 mg/L). Ceftriaxone, daptomycin, levofloxacin and vancomycin were also active (93.5%-100.0% susceptible) against VGS, whereas clindamycin, erythromycin, penicillin and tetracycline had lower activity.

Conclusions:

Dalbavancin appears to be a viable candidate for treating serious infections caused by GPC.

Εμπειρία στο ΠΓΝΛ

- *Staphylococcus aureus* (MRSA+MSSA) $MIC_{DALBACANCIN}$: 0.032-0.064 mg/L
- Enterococci -VSE $MIC_{DALBACANCIN}$: 0.023-0.047 mg/L
- Enterococci -VRE (*vanA, vanB*) $MIC_{DALBACANCIN}$: 0.023- 32 mg/L

Table 1. *Cont.*

Drug	Approval Time	Antibiotic Class	Company	Spectrum Against Organisms	Indication	Dose [1]	Comments/Warnings [2]
Tedizolid Phosphate (Sivextro)	FDA: June 2014 EMA: March 2015	Oxazolidinone	Cubist Pharmaceuticals	MRSA, vancomycin-intermediate *Enterococcus* spp.	FDA: ABSSSI EMA: ABSSSI	IV: 200 mg single dose over 1 h for 6 days [3] PO: 200 mg once daily [18]	• Safety and efficacy not adequately evaluated in neutropenic patients
Besifloxacin (Besivance)	FDA: June 2009	Fluoroquinolone	SSP Co. Ltd.	MRSA, *S. epidermidis*, *S. pneumoniae*, and *H. influenzae*	FDA: bacterial conjunctivitis	Instill one drop in the affected eye(s) 3 times a day, four to 12 h apart for 7 days [19]	• Not for injection into the eye • Prolonged use may result in the overgrowth of non-susceptible organisms resulting in a super-infection • Avoid contact lens wear during course of therapy
Delafloxacin (Baxdela)	FDA: June 2017	Fluoroquinolone	Melinta Therapeutics Inc.	*S. aureus* (including MRSA), *S. pneumoniae*, other fluoroquinolone resistant strains (Ineffective against Fluoroquinolone-resistant enterococci)	FDA: ABSSSI	IV: 300 mg over 1 h every 12 h PO: 450 mg tablet every 12 h for 5 to 14 days [20]	• Hypersensitivity reactions may occur after first or subsequent doses
Ozenoxacin (Ozanex/Xepi)	FDA: December 2017	Non-fluorinated quinolone	Ferrer Internacional S.A.	MRSA, MSSA, MRSE and *S. pyogenes*	FDA: impetigo	Topical: apply a thin layer to the affected area twice daily for 5 days [21]	• Prolonged use of ozenoxacin may result in the overgrowth of non-susceptible organisms resulting in a super-infection
Omadacycline (Nuzyra)	FDA: October 2018	Tetracycline	Paratek Pharmaceuticals	MRSA, penicillin-resistant and multidrug-resistant *S. pneumoniae*, and vancomycin-resistant *Enterococcus* spp.	FDA: CABP, ABSSSI	Duration: 7–14 days Loading IV Day1: 200 mg over 1 h once daily or 100 mg over 30 min twice daily *Maintainance:* 100 mg over 30 min or 300 mg po once daily [4] *Loading PO (ABSSSI)* Day 1&2: 450 mg once daily *Maintainance PO (ABSSSI)* 300 mg once daily [22]	• Commonest adverse reactions: Nausea, vomiting, hypertension, headache, diarrhea, insomnia and constipation • Mortality imbalance observed in the CABP clinical trial: 8 deaths in the omadacycline group vs. 4 in the moxifloxacin group • Omadacycline use during tooth development (last half of pregnancy, infancy and childhood >8 years) may cause permanent teeth discoloration and enamel hypoplasia • Omadacycline use during the 2nd and 3rd trimester of pregnancy, infancy and childhood >8 years may cause reversible bone growth inhibition

Staphylococcus spp.

Expert Rules and Intrinsic Resistance Tables

EUCAST Clinical Breakpoint Tables v. 10.0, valid from 2020-01-01

Oxazolidinones	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
	S ≤	R >	ATU		S ≥	R <	ATU	
Linezolid	4	4		10	21	21		1A. Isolates susceptible to linezolid can be reported susceptible to tedizolid.
Tedizolid	0.5[1]	0.5		2	21[A]	21		~~A. Examine zone edges with transmitted light (plate held up to light).~~ ~~B. Isolates susceptible to linezolid can be reported susceptible to tedizolid. For isolates resistant to linezolid, perform an MIC test.~~

Enterococcus spp.

Expert Rules and Intrinsic Resistance Tables

EUCAST Clinical Breakpoint Tables v. 10.0, valid from 2020-01

Oxazolidinones	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
	S ≤	R >	ATU		S ≥	R <	ATU	
Linezolid	4	4		10	20	20		
Tedizolid	IE	IE			IE	IE		

Streptococcus pneumoniae

Expert Rules and Intrinsic Resistance Tables

EUCAST Clinical Breakpoint Tables v. 10.0, valid from 2020-01-01

Oxazolidinones	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
	S ≤	R >	ATU		S ≥	R <	ATU	
Linezolid	2	2		10	22	22		
Tedizolid	IE	IE			IE	IE		

Tedizolid susceptibility in linezolid- and vancomycin-resistant *Enterococcus faecium* isolates. Eur J Clin Microbiol Infect Dis 2016 ;35(12):1957-1961

Here we tested tedizolid activity in a collection of 30 LR *Enterococcus faecium* VRE (MIC range 32-256 mg/l) isolated between 2012 and 2015 from clinical and screening specimens. All isolates, carried mutations within the 23S rDNA. **Compared to linezolid, tedizolid MICs were lower in all isolates (MIC range 2-32 mg/l), but remained above the FDA tedizolid breakpoint for *E. faecalis* at 0.5 mg/l.** Thus, related to the predominant resistance mechanism, tedizolid is of limited value for treatment of most LR-VRE and represents a therapeutic option only for a limited subset of isolates.

Σε στελέχη που φέρουν το *cfr* η MIC στην telizolid είναι πολύ χαμηλότερη από τη linezolid

Καμία διαφορά σε στελέχη με το *optrA* γονίδιο

Εμπειρία στο ΠΓΝΛ

	Μηχανισμός αντοχής	$MIC_{linezolid}$	$MIC_{tedizolid}$
• *Staphylococcus epidermidis*	G2576T	24mg/L	4mg/L
• *Staphylococcus epidermidis*	T2504A+2534	>256mg/L	12mg/L
• *Enterococcus faecium*	G2576T	>256mg/L	32mg/L
• *Enterococcus faecium*	*poxtA*	24mg/L	0.75mg/L
• *Enterococcus faecalis*	G2576T	>256mg/L	32mg/L
• *Enterococcus faecalis*	*optrA*	32mg/L	

ΕΥΧΑΡΙΣΤΩ ΠΟΛΥ ΓΙΑ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