“Il nuovo scenario dell’antibioticoterapia”.

Silvano Esposito

Dipartimento di Medicina e Chirurgia
Università degli studi di Salerno

ORIGINAL ARTICLE BACTERIOLOGY

Clin Microbiol Infect 2012; **18**: 268–281
10.1111/j.1469-0691.2011.03570.x

Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance

A.-P. Magiorakos[1], A. Srinivasan[2], R. B. Carey[2], Y. Carmeli[3], M. E. Falagas[4,5], C. G. Giske[6], S. Harbarth[7], J. F. Hindler[8], G. Kahlmeter[9], B. Olsson-Liljequist[10], D. L. Paterson[11], L. B. Rice[12], J. Stelling[13], M. J. Struelens[1], A. Vatopoulos[14], J. T. Weber[2] and D. L. Monnet[1]

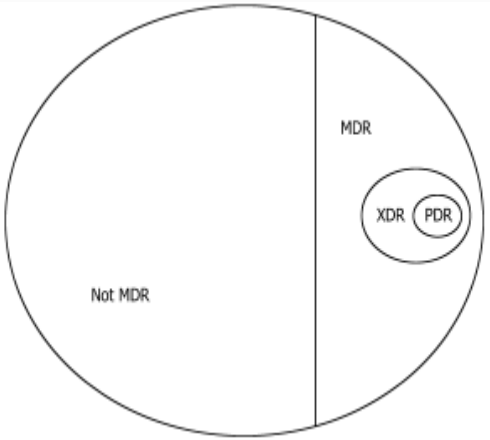


TABLE 6. Definitions for multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) bacteria

Bacterium	MDR	XDR	PDR
Staphylococcus aureus	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 1[a]	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 1.	Non-susceptibility to all agents in all antimicrobial categories for each bacterium in Tables 1–5
Enterococcus spp.	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 2	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 2.	
Enterobacteriaceae	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 3	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 3.	
Pseudomonas aeruginosa	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 4	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 4.	
Acinetobacter spp.	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 5	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 5.	

[a]All MRSA isolates are defined as MDR because resistance to oxacillin or cefoxitin predicts non-susceptibility to all categories of β-lactam antimicrobials listed in this document, with the exception of the anti-MRSA cephalosporins (i.e. all categories of penicillins, cephalosporins, β-lactamase inhibitors and carbapenems currently approved up until 25 January 2011).
http://www.ecdc.europa.eu/en/activities/diseaseprogrammes/ARHAI/Pages/public_consultation_clinical_microbiology_infection_article.aspx.

From Eskape to Escape, from KPC to CCC

De Rosa FG, Clin. Infect Dis.2015 Apr 15;60(8)

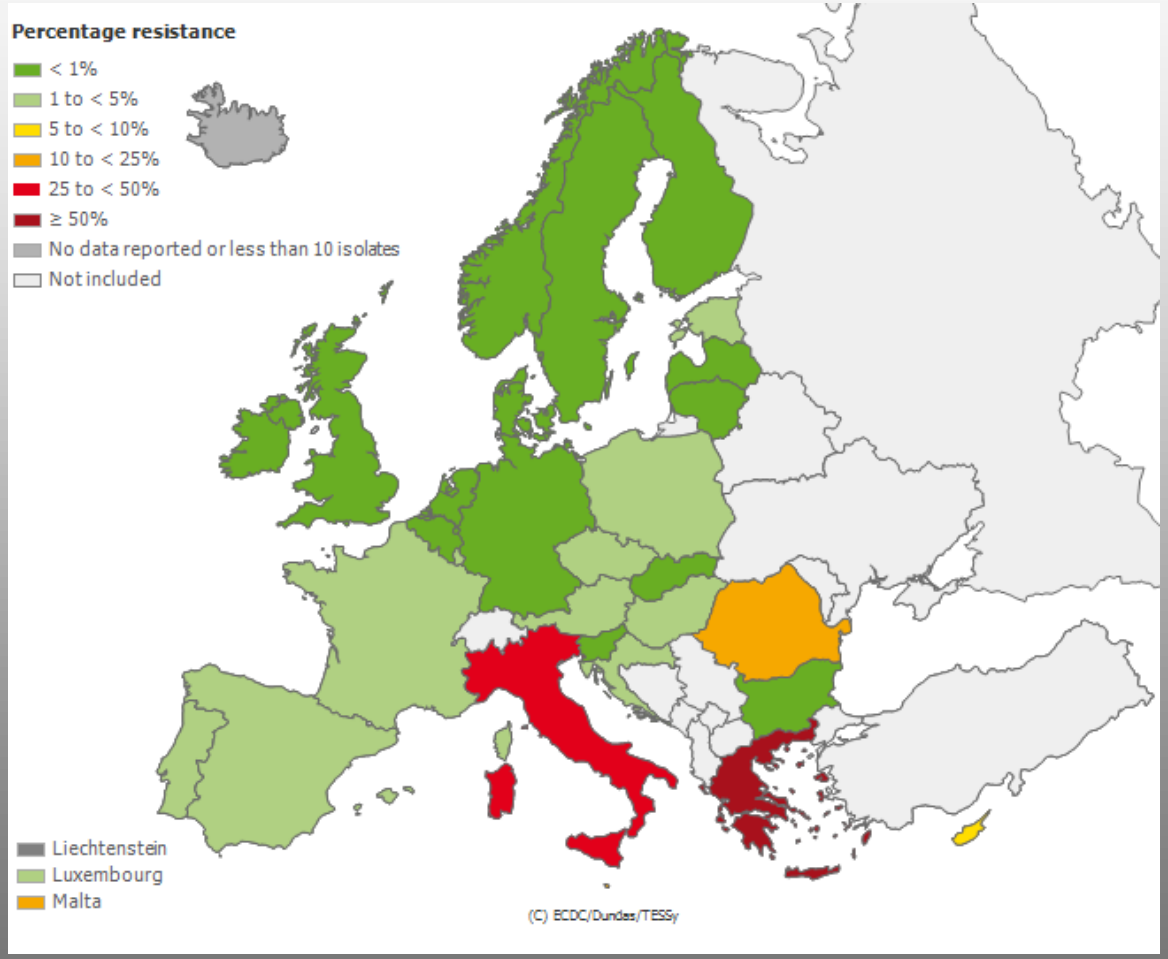
- **Eskape**
  - *E. faecium,*
  - *S. aureus,*
  - *K. pneumoniae,*
  - *A. baumannii,*
  - *P. aeruginosa,*
  - *Enterobacter spp.*
- **Escape**
  - Enterococchi ,
  - *S. aureus,*
  - *C. difficile,*
  - *A. baumannii,*
  - *P. aeruginosa,*
  - Enterobacteriacee

- **KPC-Kp**
- **CCC**
  - Carbapenemases
  - *C. difficile*
  - Candida spp.

Main Etiology & Syndromes

Etiology	Syndromes
• MDR Enterobacteriacee – FQ-R – AG-R – ESBL – Carbapenemases • MDR *P. aeruginosa* • MDR *A. baumanni* • XDR / PDR	• Pneumonia • BSI & CVC-BSI • Complicated Intrabdominal infections (cIAIs) • Complicated Urinary tract infections (cUTI) • Device- associated & -related infections • cSSTIs

Proportion of Carbapenems Resistant (R+I) Klebsiella pneumoniae Isolates in Participating Countries in 2013



AOU S.GIOVANNI DI DIO E RUGGI D'ARAGONA

Cliente bioMerieux:

Rapporto grafico Microbiologia

Stampato 20-mag-2013 12:23 CDT

Nome paziente:
Posizione:
ID lab.: [redacted]

ID paziente:
Medico:
Numero di isolato: 1

Organismo selezionato: Klebsiella pneumoniae ssp pneumoniae

Origine:

Prelevato:

Commenti:	

Informazioni sull'identificazione	Tempo di analisi:	4,00 ore	Stato: Finale
Organismo selezionato	99% Probabilità Bionumero:	Klebsiella pneumoniae ssp pneumoniae 2605734653564010	
Quantità organismo:			
Messaggi di analisi ID			

