2017 MOTORE SANITÀ
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NUOVI APPROCCI
ALL'ANTIBIOTICO-TERAPIA:
dalla **gestione clinica**
alla **sostenibilità**
del **sistema**

20 aprile 2017 Padova
Caffè Pedrocchi, Sale Egizia e Rossini - Piano Nobile
Via VIII Febbraio 15

FEDER SANITÀ anci

AZIENDA OSPEDALIERA UNIVERSITA' PADOVA

Il nuovo scenario dell'antibiotico-terapia

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Our microbes - Some important facts

Our microbe are part of human life, living on all the surfaces and cavites of the human body

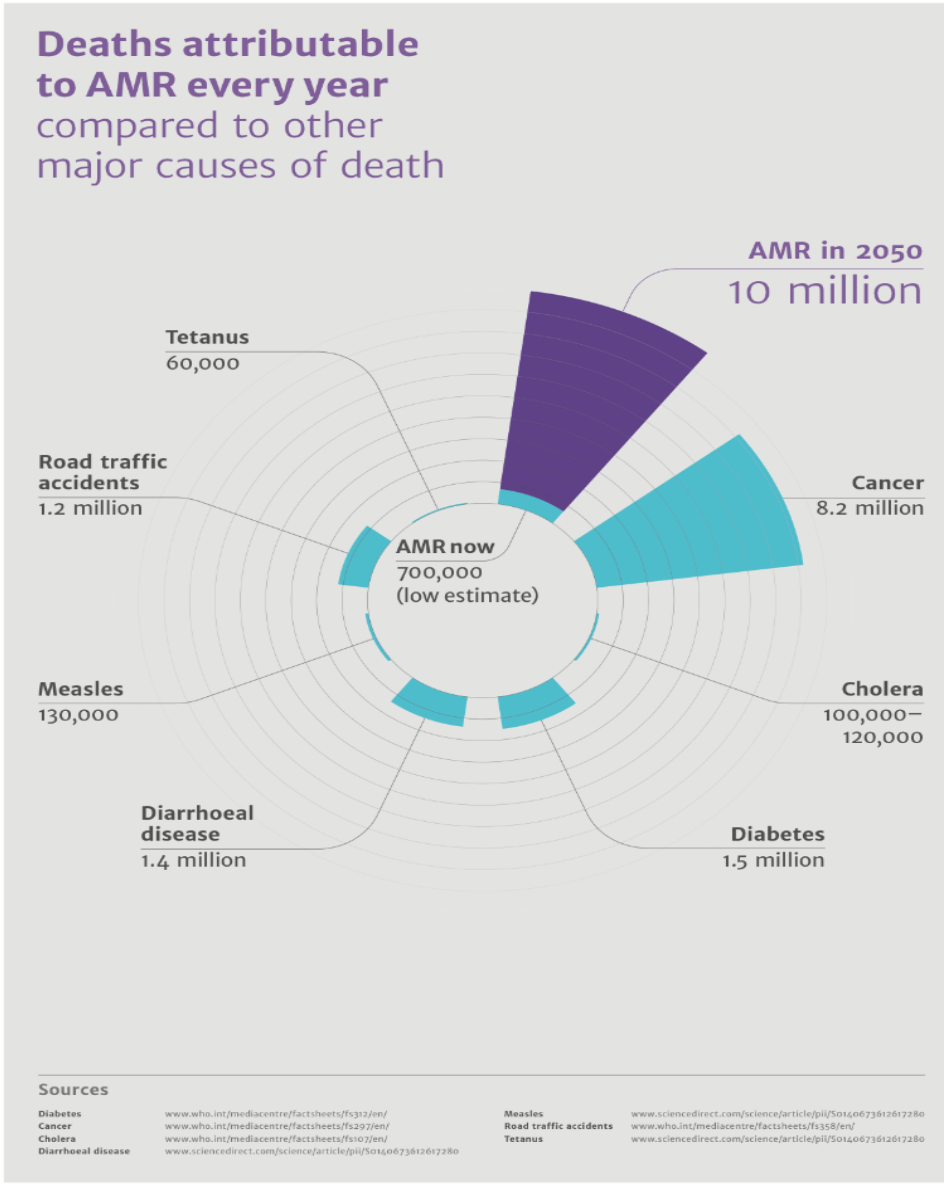
Majority of these microbes are found in the gut (but those located at other sites can also have significant roles)

Table 1 Diversity of recent microbiome research, which has focused mainly on the gut

	Publications	
Terms	All	2011–2016
Gut | colon | intestinal	17,546	10,707
0ral | mouth | tongue | tooth | subgingival | supragingival	4843	2089
Urogenital | vaginal | penile	1477	706
Skin | cutaneous	1372	754
Airway | lung	764	524
Placenta | breast milk	702	426
Ocular | eye	152	82

Lloyd-Price et al. Genome Medicine (2016) 8:51

Antimicrobial Resistance (AMR) scenario



10 million extra deaths
Per year by 2050

Macroeconomic loss

8 trillions $ loss per year

100 trillions $ by 2050

AMR Burden of disease in Europe (based on AMR data from 2007 for 5 MDR pathogens

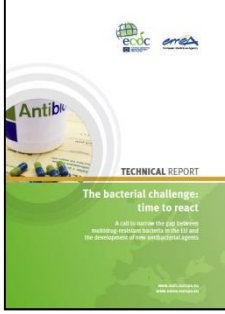


Table 2. Estimated yearly human burden of infections due to the selected antibiotic-resistant bacteria and percentage of this burden due to bloodstream infections, EU Member States, Iceland and Norway, 2007.

Antibiotic-resistant bacteria[a]	No. cases of infection (four main types)[b] (% bloodstream infections)	No. extra deaths (% from bloodstream infections)	No. extra hospital days (% from bloodstream infections)
Antibiotic-resistant Gram-positive bacteria			
Methicillin-resistant *Staphylococcus aureus* (MRSA)	171 200 (12%)	5 400 (37%)	1 050 000 (16%)
Vancomycin-resistant *Enterococcus faecium*	18 100 (9%)	1 500 (28%)	111 000 (22%)
Penicillin-resistant *Streptococcus pneumoniae*[c]	3 500 (27%)	–[f]	–
Sub-total	*192 800 (12%)*	*6 900 (35%)*	*1 161 000 (16%)*
Antibiotic-resistant Gram-negative bacteria			
Third-generation cephalosporin-resistant *Escherichia coli*[d]	32 500 (27%)	5 100 (52%)	358 000 (27%)
Third-generation cephalosporin-resistant *Klebsiella pneumoniae*	18 900 (27%)	2 900 (52%)	208 000 (27%)
Carbapenem-resistant *Pseudomonas aeruginosa*[e]	141 900 (3%)	10 200 (7%)	809 000 (3%)
Sub-total	*193 300 (9%)*	*18 200 (27%)*	*1 375 000 (13%)*
Total	386 100 (11%)	25 100 (29%)	2 536 000 (14%)