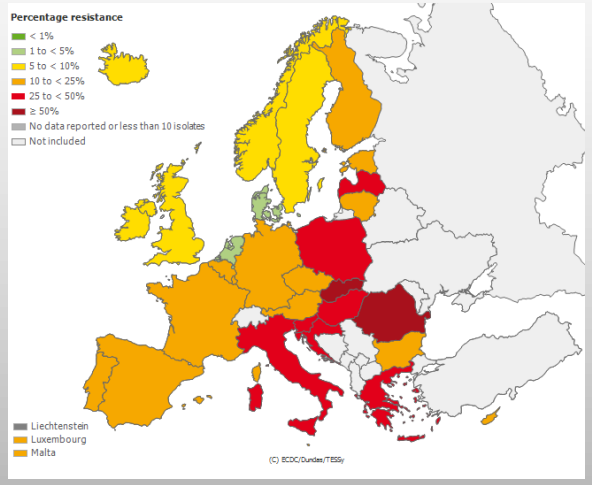
Informazioni sull'antibiogramma	Tempo di analisi: 9,25 ore			Stato: Finale	
Antimicrobico	MIC	Interpretazione	Antimicrobico	MIC	Interpretazione
ESBL	NEG	-	Amikacina	>= 64	R
Amoxicillina/acido clavulanico	>= 32	R	Gentamicina	<= 1	S
Piperacillina/tazobactam	>= 128	R	Ciprofloxacina	>= 4	R
Cefotaxime	>= 64	R	Fosfomicina	128	R
Ceftazidime	>= 64	R	Nitrofurantoina		
Cefepime	>= 64	R	Colistina	<= 0,5	S
Imipenem	>= 16	R	Trimetoprim/Sulfametossazolo	>= 320	R
Meropenem	>= 16	R			

+= Antibiotici dedotti *= Modificato AES **= Modificato utente

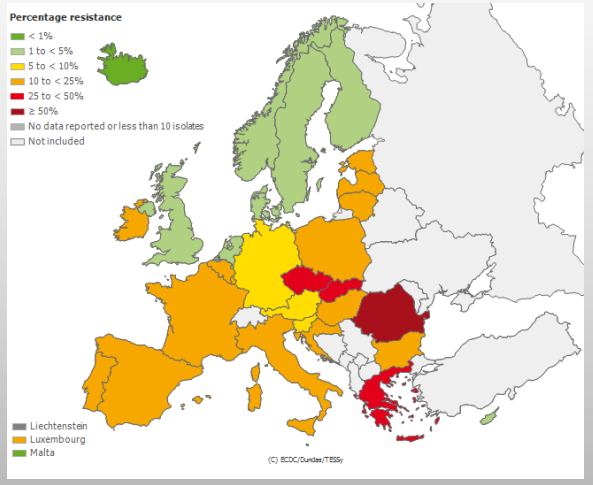
Conclusioni di AES		
Affidabilità:	Coerente	
Fenotipo:	BETA-LATTAMICI	ESBL + CARBAPENEMASI (METALLO- O KPC)

Proportion of antibiotic resistant *P. aeruginosa* isolates in Europe - 2013

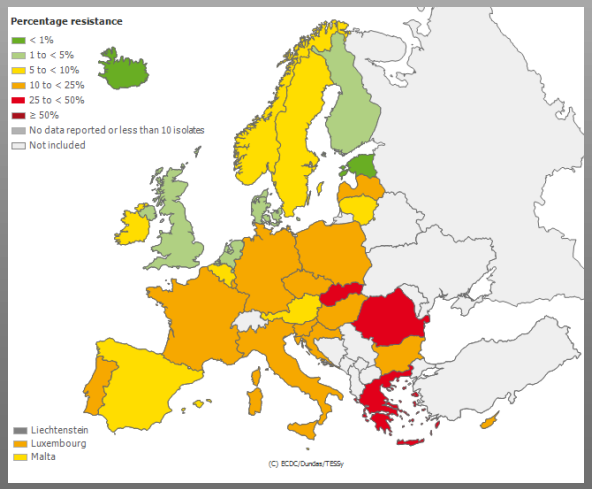
Carbapenems



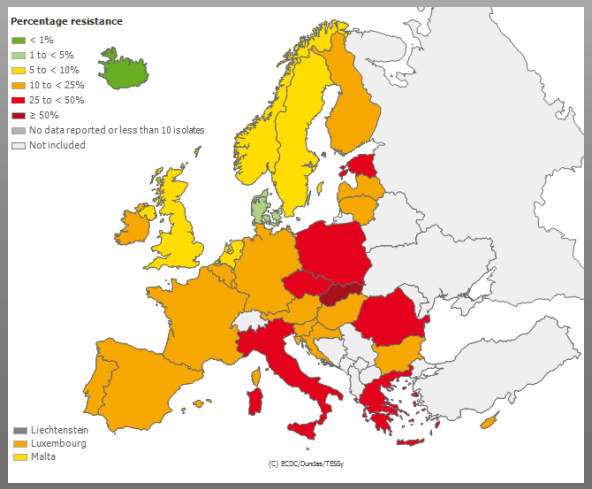
Aminoglycosides



Ceftazidime



Fluoroquinolones



AOU S.GIOVANNI DI DIO E RUGGI D'ARAGONA

Cliente bioMerieux:
N. sistema:

Lab report

Stampato 15-ott-2015 09:28 CDT
Stampato da: vitek2

Nome paziente: [redacted]
ID paziente: OLW0000018308901

Gruppo di isolati: 5010709599-1

Bionumero: 0003451303500240
Organismo selezionato: Pseudomonas aeruginosa

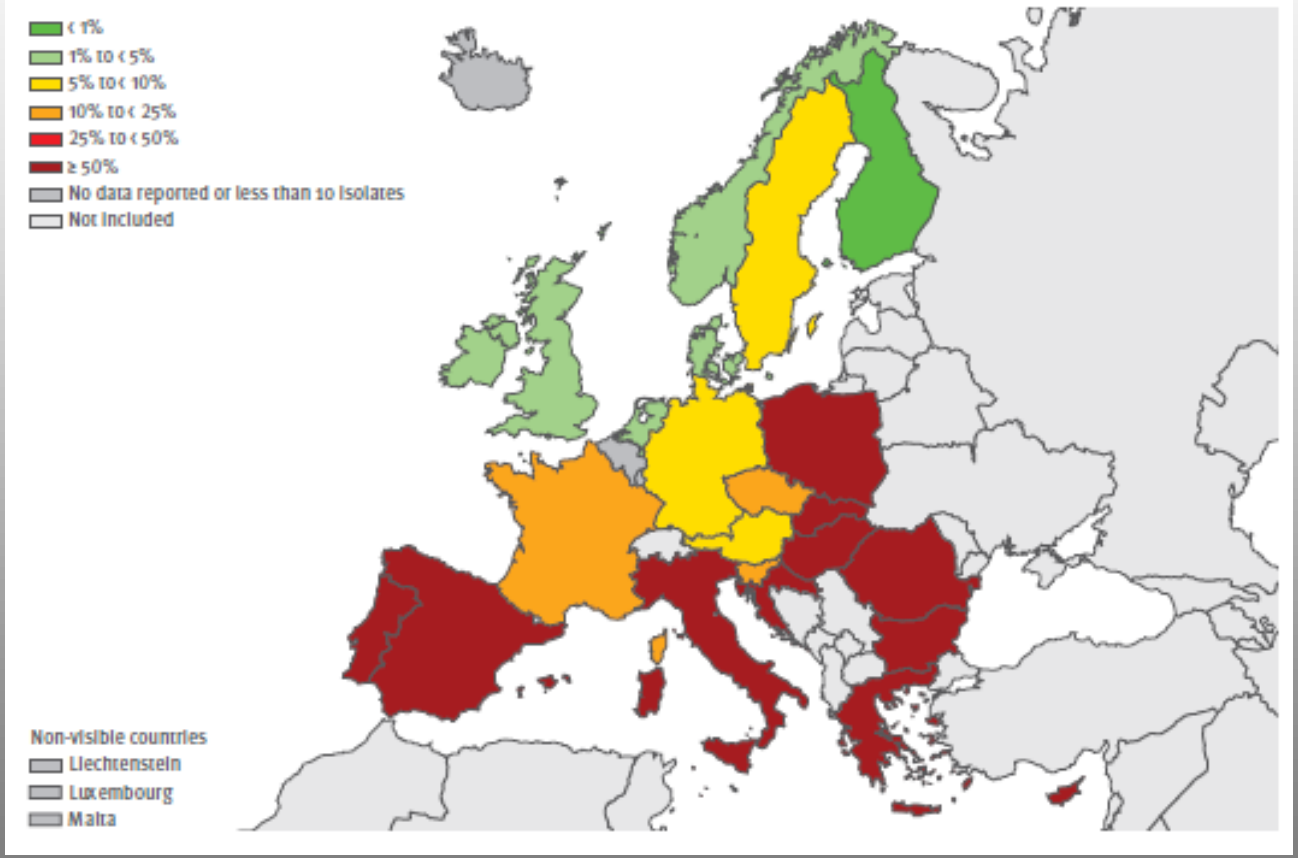
Informazioni sull'antibiogramma	Card: AST-N202		Numero di lotto: 572311640	Scade: 26-giu-2015 13:00 CDT	
	Completato: 11-gen-2015 00:29 CST		Stato: Finale	Tempo di analisi: 12,50 ore	
Antimicrobico	**MIC**	**Interpretazione**	**Antimicrobico**	**MIC**	**Interpretazione**
ESBL			Amikacina	<= 2	S
Amoxicillina/acido clavulanico	>= 32	R	Gentamicina	<= 1	S
Piperacillina/tazobactam	>= 128	R	Ciprofloxacina	>= 4	R
Cefotaxime	>= 64	R	Tigeciclina	>= 8	R
Ceftazidime	>= 64	R	Fosfomicina		
Cefepime	>= 64	R	Nitrofurantoina		
Ertapenem	>= 8	R	Colistina	2	S
Imipenem	>= 16	R	Trimetoprim/Sulfametossazolo	>= 320	R
Meropenem	4	I			

+= Antibiotici dedotti *= Modificato AES **= Modificato utente

Conclusioni AES:	Ultima modifica: 15-apr-2014 14:13 CDT	Set di parametri: EUCAST2014+MICET Ivers. 5.04_25.03.2014
Livello di affidabilità:	Coerente	

Azione	Nome (ID utente)	Data/Ora	Commento
Revisionato da:	**(vitek2)**	**12-gen-2015 08:46 CST**	

Acinetobacter spp. percentage of invasive isolates with resistance to fluoroquinolones, aminoglycosides and carbapenems, 2013



AOU S.GIOVANNI DI DIO E RUGGI D'ARAGONA

Cliente bioMerieux:

Rapporto grafico Microbiologia

Stampato 8-ott-2015 07:53 CDT

Nome paziente:
Posizione:
ID lab.: [redacted]

ID paziente:
Medico:
Numero di isolato: 1

Organismo selezionato: Acinetobacter baumannii complex

Origine:

Prelevato:

Commenti:	

Informazioni sull'identificazione	Tempo di analisi:	6,00 ore	Stato: Finale
Organismo selezionato	99% Probabilità Bionumero:	Acinetobacter baumannii complex 0201010103500212	
Quantità organismo:			
Messaggi di analisi ID			

Informazioni sull'antibiogramma	Tempo di analisi: 10,75 ore			Stato: Finale	
Antimicrobico	MIC	Interpretazione	Antimicrobico	MIC	Interpretazione
ESBL			Amikacina		
Amoxicillina/acido clavulanico	>= 32	R	Gentamicina	>= 16	R
Piperacillina/tazobactam			Ciprofloxacina	>= 4	R
Cefotaxime	>= 64	R	Tigeciclina	2	
Ceftazidime			Fosfomicina		
Cefepime			Nitrofurantoina		
Ertapenem	>= 8	R	Colistina	<= 0,5	S
Imipenem	>= 16	R	Trimetoprim/Sulfametossazolo	160	R
Meropenem					

+= Antibiotici dedotti *= Modificato AES **= Modificato utente

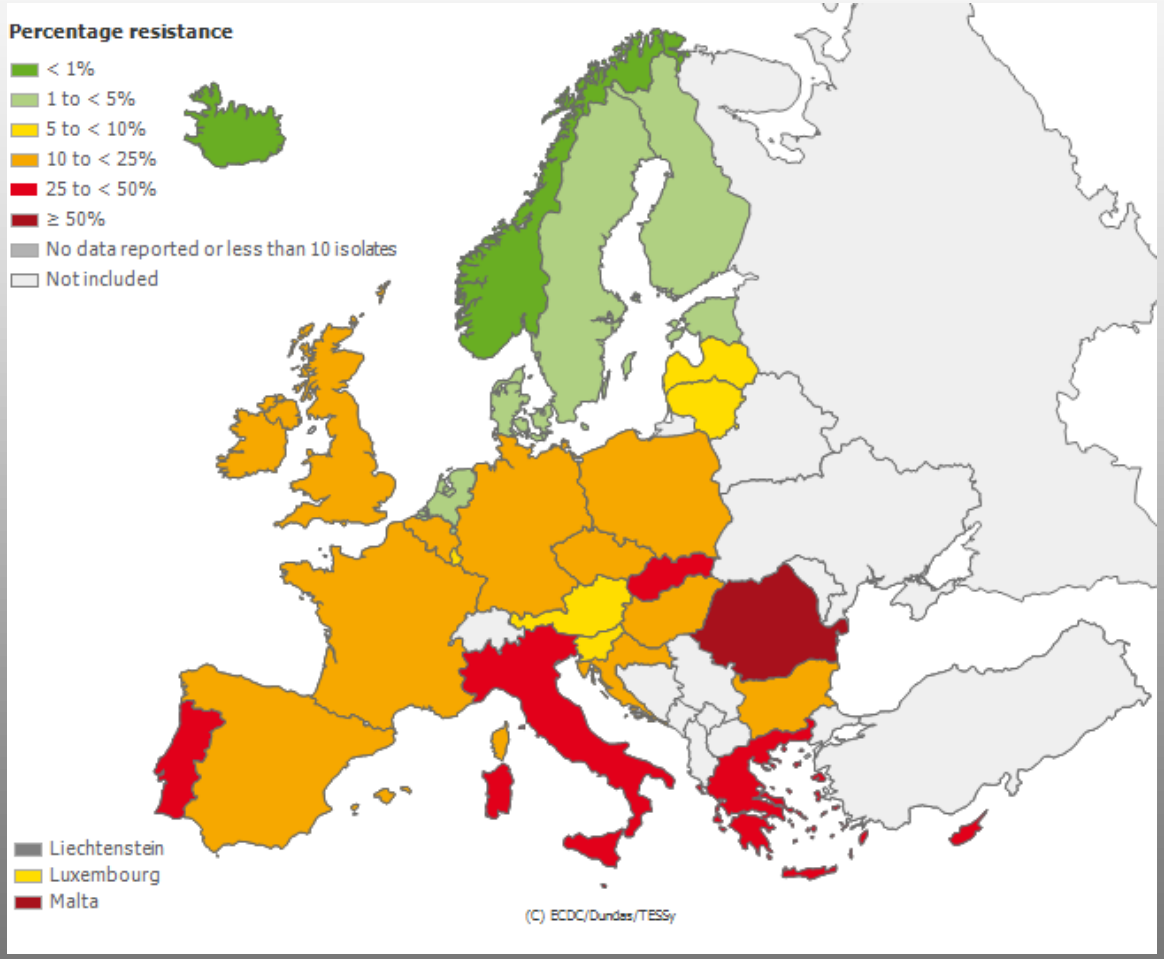
Conclusioni di AES		
Affidabilità:	Coerente	
Fenotipo:	BETA-LATTAMICI	CARBAPENEMASI (METALLO- OR OXA)

Treatment options for carbapenem-resistant and extensively drug-resistant *Acinetobacter baumannii* infections.

Drug	Dosing for *A. baumannii* infections (normal renal function)	Advantages	Drawbacks	Ongoing questions
Colistin (as colistimethate) [62–64, 75, 76]	5 mg CBA/kg/day loading dose followed by 5 mg CBA/kg/day divided in 2 or 3 doses	Mainstay of therapy; used in combination with other agents	Nephrotoxicity; low serum concentrations especially early in therapy; resistance via lipid A modification	Efficacy when optimally dosed; optimal companion agent for combination therapy
Fosfomycin* [127, 128]	4 g every 12 hours used in a randomized trial; potential for higher doses; used in combination	Bactericidal; relatively well tolerated	No approved intravenous formulation in the U.S.; modest activity alone; difficulties with MIC determinations	Larger trials to prove added benefit in the context of combination therapy
Rifampin* [124, 125]	600 mg every 12 or 24 hours; used in combination	Widely available; no renal toxicity	Monotherapy can quickly lead to resistance; liver toxicity and drug-drug interaction	Randomized trial data conflicting regarding overall benefit of adding rifampin
Sulbactam (ampicillin-sulbactam) [79, 80, 96]	3 to 9 g/day (9 to 27g/day of ampicillin-sulbactam); alone or in combination	Widely available in combination with ampicillin; relatively inexpensive	Increasing resistance; not available alone in many countries including the U.S.	Clinical correlation between MIC and outcome; optimal dosing regimen
Tigecycline [102–106]	100 mg loading dose followed by 50 mg every 12 hours; alone or in combination	Widely available; active against most strains *in vitro*	Low serum concentrations; bacteriostatic activity; may be inferior to comparators in critically ill patients	Clinical correlation between MIC and outcome; optimal dosing regimen; benefit of combination regimens
Vancomycin* [134, 135]	10 to 15 mg/kg every 12 hours; in combination with colistin	Widely available; strong *in vitro* synergy with colistin; often included in empiric sepsis therapy	Potential for increased nephrotoxicity; no prospective validation of clinical efficacy	Optimal dosing regimen and duration; efficacy in colistin-resistant cases

Viehman JA, Drugs. 2014 Aug;74(12):1315-33.