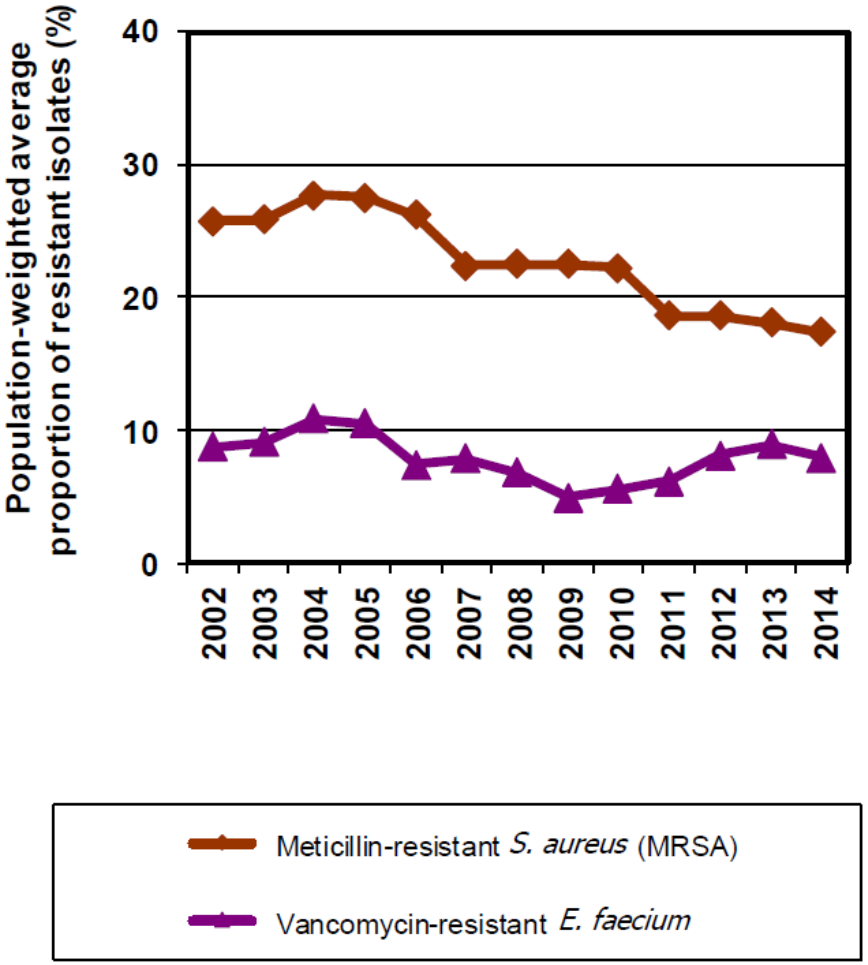
25.000 extra deaths

2.5 Million extra hospital days

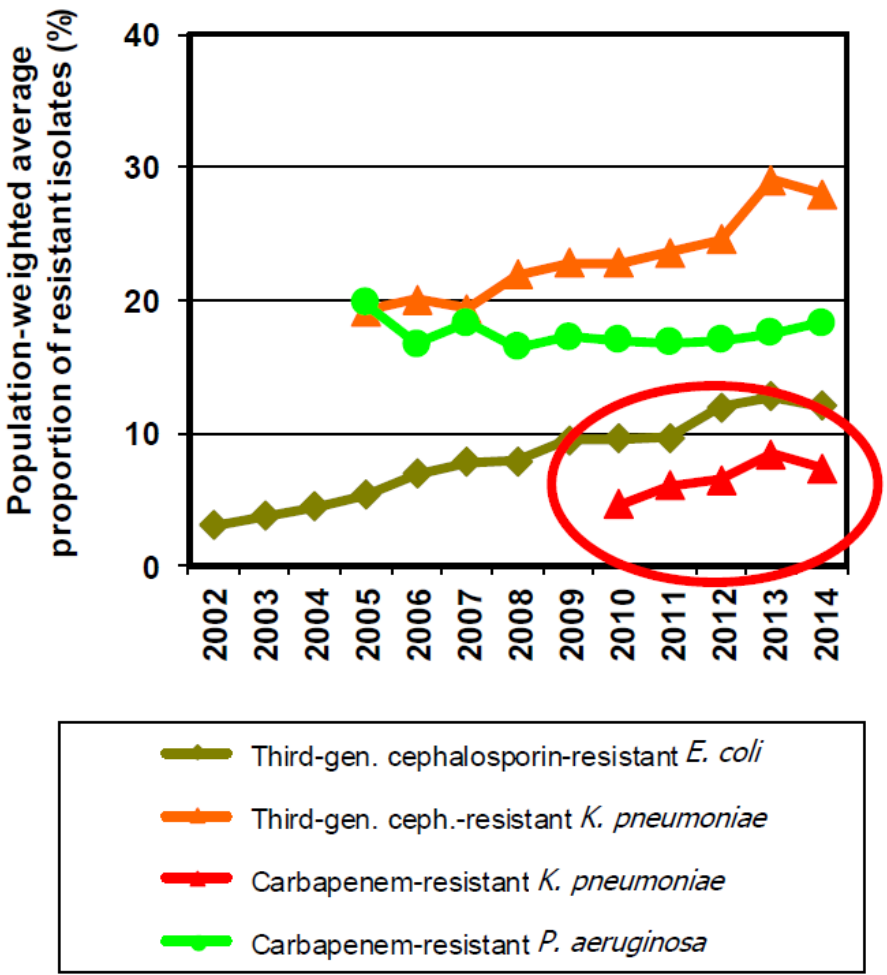
1.5 Billion EURO of extra hospital costs and loss of productivity

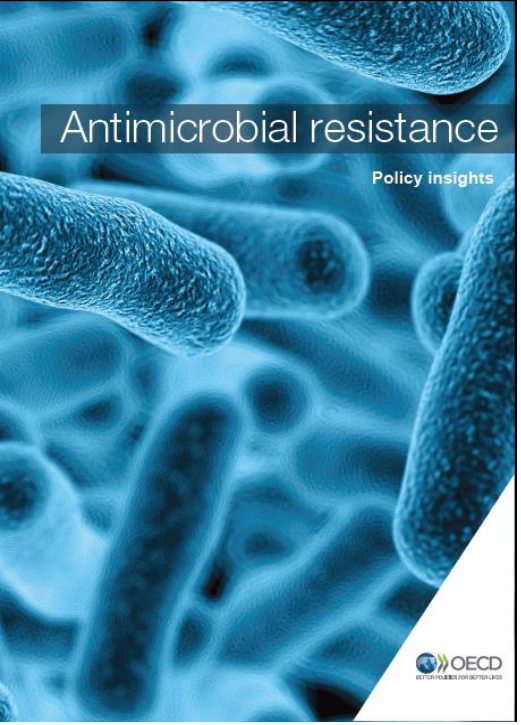
Population-weighted, average %resistant isolates among bacteria from bloodstream infections, EU/EEA, 2002-2014