Proportion of Methicillin Resistant Staphylococcus aureus (MRSA) Isolates in Participating Countries in 2013



AOU S.GIOVANNI DI DIO E RUGGI D'ARAGONA

Cliente bioMerieux:

Rapporto grafico Microbiologia

Stampato 14-ott-2015 11:00 CDT

Nome paziente: [redacted]E
ID paziente: 1018197
Posizione: 360
ID lab.: 5100305199
Numero di isolato: 1

Organismo selezionato: Staphylococcus aureus

Origine: SANGUE
Prelevato: 3-ott-2015 1402

Commenti:	

Informazioni sull'identificazione	Tempo di analisi:	4,00 ore	Stato:	Finale
Organismo selezionato	99% Probabilità Bionumero:	Staphylococcus aureus 010402062663031		
Quantità organismo:				
Messaggi di analisi ID				

Informazioni sull'antibiogramma	Tempo di analisi: 11,00 ore			Stato: Finale	
Antimicrobico	MIC	Interpretazione	Antimicrobico	MIC	Interpretazione
Cefoxitina screening	POS	+	Linezolid	1	S
Benzilpenicillina	>= 0,5	R	Daptomicina	0,25	S
Oxacillina	>= 4	R	Teicoplanina	<= 0,5	S
Gentamicina	>= 16	R	Vancomicina	1	S
Levofloxacina	>= 8	R	Tetraciclina	<= 1	S
Resistenza inducibile alla Clindamicina	NEG	-	Tigeciclina	<= 0,12	S
+Azitromicina		R	Fosfomicina		
+Claritromicina		R	Acido fusidico	<= 0,5	S
Eritromicina	>= 8	R	Rifampicina	>= 4	R
Clindamicina	>= 4	R	Trimetoprim/Sulfametossazolo	<= 10	S

+= Antibiotici dedotti *= Modificato AES **= Modificato utente

Conclusioni di AES		
Affidabilità:	Coerente	
Fenotipo:	BETA-LATTAMICI	MODIFICA DELLE PBP (mecA)

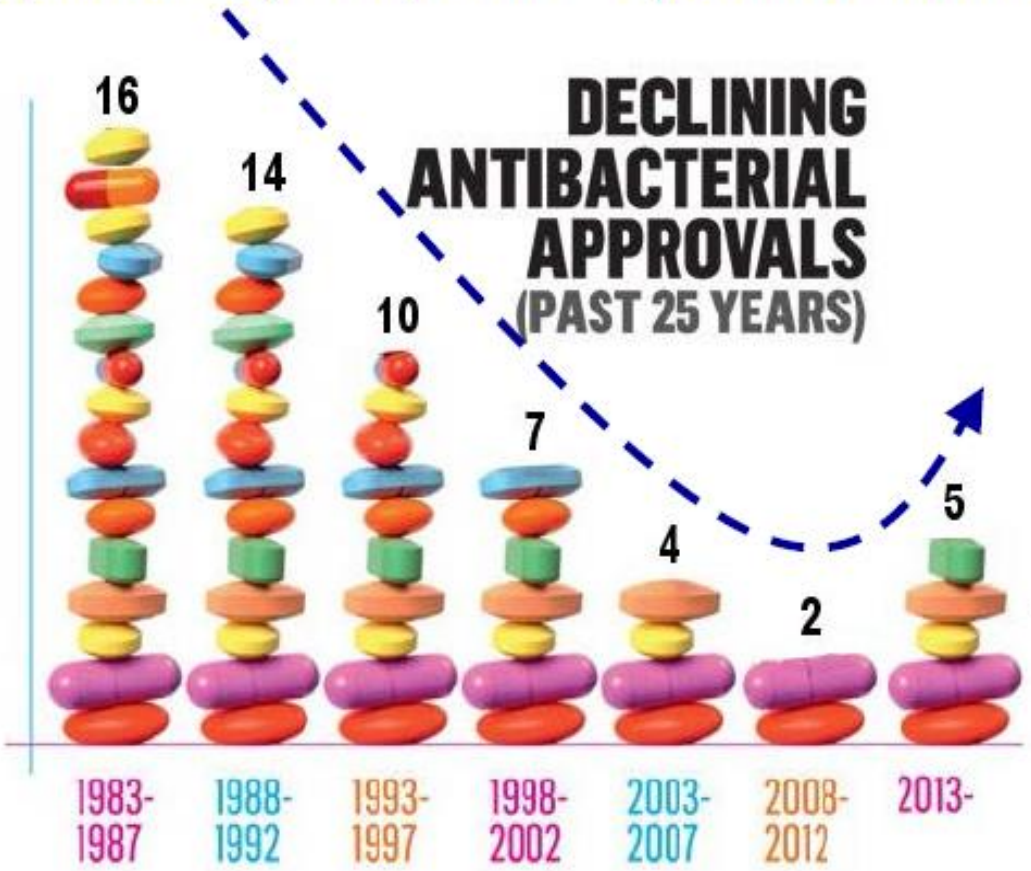
Principal characteristics of old agents for MRSA

Agent	Bacterial Effect and Mechanism of Action	Route of Administration and Dosing Recommendations	Dosage Adjustment for Renal and Hepatic Impairment	Adverse Events	Advantages	Disadvantages
Vancomycin	"Slow" bactericidal activity (concentration independent); cell wall inhibition	IV: 500 mg q6h or 1000 mg q12h; high-dose therapy (15 to 20 mg/kg total body weight q8 to 12 h) currently recommended when MIC values are 1 μg/mL	*Renal:* Dosing adjustments are necessary; dosing nomograms and monitoring trough serum vancomycin concentration recommended *Hepatic:* no adjustment needed	Nephrotoxicity; red man syndrome	Inexpensive; >50 y of clinical experience	VISA, hVISA, VRSA; increasing MIC values associated with poor outcomes; nephrotoxicity with higher doses
Linezolid	Bacteriostatic; protein synthesis inhibition (23S RNA at 50S ribosomal subunit)	IV or PO: 600 mg q12h	*Renal:* None *Hepatic:* No specific recommendations	Thrombocytopenia and anemia (duration dependent); peripheral and optic neuropathy; lactic acidosis; serotonin syndrome	100% bioavailable oral formulation; good drug penetration into lung; active against VRE	Bacteriostatic; serious adverse events with long-term use (>14 d); increasing linezolid-resistant *S. aureus*; high drug cost
Daptomycin	Bactericidal (concentration dependent); membrane depolarization (Ca++ dependent)	IV: cSSSI: 4 mg/kg (total body weight) q24h; *S. aureus* bacteremia: 6 mg/kg (total body weight) q24h; some experts recommend higher doses (8 to 10 mg/kg) for bacteremia/infective endocarditis indications	*Renal:* For CrCl <30 mL/min, q48h *Hepatic:* No specific recommendations	CPK elevation; myopathy; peripheral neuropathy; case reports of rhabdomyolysis and eosinophilic pneumonia	Rapidly bactericidal; effective for MRSA bloodstream infections and right-side endocarditis; active against VRE; extensive published literature on treatment experiences for a wide range of MRSA infections	Inactivated by pulmonary surfactant and should not be used to treat pneumonia; increasing MIC values correlated to vancomycin increasing MIC values; suboptimal clinical outcomes in patients with reduced renal function; high drug cost
Tigecycline	Bacteriostatic; protein synthesis inhibition (at 30S ribosomal subunit)	IV: loading dose of 100 mg followed by 50 mg q12h	*Renal:* None *Hepatic:* Child-Pugh class C, 100 mg single dose, maintenance 25 mg q12h	GI side effects (nausea and vomiting are common)	Active against VRE	Bacteriostatic; low serum and ELF drug concentrations; not approved for HAP/VAP; high rates of GI adverse events; higher risk of mortality than comparator agents; high drug cost

Rodvold KA; Clin Infect Dis. 2014; 58 Suppl 1:S20-7.

New antibiotics: where are we ?

Approvals by FDA/EMA – systemic antibiotics



- dalbavancin
- oritavancin
- tedizolid
- ceftazidime/avibactam
- ceftolozane/tazobactam

- telavancin
- ceftaroline

Ceftolozane/tazobactam and ceftazidine/avibactam

	Ceftolozane/tazobactam	Ceftazidime/avibactam
Brand name	Zerbaxa™	Avycaz™
FDA indications	cIAI (with metronidazole), cUTI (including pyelonephritis)	cIAI (with metronidazole), cUTI (including pyelonephritis)
Dosing		
CL_{Cr} >50 mL/min	1.5 g i.v. q8h	2.5 g i.v. q8h
CL_{Cr} 30–50 mL/min[a]	750 mg i.v. q8h	1.25 g i.v. q8h
CL_{Cr} 15–29 mL/min[b]	375 mg i.v. q8h	0.94 g i.v. q12h
CL_{Cr} 6–15 mL/min	N/A	0.94 g i.v. q24h
CL_{Cr} ≤5 mL/min	N/A	0.94 g i.v. q48h
ESRD on HD	Load 750 mg i.v. × 1, then 150 mg i.v. q8h	N/A
Infusion time	1 h	2 h
Ratio of cephalosporin to BLI	2:1 ceftolozane:tazobactam	4:1 ceftazidime:avibactam
Pregnancy category	B	B
Hepatic dosage adjustment	No	No
Drug interactions	No clinically significant CYP450 interactions. No other enzymatic interactions anticipated	No clinically significant CYP450 interactions. Avibactam is a substrate of OAT1 and OAT3. Whilst not studied, avoid probenecid.
In vivo[c] Gram-negative activity	*Enterobacter cloacae* *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Proteus mirabilis* *Pseudomonas aeruginosa*	*Citrobacter freundii* *Citrobacter koseri* *Enterobacter aerogenes* *Enterobacter cloacae* *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Proteus mirabilis* *Pseudomonas aeruginosa*
In vivo[c] anaerobic activity	*Bacteroides fragilis*	N/A
β-Lactamase activity	Class A (TEM, SHV, CTX-M) Class C (AmpC) Class D (OXA)	Class A (TEM, SHV, CTX-M) Class C (AmpC) Class D (OXA) Carbapenemases (KPC)

cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; CL_{Cr}, creatinine clearance; i.v., intravenous; q8h, every 8 h; q12h, every 12 h; N/A, not available; q24h, every 24 h; q48h, every 48 h; ESRD, end-stage renal disease; HD, haemodialysis; BLI, β-lactamase inhibitor; OAT, organic anion transporters.

[a] For ceftazidime/avibactam, the CL_{Cr} range is 31–50 mL/min.

[b] For ceftazidime/avibactam, the CL_{Cr} range is 16–30 mL/min.

Liscio JL, Int J Antimicrob Agents. 2015 Sep;46(3):266-71.

Ceftolozane/Tazobactam Overview

Class

- Antipseudomonal cephalosporin + β-lactamase inhibitor
- Fixed 2:1 ratio

Mechanism of action

- Rapidly bactericidal
- Inhibits cell-wall synthesis
- Active against *Pseudomonas aeruginosa* with porin deficiencies or mutations
- Inhibits β-lactamases, broadens coverage against most ESBL-producing Enterobacteriaceae

In vitro activity

- ***P. aeruginosa*, including drug-resistant strains**
- ***Escherichia coli*, including ESBL-positive strains**
- ***Klebsiella pneumoniae*, including ESBL-positive strains**
- Limited activity against Gram-positive bacteria
- Activity against select anaerobes
- **No activity against KPC, MBL-producers**

Development stage

- **US FDA approved for treatment of cIAI and cUTI**
- **Phase 3 trial underway for nosocomial pneumonia**

Pharmacokinetics of ceftolozane

- Linear PK
- Lung penetration
- Rapid tissue distribution
- Minimal accumulation
- Extensive renal excretion
- Low protein binding
- Minimal CYP450 drug-drug interactions

Zhanel et al. *Drugs.* 2014;74:31-51. ZERBAXA [prescribing information]. Cubist Pharmaceuticals; Lexington, MA; 2014.

Ceftazidime/avibactam

- **C/A was approved for the treatment of cIAI and cUTI**
- Avibactam can inhibit a broader class of ESBLs and thus C/A is active in vitro against class A (TEM, SHV, CTX-M) and some class C (AmpC) and class D (OXA) -lactamases
- It is not active against the MBLs (NDM-1, IMP, VIM).
- **It is the first beta-lactam/BLI to retain activity against KPC carbapenemase-producing isolates.**

Liscio JL, Int J Antimicrob Agents. 2015 Sep;46(3):266-71.

In vitro activity of new agents against staphylococci and therapeutic indications

Drugs	Class	MRSA	VISA	VRSA	Indication
Ceftaroline	β-lactam	++	++	++	ABSSSI/CAP
Ceftobiprole	β-l**a**ctam	++	++	++	CAP/HAP
Dalbavancin	lipoglyco-peptide	++	++	+	ABSSSI
Oritavancin	lipoglyco-peptide	++	++	++	ABSSSI
Tedizolid	oxazolidinone	++	++	++	ABSSSI
Telavancin	lipoglyco-peptide	++	++	+	SSSI/HAP/VAP

Zhanel GG; Drugs. 2010 May 7;70(7):859-86.
Kaushik D; Int J Antimicrob Agents. 2011 May;37(5):389-95.

In vitro activity of new agents against staphylococci and therapeutic indications

Drugs	Class	MRSA	VISA	VRSA	Indication
Ceftaroline	β-lactam	++	++	++	ABSSSI/CAP
Ceftobiprole	β-l**a**ctam	++	++	++	CAP/HAP
Dalbavancin	**lipoglyco-peptide**	**++**	**++**	**+**	**ABSSSI**
Oritavancin	lipoglyco-peptide	++	++	++	ABSSSI
Tedizolid	**oxazolidinone**	**++**	**++**	**++**	**ABSSSI**
Telavancin	lipoglyco-peptide	++	++	+	SSSI/HAP/VAP

Zhanel GG; Drugs. 2010 May 7;70(7):859-86.
Kaushik D; Int J Antimicrob Agents. 2011 May;37(5):389-95.

Dalbavancin - Phase 3 Study Program

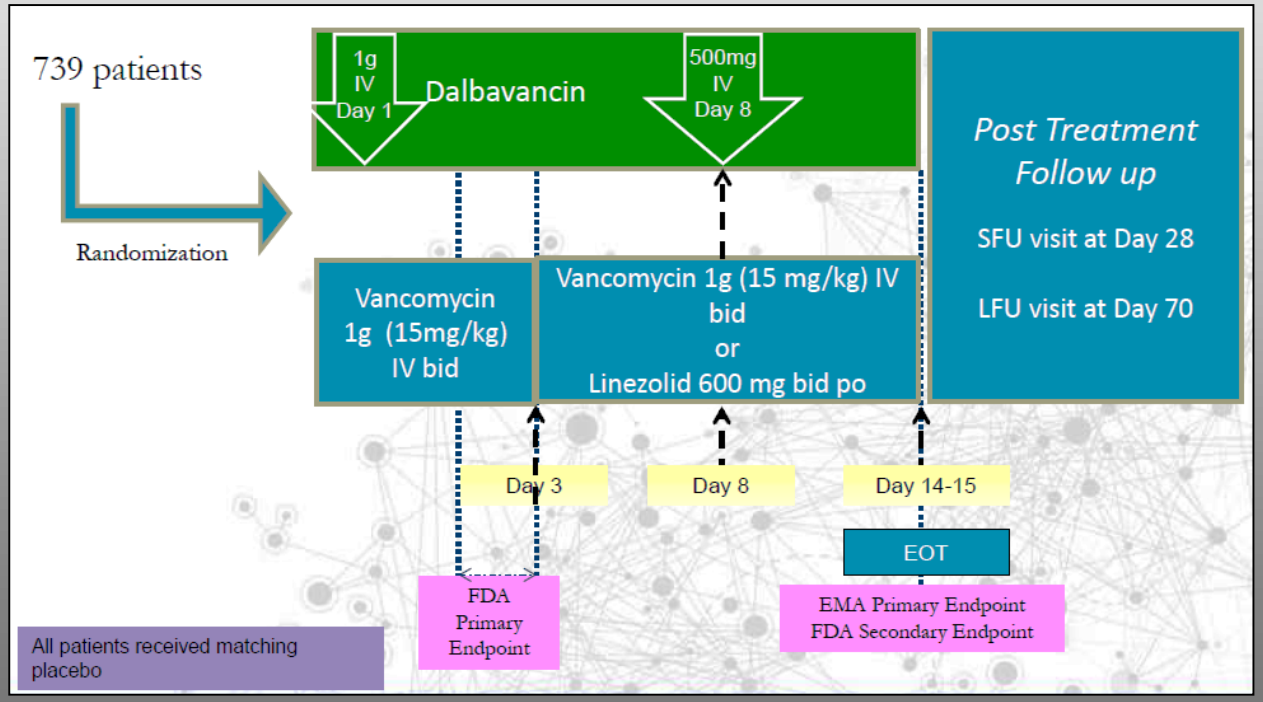
Dalbavancin for **I**nfections of the **S**kin **CO**mpared to **V**ancomycin at an **E**arly **R**esponse