Gram-positive bacteria



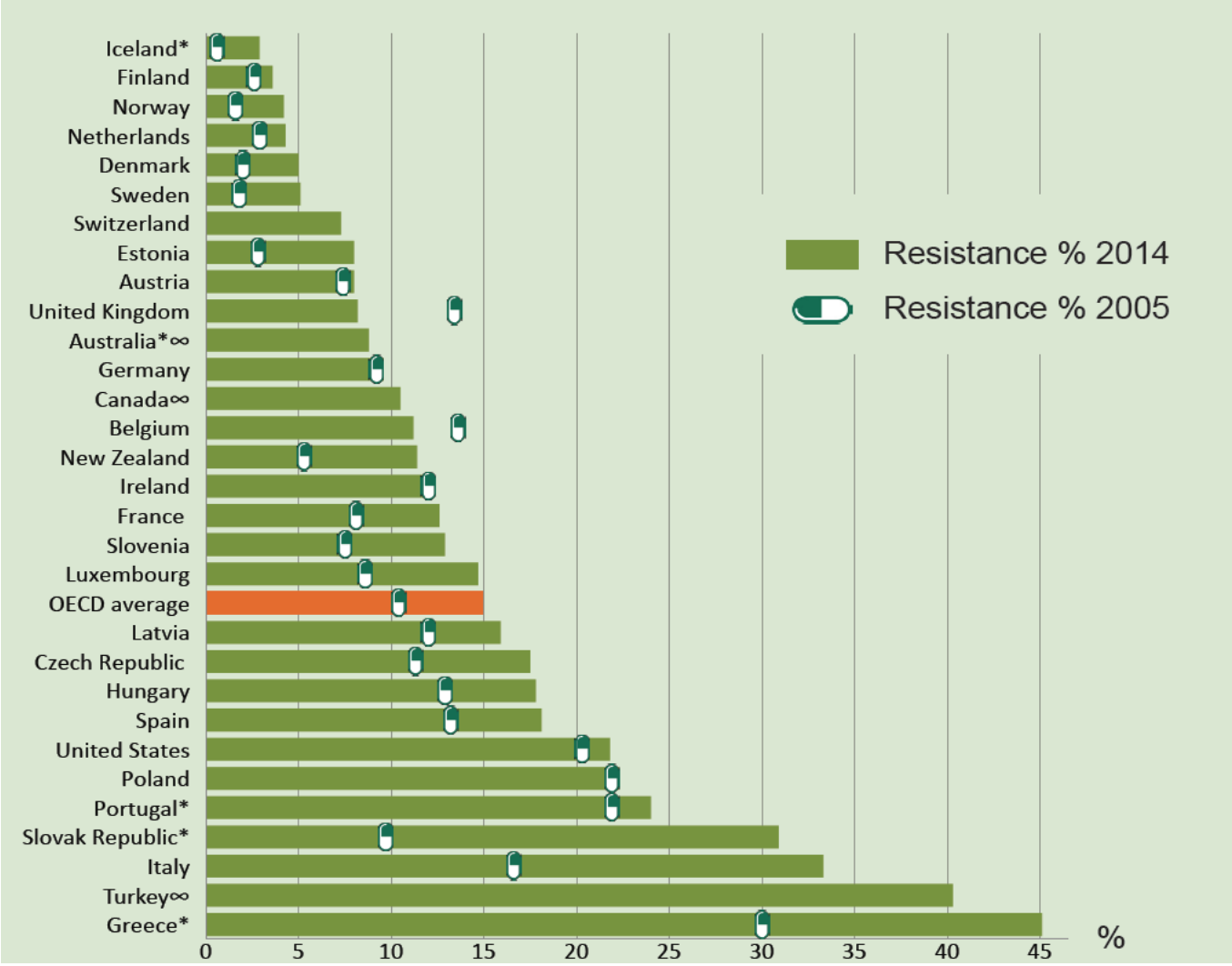
Gram-negative bacteria





Trends across OECD countries

Antibiotic resistance is growing

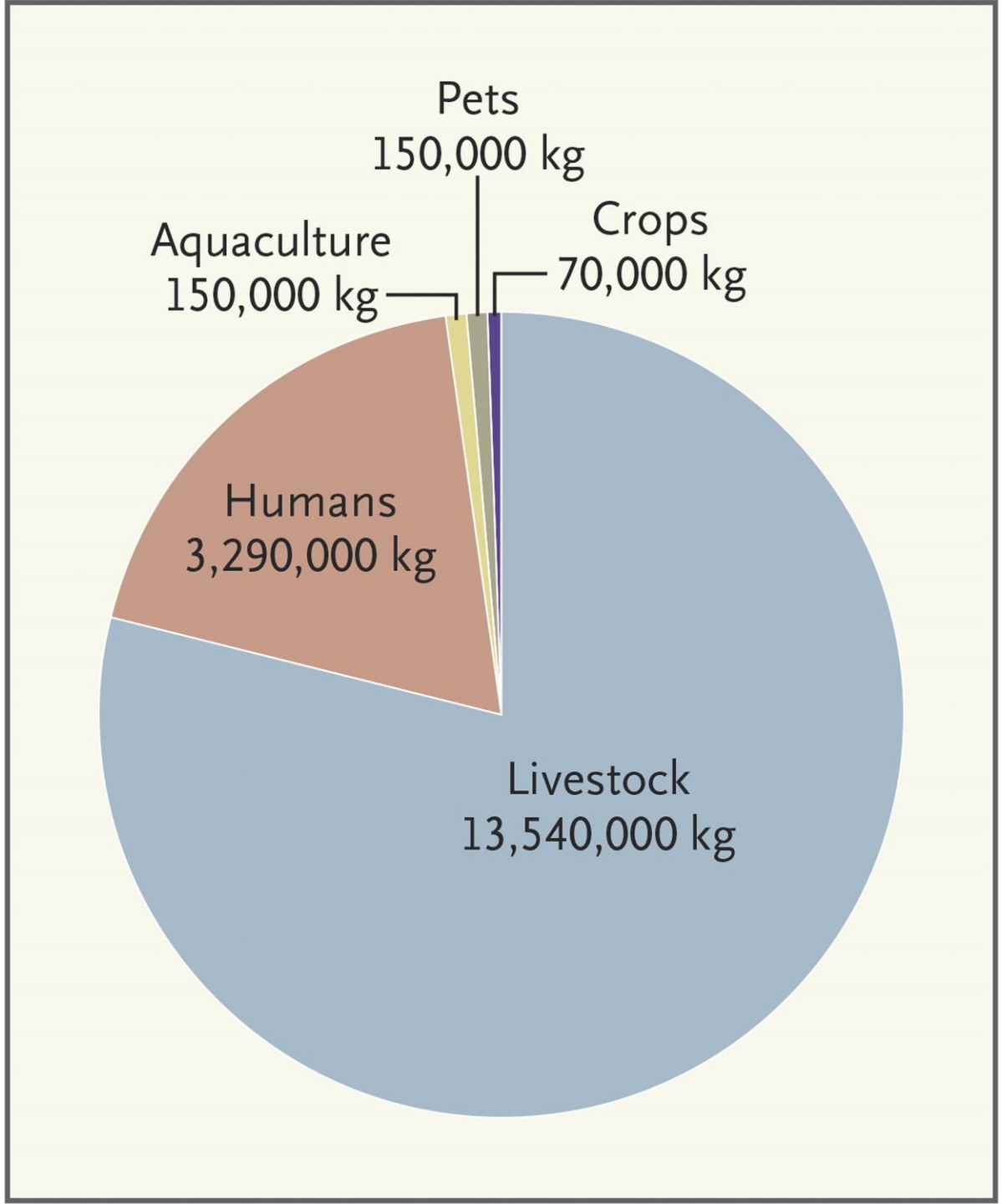


In Italia l'antibioticoresistenza è raddoppiata tra il 2005 e il 2014

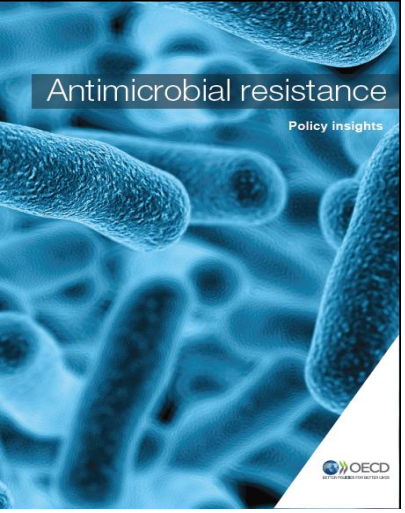
USE OF ANTIBIOTICS

Where antibiotics Are used	Types of use	Questionable use
Human use (50%)	**20% Hospital** **80% Community**	**20-50% Unnecessary**
Agricultural use (50%)	**20% Therapeutic** **80% Prophylactic /growth promotion**	**40-80% Highly questionable**