Characteristic	Dalbavancin (N=659)	Vancomycin / Linezolid N=653
(cm²) Area of Infection, median	324.0	366.8
(%) Type of infection		
Cellulitis	53.7	53.4
Major abscess	24.6	26.5
Traumatic wound/ Surgical site	21.5	20.1
(%) Systemic signs of infection		
≥ 38°C (100.4 F)	84.6	85.0
>12,000 cells/mm³) WBC	39.4	40.3
(≥10%) Immature WBC forms (bands)	23.2	22.6

Dalbavancin - Phase 3 study design

Primary Endpoint: early response at 48-72 hours post initiation of therapy cessation of spread of the erythema of the lesion, and resolution of fever.

Secondary Endpoint: Clinical Status at End of Therapy (Day 14-15, EMA primary endpoint).



Tedizolid profile

Class

- Novel oxazolidinone administered as a microbiologically inactive prodrug (tedizolid phosphate)

Mechanism of action

- Binds to the 50S subunit of the bacterial ribosome, resulting in inhibition of protein synthesis

Overview

- Efficacy in ABSSSI in a 6-day course in all patients
- Once daily treatment - 200 mg - IV and PO
- No required dose adjustments or drug monitoring

SIVEXTRO [US prescribing information]. Cubist Pharmaceuticals; Lexington, MA; 2014.

Summary of Completed Tedizolid Clinical Development Studies

Phase 2 Studies

Study	Dose and Regimen	Purpose	No. of Subjects enrolled
TR701-104[1]	Oral 200, 300, or 400 mg tedizolid phosphate once daily for 5-7 days	Clinical and microbiological response, safety, population PK	192
TR701-126[2]	Oral 200 mg tedizolid phosphate FA once daily for 6 days	Safety and exploratory skin lesion measurement	200

Phase 3 Studies

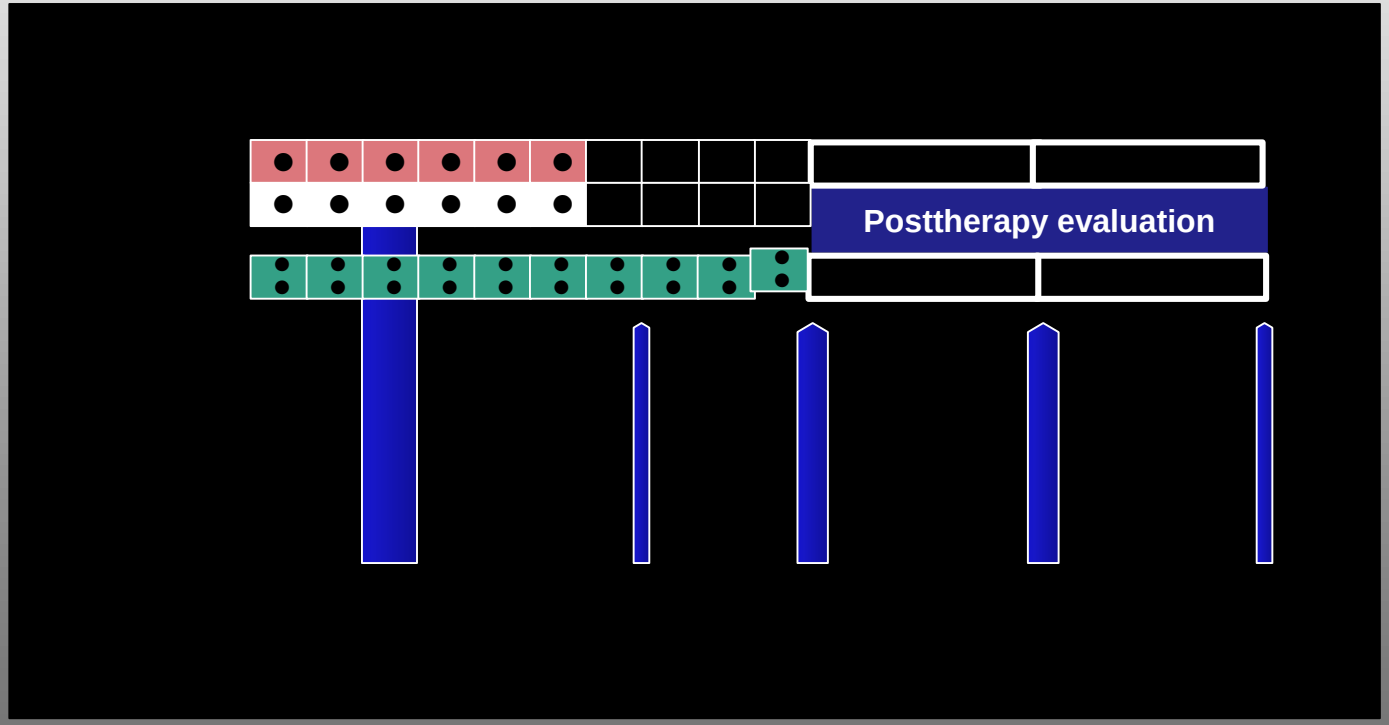
Study	Dose and Regimen	Purpose	No. of Subjects enrolled
TR701-112[3] (ESTABLISH-1)	**Oral 200 mg tedizolid phosphate FA once daily for 6 days or 600 mg linezolid twice daily for 10 days**	**Efficacy, safety, population PK in the treatment of ABSSSI**	**667**
TR701-113[4] (ESTABLISH-2)	**IV to oral 200 mg tedizolid phosphate FA once daily for 6 days or IV to oral 600 mg linezolid twice daily for 10 days**	**Efficacy and safety in the treatment of ABSSSI**	**666**

ABSSSI= acute bacterial skin and skin structure infections; FA= free acid; IV= Intravenous; PK = pharmacokinetics.

1. Prokocimer P, et al. *Antimicrob Agents Chemother.* 2011; 55(2): 583–592.
2. http://www.clinicaltrials.gov/ct2/show/NCT01519778?term=tr701-126&rank=1 (Assessed 25 Sep 2014).
3. Prokocimer P, et al. *JAMA.* 2013;309:559-569. 4. Moran GJ, et al. *Lancet Infect Dis.* 2014 ;14:696-705.

Design of Phase 3 Studies

- ESTABLISH-1: Oral tedizolid phosphate 200 mg QD x 6 days (with placebo dose to match BID administration of comparator arm), then 4 days of placebo BID
- ESTABLISH-2: Intravenous (IV) then oral tedizolid phosphate 200 mg QD x 6 days (with placebo dose to match BID administration of comparator arm), then 4 days of placebo BID
- Comparator: Linezolid 600 mg every 12 hours for 10 days (route to match tedizolid phosphate delivery)

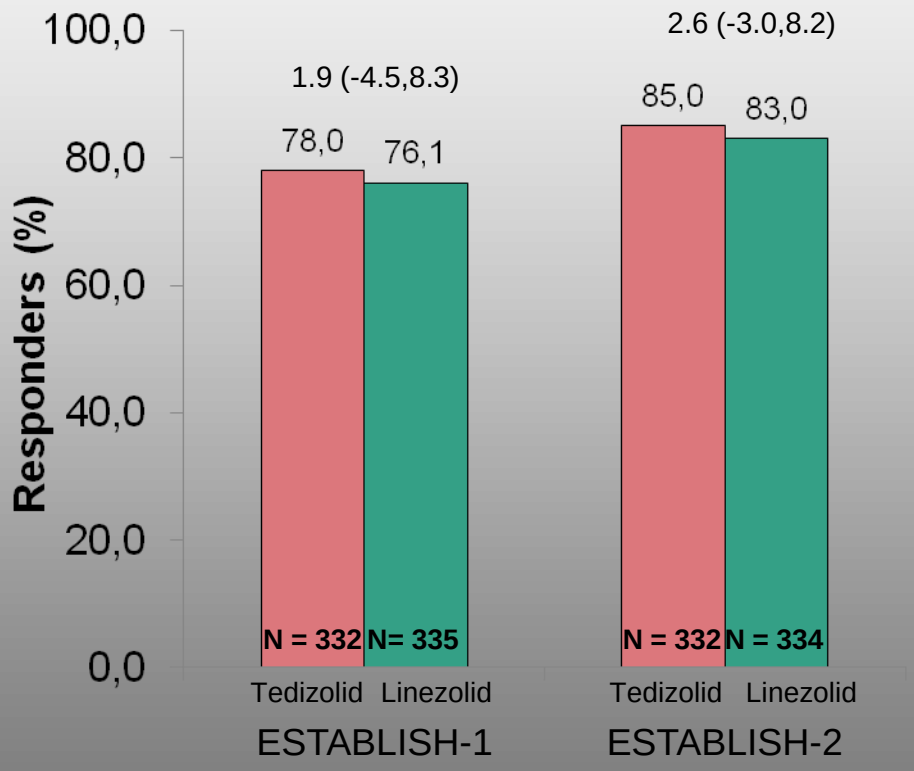


bid = twice-daily dosing; EOT = end of therapy; LFU = late follow up; PTE = posttherapy evaluation; qd = once-daily dosing.

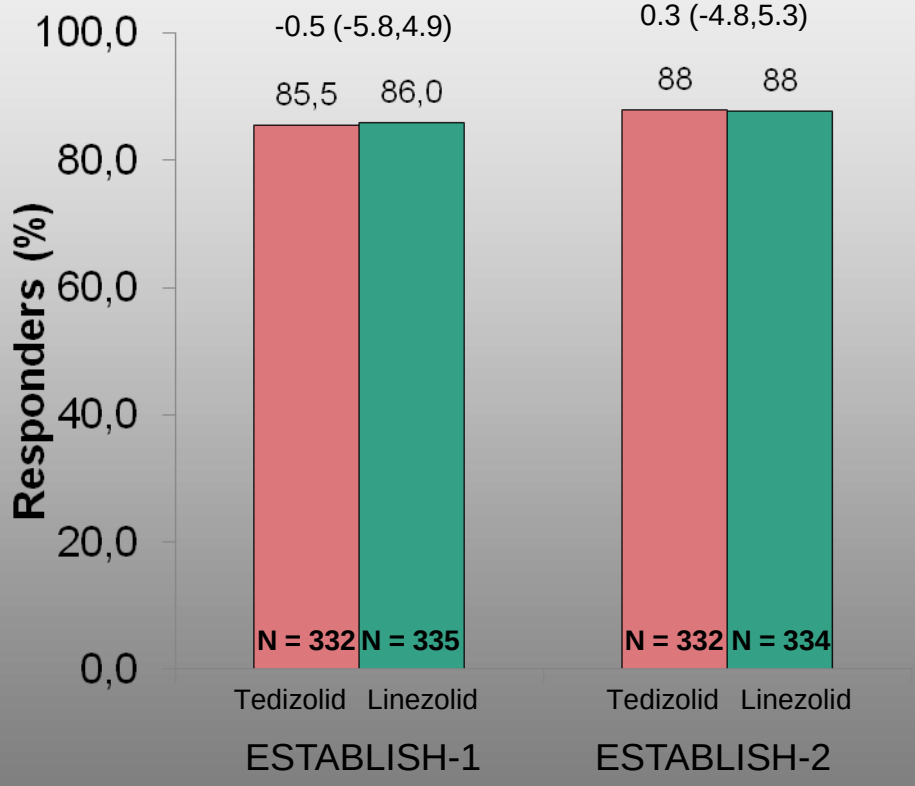
1. Prokocimer P, et al. *JAMA.* 2013;309:559-569. 2. Moran GJ, et al. *Lancet Infect Dis.* 2014 ;14:696-705.

ESTABLISH-1 and ESTABLISH-2 Efficacy Analysis

≥20% decrease from baseline in lesion area at 48-72 hours[1,2]



Investigator assessment of clinical response at PTE[1,2,3]

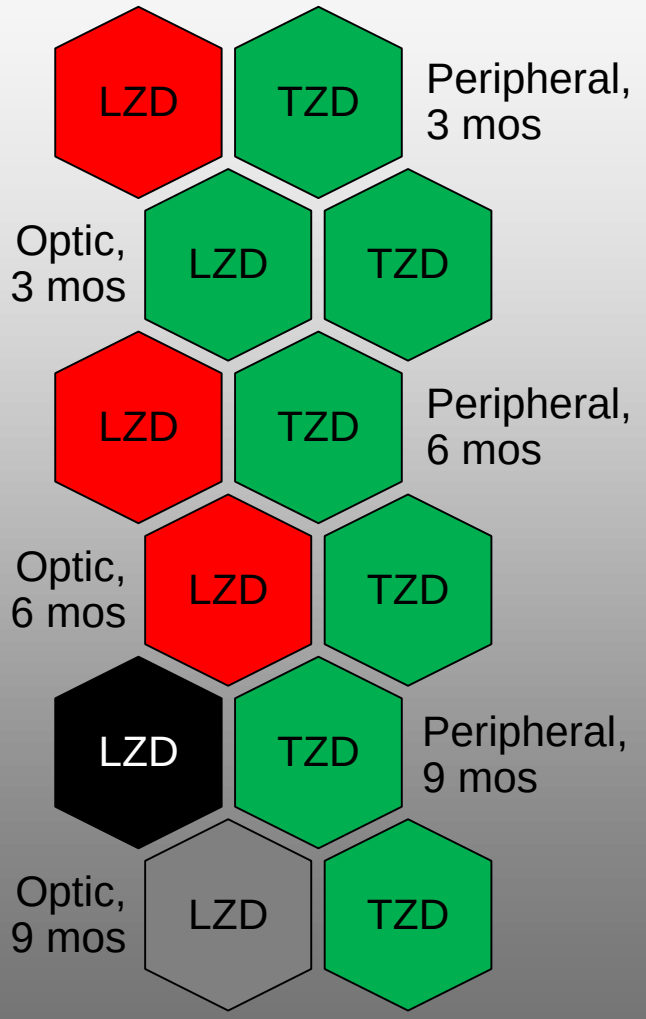


ITT population. ITT=intent-to-treat; PTE = posttherapy evaluation.

1. Prokocimer P, et al. *JAMA.* 2013;309:559-569. 2. Moran GJ, et al. *Lancet Infect Dis.* 2014 ;14:696-705.

Peripheral and Optic Neuropathy Non clinical Rat Models

- Tedizolid (TZD): dosed up to 8.4-fold higher than daily human exposure at 200 mg dose[1]
- Linezolid (LZD): dosed at the equivalent to the daily human exposure of 1200 mg[2]



1. Hosako H, et al. ICAAC 2013. A-017b. 2. Zyvox [prescribing information]. Pfizer Inc: New York, NY; 2014.

ORIGINAL ARTICLE 10.1111/1469-0691.12632

Pan-European early switch/early discharge opportunities exist for hospitalized patients with methicillin-resistant *Staphylococcus aureus* complicated skin and soft tissue infections

D. Nathwani[1], C. Eckmann[2], W. Lawson[3], J. M. Stephens[4], C. Macahilig[5], C. T. Solem[4], D. Simoneau[6], R. Chambers[7], J. Z. Li[8] and S. Haider[9]