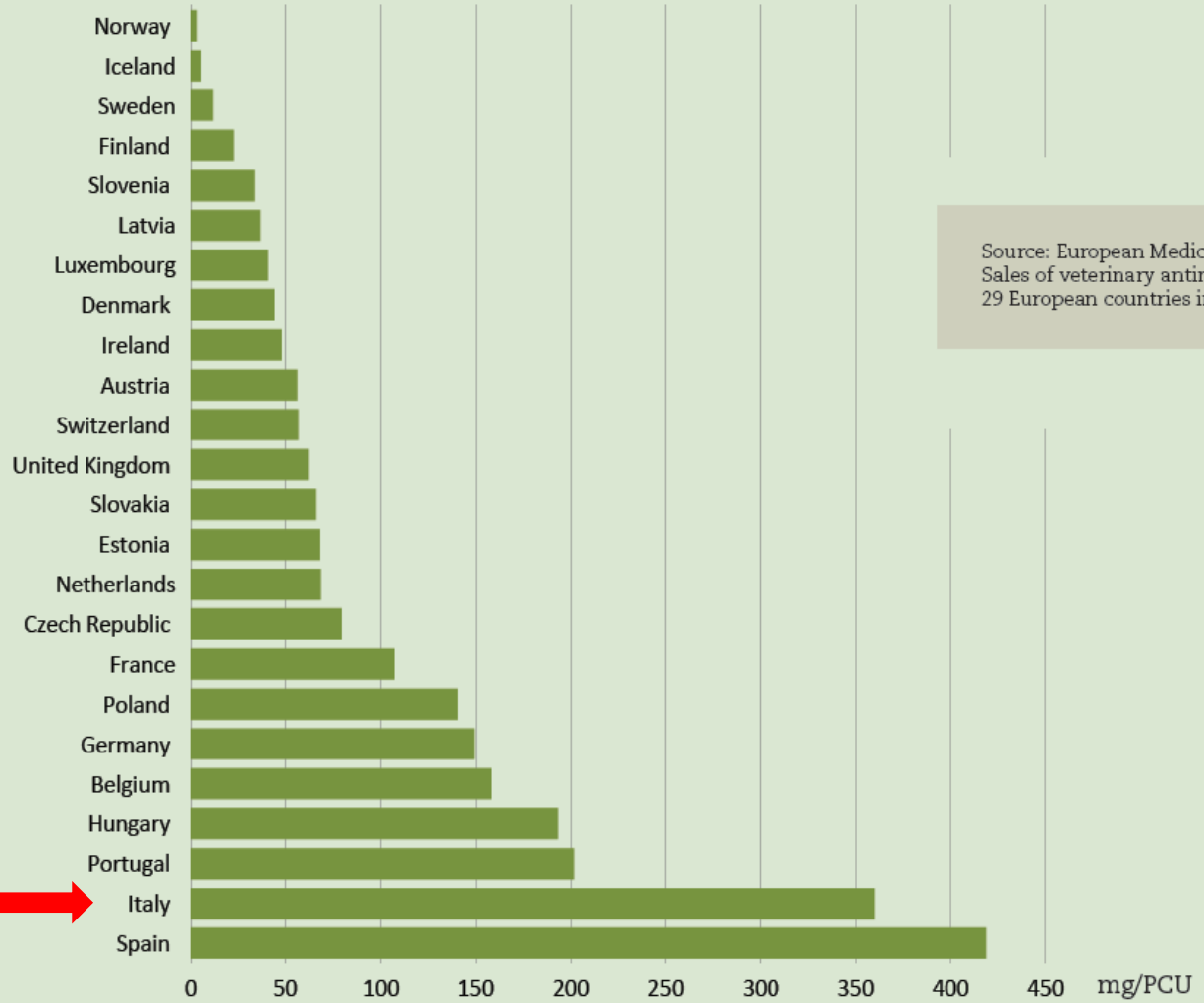
P.F Harrison 1998


Pets
150,000 kg
Crops
70,000 kg
Aquaculture
150,000 kg
Humans
3,290,000 kg
Livestock
13,540,000 kg

USA 2013



Consumption of antibiotics in agriculture accounts for the majority of total antibiotic use



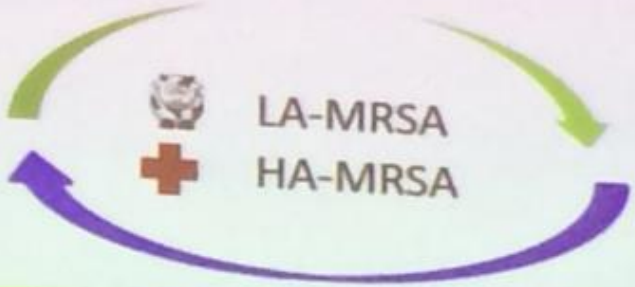
Source: European Medicines Agency (2016). Sales of veterinary antimicrobial agents in 29 European countries in 2014.

Percentuali di resistenza riscontrate nei POLLI

AMPICILLINA	73
CEFOTAXIME	19
GENTAMICINA	62
STREPTOMICINA	65
TETRACICLINE	62
TRIMETOPRIM	65
CIPROFLOXACINA	58
CLORAMFENICOLO	25
COLISTINA	0

Study of MRSA in milk farms in North-East Italy

Comparison of genotypes of MRSA from cow milk and MRSA from nasal carriage of farmers



A	t4208/ ST398	t899/ ST398
C	t032/ ST22	t032/ ST22
E	t899/ ST398	t899/ ST398
G	t127/ST1	t127/ ST1
I	t899/ ST398	t899/ ST398
S	t127/ ST1	t127/ ST1
T	t127/ ST1	t852/ST22
Z	t899/ ST398	t899/ ST398

Skin and soft tissue infections

- **The incidence of ambulatory visits and hospital admissions for SSTIs is increased overtime because of the ageing of the general population, the increased number of critically ill patients, the increased number of immunocompromised patients and the recent emergence of multidrug resistant pathogens**
- **S. aureus is the most common cause of SSTIs worldwide**
- **Infections caused by Methicillin-Resistant St. aureus (MRSA) are associated with increased morbidity, mortality, and costs**

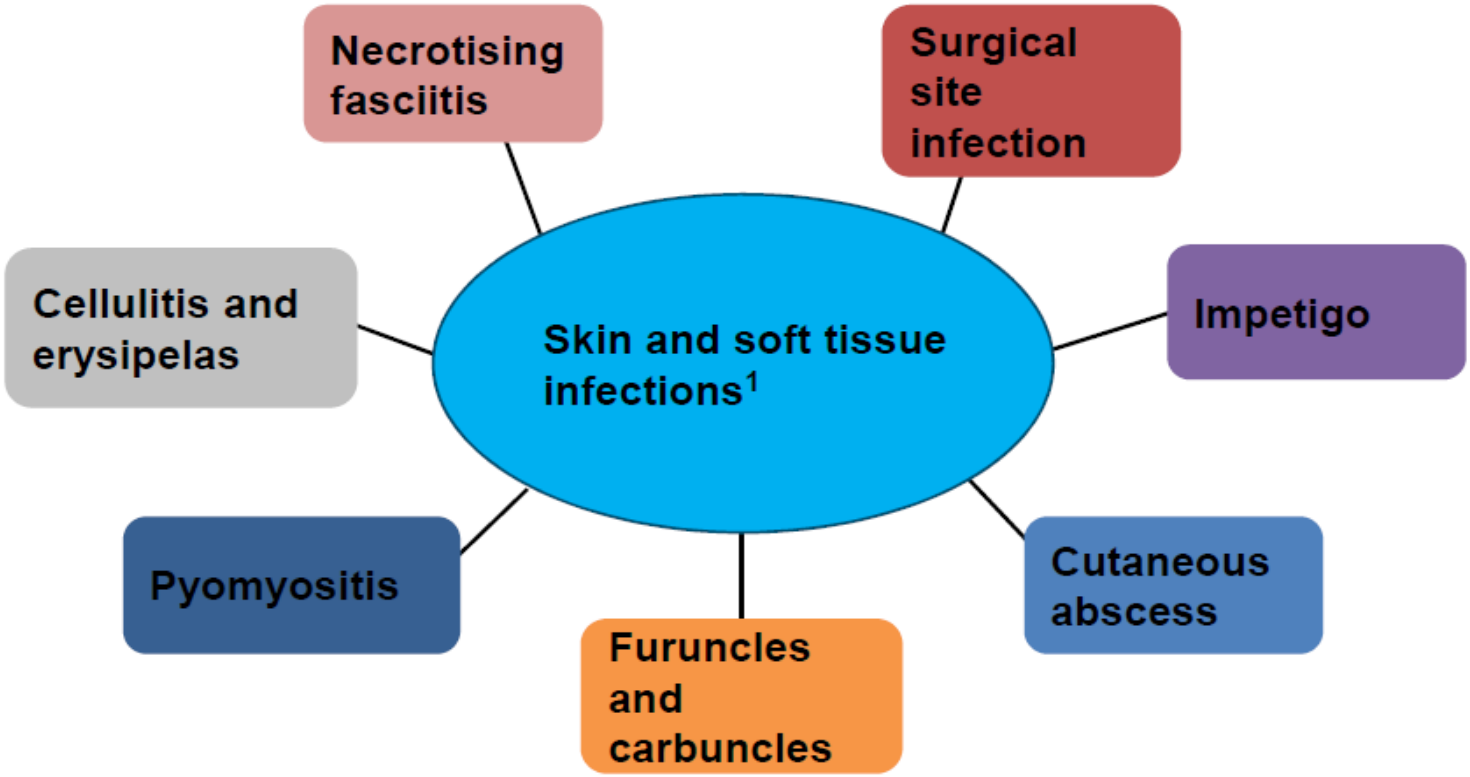
Skin and soft tissue infections

The Food and Drug Administration (FDA) proposed a new classification of skin and soft tissue infections, namely acute bacterial skin and skin structure infections (ABSSSIs), incorporating erysipelas, cellulitis, major subcutaneous abscesses and wound infections.

An ABSSSI is a bacterial infection of the skin with a lesion area of at least 75 cm^2, measured by redness, edema, or induration

Food and Drug Administration. Guidance for industry acute bacterial skin and skin structure infections: developing drugs for treatment. 2013. Available from: http://www.fda.gov/downloads/Drugs/Guidances/ucm071185.pdf. October 2013.