Article published online: 27 March 2014

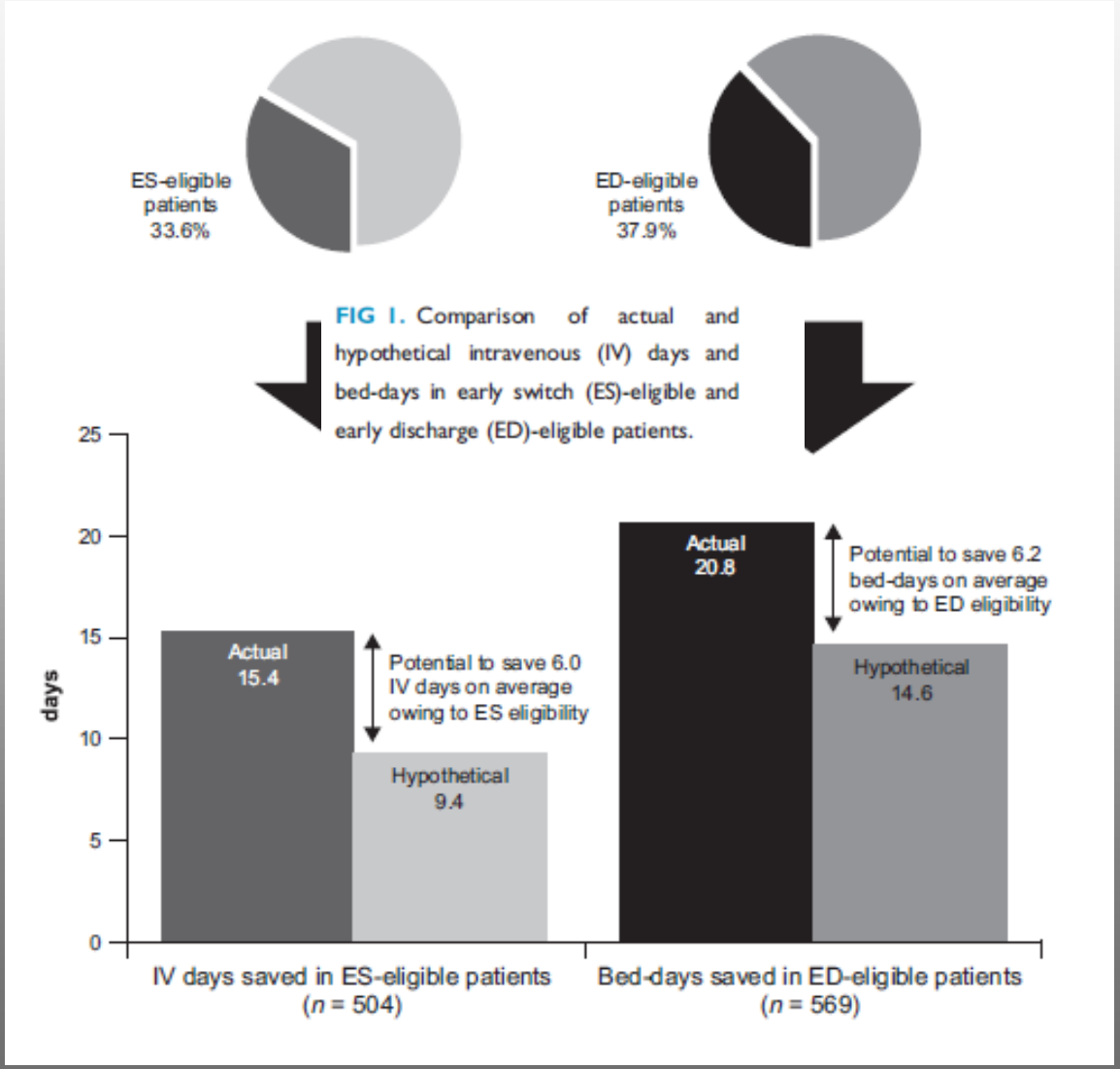
Clin Microbiol Infect

The objective of this study was to document pan-European real-world treatment patterns and healthcare resource use and estimate opportunities for early switch (ES) from intravenous (IV) to oral antibiotics and early discharge (ED) in hospitalized patients with methicillin-resistant *Staphylococcus aureus* (MRSA) complicated skin and soft tissue infections (cSSTIs). This retrospective observational medical chart review study enrolled 342 physicians across 12 European countries who collected data from 1542 patients with documented MRSA cSSTI who were hospitalized (July 2010 to June 2011) and discharged alive (by July 2011). Data included clinical characteristics and outcomes, hospital length of stay (LOS), MRSA-targeted IV and oral antibiotic use, and ES and ED eligibility according to literature-based and expert-validated criteria. The most frequent initial MRSA-active antibiotics were vancomycin (50.2%), linezolid (15.1%), clindamycin (10.8%), and teicoplanin (10.4%). Patients discharged with MRSA-active antibiotics (n = 480) were most frequently prescribed linezolid (42.1%) and clindamycin (19.8%). IV treatment duration (9.3 ± 6.5 vs. 14.6 ± 9.9 days; p <0.001) and hospital LOS (19.1 ± 12.9 vs. 21.0 ± 18.2 days; p 0.162) tended to be shorter for patients switched from IV to oral treatment than for patients who received IV treatment only. Of the patients, 33.6% met ES criteria and could have discontinued IV treatment 6.0 ± 5.5 days earlier, and 37.9% met ED criteria and could have been discharged 6.2 ± 8.2 days earlier. More than one-third of European patients hospitalized for MRSA cSSTI could be eligible for ES and ED, resulting in substantial reductions in IV days and bed-days, with potential savings of €2000 per ED-eligible patient.

Early switch and early discharge criteria

ES eligibility	At minimum, the following key criteria needed to be met prior to actual IV discontinuation: • Stable clinical infection • Afebrile/temperature of <38°C for 24 h • WBC count normalizing, WBC count not <4 × 10^9/L or >12 × 10^9/L • No unexplained tachycardia • Systolic blood pressure of ≥100 mm Hg • Patient tolerates PO fluids/diet and able to take PO medications with no gastrointestinal absorption problems Additional criteria related to ES that were assessed, but not required to be documented, included: • Available bacteriology for cSSTI caused by MRSA that is sensitive to PO treatment • Available bacteriology for cSSTI caused by MRSA that is sensitive to OPAT • No surgery scheduled within the next 36 h • No requirement for IV line other than administration of IV antibiotic therapy
ED eligibility	At minimum, the following criteria needed to be met prior to discharge: • All key ES eligibility criteria listed above • No other reason to stay in hospital except infection management Additional criteria related to ED that were assessed, but not required to be documented, included: • Stable mental status • Stable comorbid illnesses • Stable social situation

Comparison of actual and hypothetical intravenous days and bed-days in ealrly switch -eligible and early discharge -eligible patients



Alternative clinical indications for novel antibiotics licensed for skin and soft tissue infection?

Matthew S. Dryden

Curr Opin Infect Dis 2015, 28:117–124

KEY POINTS

- Licensed indications for novel antibiotics are very narrow, and in reality they are likely to be used in much broader clinical contexts: prosthetic device infection, endocarditis, early surgical sepsis, osteomyelitis, orthopaedic and vascular graft infection.
- Linezolid and tedizolid have the potential to avoid the use of i.v. antibiotics altogether in the treatment of SSTIs.
- Drugs with longer half-lives and oral agents have the potential to reduce hospital costs, avoid admission and be more acceptable to patients.
- Ceftaroline and ceftobiprole could play useful roles in early complex surgical sepsis in empirical treatment of vulnerable patients with comorbidities and in combination with daptomycin.
- Tigecycline should be used more widely in SSTI, intra-abdominal infection and possibly hospital-acquired pneumonia, as a carbapenem-sparing agent as part of diverse prescribing in an antimicrobial stewardship programme.

Table 1. Novel antibiotics licensed for complicated skin and soft tissue infection and other potential clinical indications

Antibiotic	Route	Specific advantages	Potential clinical indications requiring further evidence
Linezolid	Oral and i.v.	Oral, reduce LOS and i.v.	PJI, osteomyelitis, other prosthetic device infection, infections caused by toxin producing organisms, pneumonia and MDR TB
Tedizolid	Oral and i.v.	Short course, possibly low toxicity, reduce LOS and i.v.	PJI, osteomyelitis, other prosthetic device infection, infections caused by toxin producing organisms, pneumonia, paediatric gram-positive infection and infection in renal patients
Daptomycin	i.v.	Narrow spectrum	Bacteraemia, endocarditis, combination use with ceftaroline and PJI with rifampicin
Oritavancin	i.v.	Single-dose minimal i.v. requirement and OPAT	Endocarditis, osteomyelitis and PJI, CAPD peritonitis
Dalbavancin	i.v.	Weekly dose OPAT	Prosthetic device infection, osteomyelitis and CAPD peritonitis
Ceftaroline and ceftobiprole	i.v.	Broader spectrum	Empirical treatment of infections with unknown microbial cause, unclear source, patient with comorbidity, meningitis, endocarditis and combination use
Tigecycline	i.v.	Broader spectrum	Carbapenem sparing, unknown microbial cause, unclear source, patient with comorbidity and combination use

CAPD, continuous ambulatory peritoneal dialysis; LOS, length of stay; MDR TB, multidrug-resistant tuberculosis; OPAT, outpatient parenteral antibiotic therapy; PJI, prosthetic joint infection.

- **Era pre-antibiotica fino al 1940**
- **Era antibiotica 1940 - 2000**
- **Era post-antibiotica 2000 – 2015**
- **Nuova era antibiotica……**