Clinical presentations of skin and soft tissue infections (SSTIs)

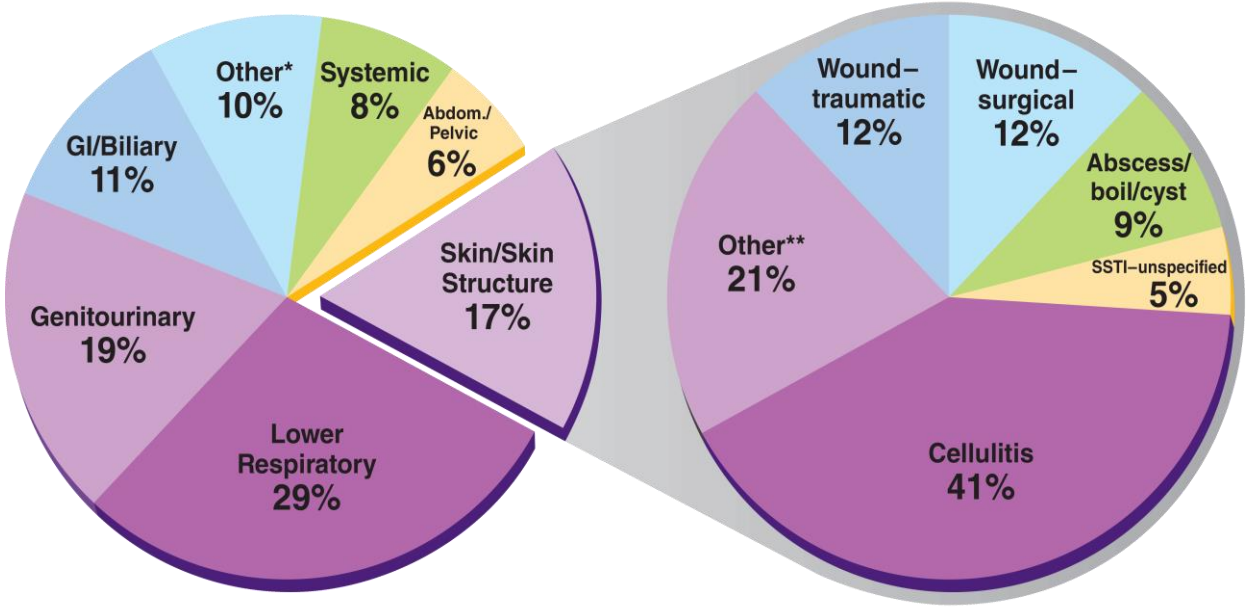


1. May AK, *et al. Surg Infect* 2009;10:467–99; 2. Arias CA, *et al. N Engl J Med* 2009; 360:439–43

Cellulitis, Wound Infection, and Abscess Represent Nearly 13% of All Infections in U.S. Hospitals

- For the six month period of January to June 2010, a projected 9.2 million patients were treated in U.S. hospitals for infections of any type

Percentage of Presentations by Diagnostic Category



Percentage of Presentations by SSSI Diagnosis

Of the presentations for SSSI/SSTI, approximately 74% were disease types that included cellulitis, wound infection, and abscess, without size specification

The Hospital Antibiotic Market Guide–Book 2: Diagnosis and Surgery Reports, January 2010–June 2010. AMR. United States Edition.

* Other diagnostic categories include fever of unknown origin, upper respiratory infections, bone/joint infections, non-surgical prophylaxis, CNS infections, cardiovascular infections and eye infections.

** Other diagnoses include ulcer–diabetic foot/leg, ulcer–decubitus, gangrene, dental infection, burn infection, mastitis and lymphadenitis/lymphangitis

Primi 10 agenti patogeni batterici responsabili in Europa, 2004

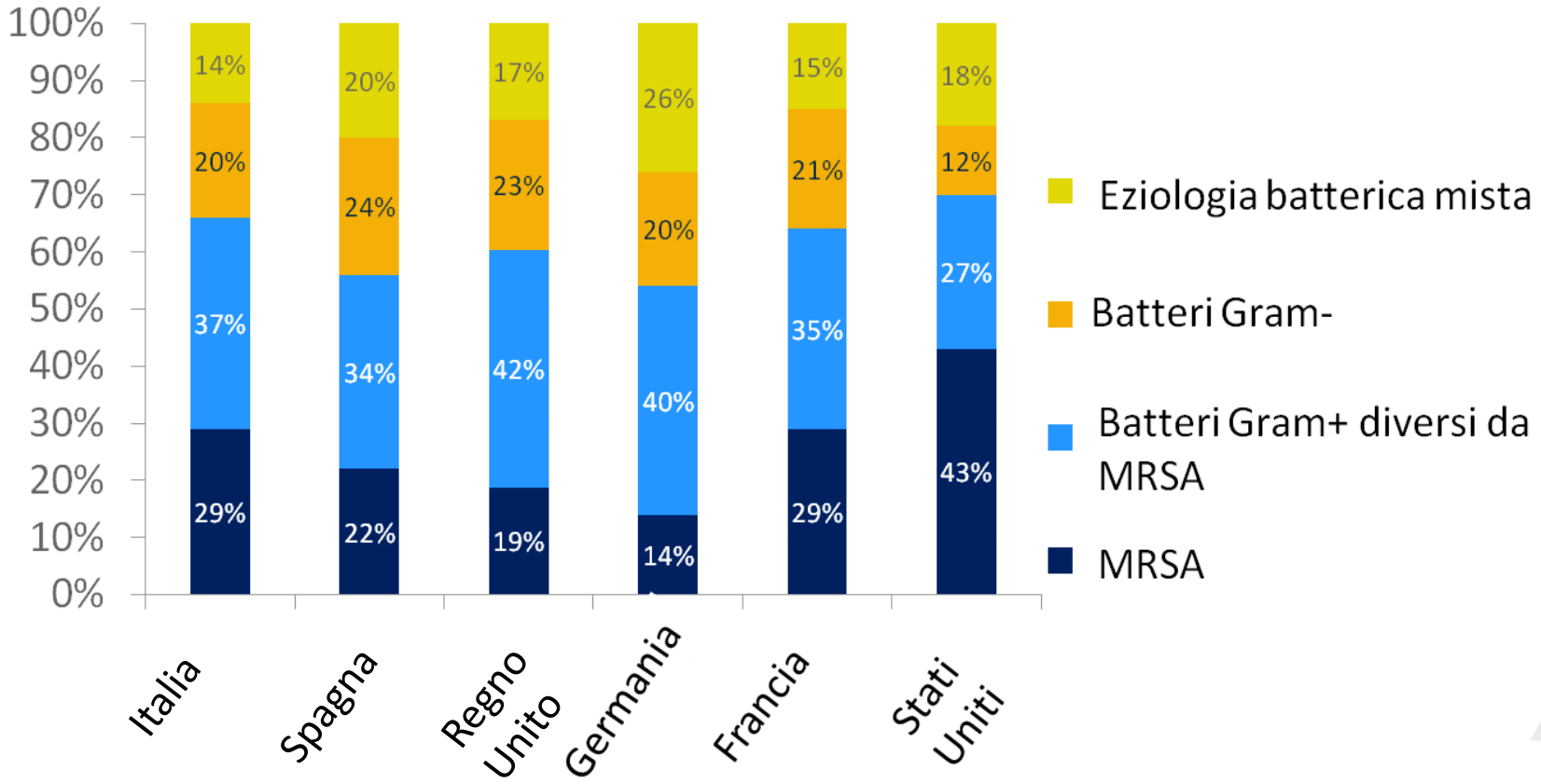
Ordine di rilevanza di agenti patogeni batterici responsabili di SSTI per regione per gli anni dal 1998 al 2004, determinato in base al programma SENTRY

Regione/rilevanza	Totale 7 anni (%)	Insorgenza (%) per anno					
Europa		1998	1999	2000	2002	2003	2004
S. aureus	1732 (37,5)	437 (35,7)	16 (15,8)	216 (31,0)	40 (34,8)	550 (41,8)	473 (40,5)
P. aeruginosa	555 (12,0)	179 (14,6)	24 (23,8)	97 (13,9)	14 (12,2)	131 (9,9)	110 (9,4)
E. coli	501 (10,8)	123 (10,0)	23 (22,8)	94 (13,5)	11 (9,6)	119 (9,0)	133 (11,4)
Enterococcus spp.	281 (6,1)	84 (6,9)	3 (3,0)	51 (7,3)	8 (7,0)	70 (5,3)	65 (5,6)
Enterobacter spp.	243 (5,3)	53 (4,3)	12 (11,9)	40 (5,7)	6 (5,2)	70 (5,3)	62 (5,3)
CoNS	235 (5,1)	69 (5,6)	4 (4,0)	34 (4,9)	2 (1,7)	69 (5,2)	57 (4,9)
B-Streptococcus	215 (4,7)	31 (2,5)	1 (1,0)	12 (1,7)	12 (10,4)	65 (4,9)	62 (5,3)
Klebsiella spp.	205 (4,4)	59 (4,8)	7 (6,9)	40 (5,7)	5 (4,3)	44 (3,3)	50 (4,3)
P. mirabilis	145 (3,1)	39 (3,2)	1 (1,0)	23 (3,3)	3 (2,6)	35 (2,7)	44 (3,8)
Acinetobacter spp.	87 (1,5)	30 (2,4)	5 (5,0)	21 (3,0)	2 (1,7)	31 (2,4)	18 (1,5)
Totale isolati testati (% dei primi 10)	4622 (90,8)	1225 (90,1)	101 (95,0)	697 (90,1)	115 (89,6)	1317 (89,9)	1167 (92,0)

Moet 2007, Contemporary causes of skin and soft tissue infections in North America, Latin America, and Europe: Report from the SENTRY Antimicrobial Surveillance Program (1998–2004)

Tipologie di agenti patogeni batterici individuati in pazienti affetti da cSSSI sottoposti a diagnosi eziologica negli USA e in cinque principali mercati dell'UE,

Proporzione complessiva di MRSA: 23,2%



MRSA = *Staphylococcus aureus* meticillino-resistente

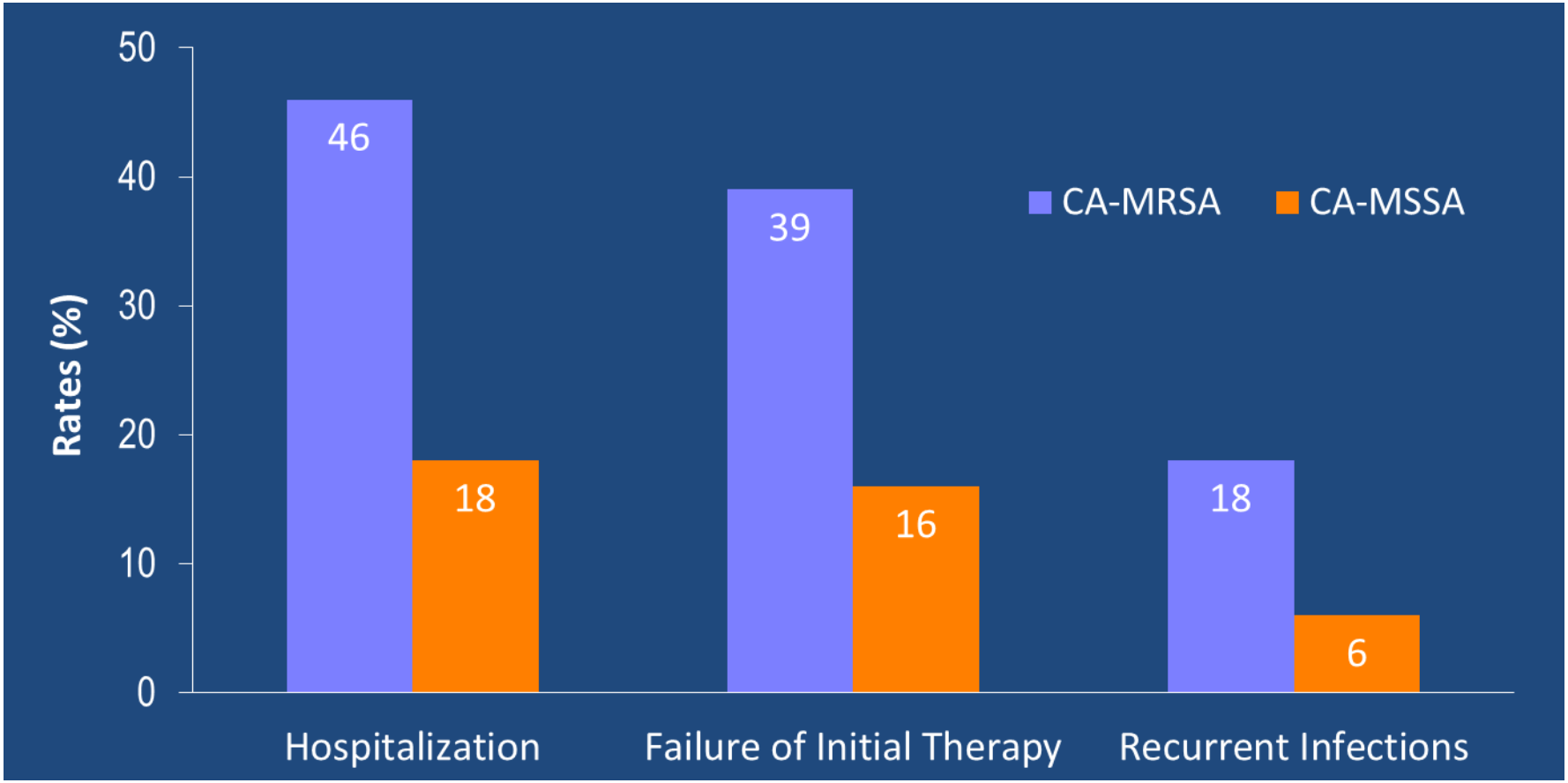
Indagine sulle cSSSI di Datamonitor Healthcare, aprile 2014

Isolamenti di St. aureus e oxacillino-resistenza in AOP

	Anno 2012	Anno 2013	Anno 2014	Anno 2015	Anno 2016
Totale isolati	849	864	1265	995	1728
Oxa-R	43%	44%	60%	46%	39%
Isolati da emocoltura (%) (CVC,+ periferico)	152 (18%)	157 (18%)	149 (11%)	82 (8%)	334 (19%)
Oxa-R	50%	50%	55%	53%	23%

Nel 2016 il 48% (233/480di MRSA) negli isolati da pus da lesione cutanea

Higher Burden of Infection with CA-MRSA Versus CA-MSSA*



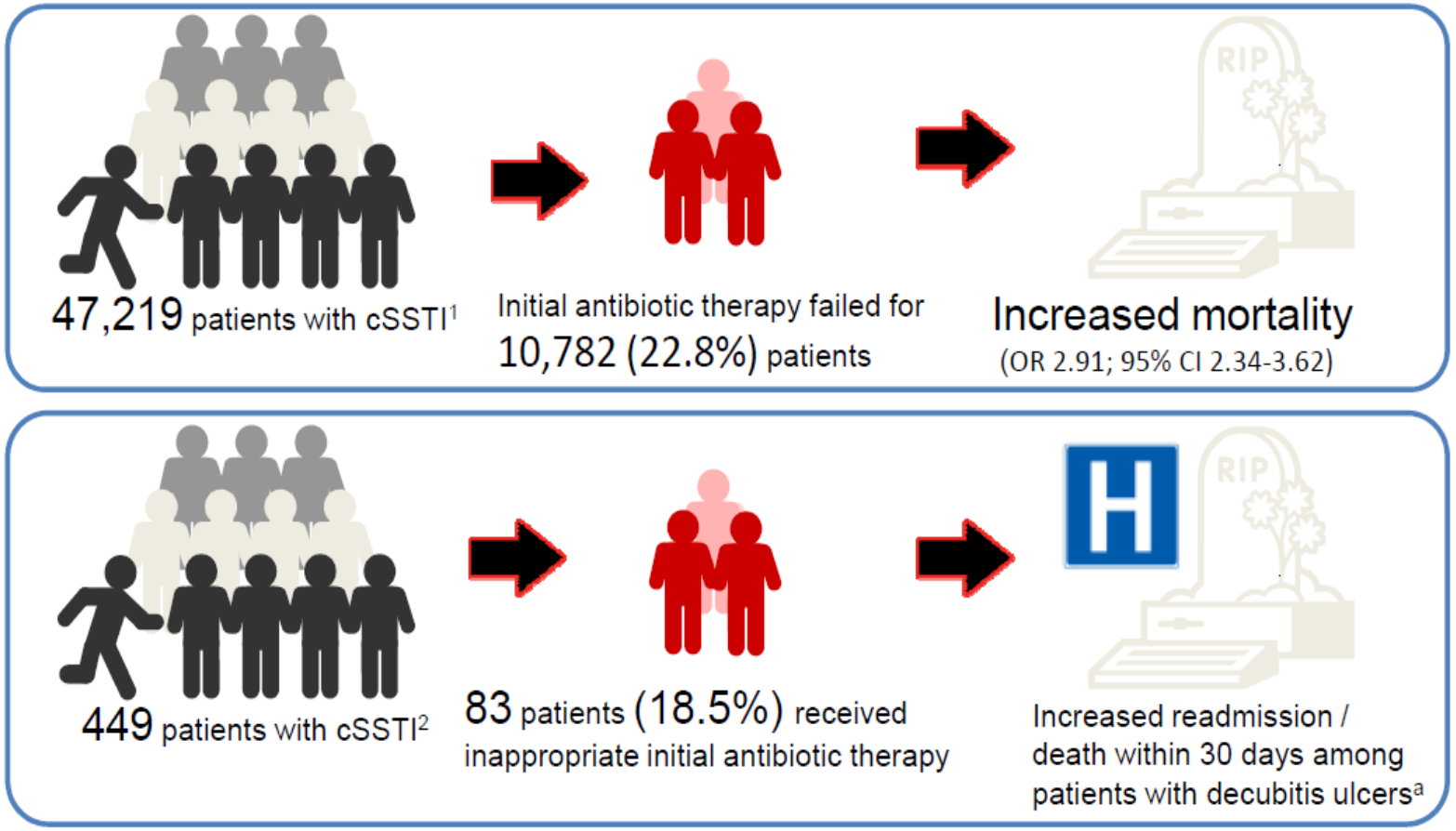
Infection with CA-MRSA leads to significantly higher rates of hospitalization, initial therapy failure, and recurrent infections compared with CA-MSSA

*Pathogens were isolated from several sources, but skin was the most common site of infection in both groups of patients: CA-MRSA, 80%; CA-MSSA, 93%. In the MRSA group, N=102; in the MSSA group, N=102. (These N values are for all sources, not only skin).

CA-MRSA = community-acquired methicillin-resistant *S. aureus;* CA-MSSA = community-acquired methicillin-sensitive *S. aureus*.

Davis SL et al. *J Clin Microbiol.* 2007;45(6):1705-1711.

Adverse clinical outcomes are more likely in cSSTI patients who receive inappropriate initial antibiotic therapy



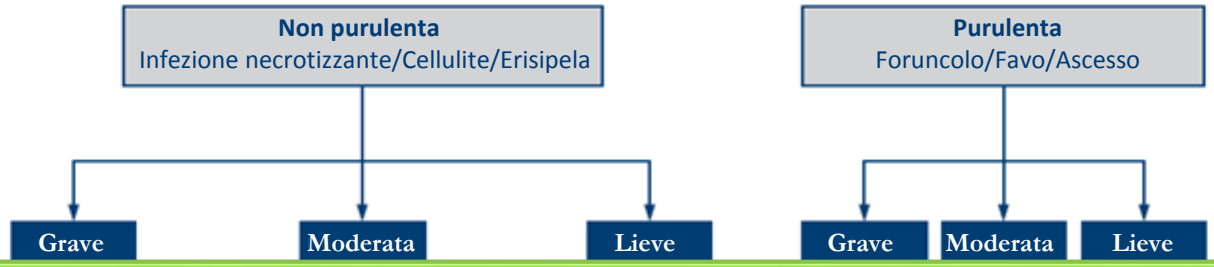
[a]Overall, there were no significant differences

1. Edelsberg et al. Infect Control Hosp Epidemiol 2008;29:160-9;
2. Zervos et al. J Clin Microbiol 2012;50:238-45

Fattori di rischio di batteriemia da MRSA al momento del ricovero

- Diabete mellito (**p<0,03)**
- Ospedalizzazione nei 6 mesi precedenti (**p<0,02)**
- Terapia chinolonica nel mese precedente (**p<0,02)**
- Cellulite od ulcera cutanea al ricovero (**p<0,0065)**
- Infezione/colonizzazione da MRSA nei 3 mesi precedenti (**p<0,001)**
- Presenza di CVC (**p<0,001)**

Gestione clinica delle infezioni della cute e dei tessuti molli



Caveats

1. Progressive increase in vancomycin minimum inhibitory concentrations (MICs) in MRSA (the choice of an alternative antibiotic regimen is suggested when vancomycin MIC is greater than 1mg/l)
2. Vancomycin requires a twice daily intravenous administration, not allowing the treatment of outpatients
3. Therapeutic drug monitoring (TDM) is needed to minimize the risk of nephrotoxicity and ensure the achievement of adequate plasmatic concentrations

Antibiotics for MRSA cSSTIs have different tissue penetration

	Molecular weight	Ratio of skin and soft tissue: plasma penetration
Linezolid	337.35[1]	104%[9,a]
Vancomycin	1485.74[2]	10-30%[10,b]
Teicoplanin	1879.7[3]	24-77%[11,12,a]
Daptomycin	1620.67[4]	68%[13,a]
Clindamycin	424.98[5]	24-82%[14]
Tigecycline	585.65[6]	380%[15,c]
Ceftaroline	762.75[7]	Not available
Fusidic acid	516.71[8]	49%[16,d]

[a]Healthy volunteers/patients; [b]Diabetic vs non-diabetic post-cardiac surgery patients; [c]cSSTI patients requiring surgical intervention, 1 hr post infusion (peak); [d]Healthy volunteers, after 5.5 days repeated oral administration (1g/d)

1. ZYVOX® [package insert]. New York, NY: Pfizer Inc., 2012;
2. Vancomycin Hydrochloride [package insert]. Lake Forest, IL: Hospira, Inc., 2010;
3. Teicoplanin Complex [product data sheet]. Bioaustralis.com;
4. Cubicin [package insert]. Lexington, MA: Cubist Pharmaceuticals, Inc., 2010;
5. http://www.drugbank.ca/drugs/DB01190;
6. http://www.drugbank.ca/drugs/DB00560;
7. Saravolatz et al. Clin Infect Dis 2011;52:1156-63;
8. http://www.chemnet.com/cas/en/6990-06-3/fusidic-acid.html;
9. Gee et al. Antimicrob Agents Chemother 2001;45:1843-6;
10. Skhirtladze et al. Antimicrob Agents Chemother 2006;50:1372-5;
11. Wise et al. J Hosp Infect 1986;7 Suppl A:47-55;
12. de Lalla et al. Antimicrob Agents Chemother 1993;37:2693-8;
13. Wise et al. Antimicrob Agents Chemother 2002;46:31-3;
14. Stoehr et al. Clin Pharm 1988;7:820-4;
15. Stein et al. Surg Infect (Larchmt) 2011;12:465-7;
16. Vaillant et al. Ann Dermatol Venereol 2000;127:33-9

Characteristics of new therapeutic options for cSSTI (1)

Drug	Mechanism of action	Spectrum of activity	Dosage and administration route	Adjustment in renal impairment	Adjustment in liver impairment	Adverse events
Daptomycin	Rapid depolarization of bacterial membrane	Gram-positive pathogens	8–10 mg/kg every 24 h intravenous	CrCl <30 ml/min: 8–10 mg/kg every 48 h	None	CPK elevation (reversible), eosinophilic pneumonia (rare)
Tigecycline	Inhibition of bacterial protein synthesis	Gram positives (including MRSA and VRE) and Gram negatives (including ESBL-producing *Enterobacteriacae*, MDR *Acinetobacter baumanii* and KPC-*Klebsiella pneumoniae*)	100 mg (loading dose), followed by 50 mg every 12 h intravenous	None	None	Nausea and vomiting
Linezolid	Inhibition of bacterial protein synthesis	Gram-positive pathogens (including MRSA and VRE)	600 mg every 12 h (intravenous or oral)	None	None	Nausea, vomiting, diarrhea, headache, myelosuppression (reversible), lactic acidosis, peripheral or optic neuropathy, inhibition of monoamine oxidase (risk of serotoninergic syndrome with concomitant selective serotonin reuptake inhibitors)

Curr Opin Infect Dis 2016, 29:99–108

Characteristics of new therapeutic options for cSSTI (2)

Drug	Mechanism of action	Spectrum of activity	Dosage and administration route	Adjustment in renal impairment	Adjustment in liver impairment	Adverse events
Tedizolid *	Inhibition of bacterial protein synthesis	Gram-positive pathogens (including MRSA and VRE)	200 mg once daily (intravenous or oral)	None	None	Nausea, vomiting, diarrhea, headache, myelosuppression (reversible), peripheral and optic neuropathy
Oritavancin ^	Inhibition of bacterial wall synthesis and disruption of bacterial membrane function	Gram-positive pathogens (including MRSA and VRE)	1200 mg (single dose) intravenous	None (data available for renal clearance >30 ml/min)	None, for mild to moderate hepatic impairment (no data available for severe hepatic impairment)	Headache, nausea, vomiting, limb and subcutaneous abscesses, diarrhea, infusion-related reactions

•ESTABLISH 1-2 studies. 2 large, randomized, double-blinded, phase III trial ssupporting the non inferiority of a 6-day course of tedizolid (200mg once daily) in comparison with a 10-day course of linezolid (600 mg every 12 h) for the treatment of AB SSTIs. (JAMA 2013; 309:559–569. Lancet Infect Dis 2014; 14:696–705

^ SOLO 1-2 studies; randomized, double-blinded, phase III trials demonstrating the noninferiotity of a single dose of oritavancin (1200 mg) compared to a 7–10 day course of twice-daily intravenous vancomycin (1 g every 12 h) for the treatment of acute bacterial skin and skin-structure infections caused by Gram-positive pathogens (N Engl J Med 2014; 370:2180–2190. Clin Infect Dis 2015; 60:254–262)

Characteristics of new therapeutic options for cSSTI (3)

Drug	Mechanism of action	Spectrum of activity	Dosage and administration route	Adjustment in renal impairment	Adjustment in liver impairment	Adverse events
Dalbavncin			1000 mg followed by 500 mg after 1 week intravenous	No modifications for CrCl > 30 ml/min and in hemodyalisis. If CrCl < 30 ml/min, the reduction of doses is recommended (750 mg followed by 375 mg after 1 week)	No modifications recommended. In patients with moderate or severe hepatic impairment (Child-Pugh B or C), use caution (no data available in this population)	Nausea, diarrhea, vomiting, headache, alteration of liver enzymes (GGT), rash
Ceftaroline fosamil	Inhibition of cell wall synthesis by binding to penicillin-binding proteins	Gram positives (including VRSA and penicillin-resistant *Streptococcus pneumoniae*, Enterococci are nonsusceptible) and Gram negatives (with the exception of and ESBL-producing pathogens and *Pseudomonas aeruginosa*)	600 mg every 12 h	ClCr 30–50 ml/min: 400 mg every 12 h; no data available for ClCr < 30 ml/min and dyalitic ESRD	None	Positive Coombs test (never reported hemolytic anemia so far), rash, diarrhea, nausea, vomiting, abdominal pain, alteration of liver enzymes, phlebitis

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Ceftaroline fosamil (Zinforo® - AstraZeneca)

- 5th generation cephalosporin
- Low propensity for inducing resistance
- Excellent safety profile
- Gram-positive bacteria (CONS, MRSA, VISA, VRSA, resistant pneumococcus, resp gram negs)
  - 4-fold greater activity against MRSA than Vanc
  - 16-fold greater activity against MSSA than Ceftr
  - Active against daptomycin- and linezolid-resistant staph
- Avoid in ESBLs, *Pseudomonas*, *Acinetobacter*
- FDA approved in 2010 for CAP and cSSTI (adults)

REVIEWS OF ANTI-INFECTIVE AGENTS INVITED ARTICLE
Louis D. Saravolatz, Section Editor Clinical Infectious Diseases 2011;52(9):1156–1163

Ceftaroline: A Novel Cephalosporin with Activity against Methicillin-resistant *Staphylococcus aureus*

Louis D. Saravolatz, Gary E. Stein, and Leonard B. Johnson

[a]Department of medicine, St John Hospital and Medical Center, Wayne State University School of Medicine, and Michigan State University School of Medicine, East Lansing, Michigan

Table 1. Comparative in vitro MIC 90s of Ceftaroline and Other Comparators against Gram-Positive Bacteria

Organism (no. of isolates tested)	Ceftaroline*	Vancomycin	Daptomycin	Ceftriaxone	Linezolid	Erythromycin
Staphylococcus aureus						
MSSA (348)	0.25	1	0.5	NA	2	NA
MRSA (92)	1	1	1	NA	2	NA
VISA (20)	1	8	4	NA	2	NA
VRSA (10)	0.5	>64	1	NA	2	NA
Coagulase-negative staphylococci						
Methicillin susceptible (201)	0.12	2	4	NA	2	NA
Methicillin resistant (299)	0.5	2	>32	NA	2	NA
Enterococcus faecalis						
Vancomycin susceptible (157)	4	2	1	NA	2	NA
Vancomycin resistant(25)	4	>16	1	NA	2	NA
Enterococcus faecium (157)	>16	>16	4	NA	2	NA
Streptococcus pyogenes						
Erythromycin susceptible(91)	<.008	0.5	NA	<.008	1	0.06
Erythromycin resistant (10)	<.015	0.5	NA	0.12	1	>16
Streptococcus agalactiae (59)	0.015	0.5	NA	0.12	1	0.06
Streptococcus pneumoniae						
Penicillin sensitive (202)	0.015	0.5	NA	0.06	1	0.5
Penicillin intermediate (103)	0.06	0.5	NA	0.5	1	>16
Penicillin resistant (296)	0.12	0.5	NA	0.12	1	>16

NOTE. Adapted from [7, 8]. MIC_{90} values are given as μg/mL. MIC_{90},90% minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; NA, not applicable.; VISA, vancomycin-intermediate *S. aureus*; VRSA, vancomycin-resistant *S. aureus*.

* Ceftaroline MIC breakpoints areas follows: *S. aureus* = 1 for skin isolates only, *S. pneumoniae* = 0.25 μg/mL for community-acquired bacterial pneumonia isolates only, *Streptococcus pyogenes* = 0.015 for skin isolates only, and *Streptococcus agalactiae* =0 .03 μg/mL for skin isolates only.

Activity:

against multidrug-resistant (MDR) gram-positive bacteria, including S. aureus strains with reduced susceptibility to methicillin and vancomycin and isolates of Streptococcus pneumoniae with reduced susceptibility to penicillins, erythromycin, and fluoroquinolones

Ceftaroline dosage: 600 mg every 12 h

Clinical trials have demonstrated noninferiority when compared with vancomycin in the treatment of acute bacterial skin and skin structure infections and noninferiority when compared with ceftriaxone in the treatment of community-acquired bacterial pneumonia. Ceftaroline demonstrated a safety profile similar to that of comparator drugs in clinical trials.

CANVAS 1 & 2: La monoterapia con Ceftarolina Fosamil è efficace per il trattamento di cSSTI, con tassi di guarigione clinica confrontabili con quelli osservati con vancomicina più aztreonam

	Ceftarolina n/N (%)	Vancomicina + Aztreonam n/N (%)	Differenza (IC 95%)
Popolazione MITT			
CANVAS 1	304/351(86.6)	297/347(85.6)	1.0 (**- 4.2**, 6.2)
CANVAS 2	291/342 (85.1)	289/338 (85.5)	- 0.4 (**- 5.8**, 5.0)
CANVAS 1&2	595/693 (85.9)	586/685 (85.5)	0.3 **(- 3.4** , 4.0)

	Ceftarolina n/N (%)	Vancomicina+ Aztreonam n/N (%)	Differenza (IC 95%)
Popolazione CE			
CANVAS 1	288/316 (91.1)	280/300 (93.3)	- 2.2 (**- 6.6**, 2.1)
CANVAS 2	271/294 (92.2)	269/292 (92.1)	0.1 (**- 4.4**, 4.5)
CANVAS 1&2	559/610 (91.6)	549/592 (92.7)	-1.1(**- 4.2** , 2.0)

Corey GR *et al.* (CANVAS 1) *J Antimicrob Chemother.* 2010;65 (Suppl. 4):iv 41–51.
Wilcox MH *et al.* (CANVAS 2) *J Antimicrob Chemother.* 2010;65 (Suppl. 4):iv 53–65.
Corey GR *et al.* (CANVAS 1 & 2) *Clin Infect Dis.* 2010;51:641–50.

Place in therapy Ceftaroline

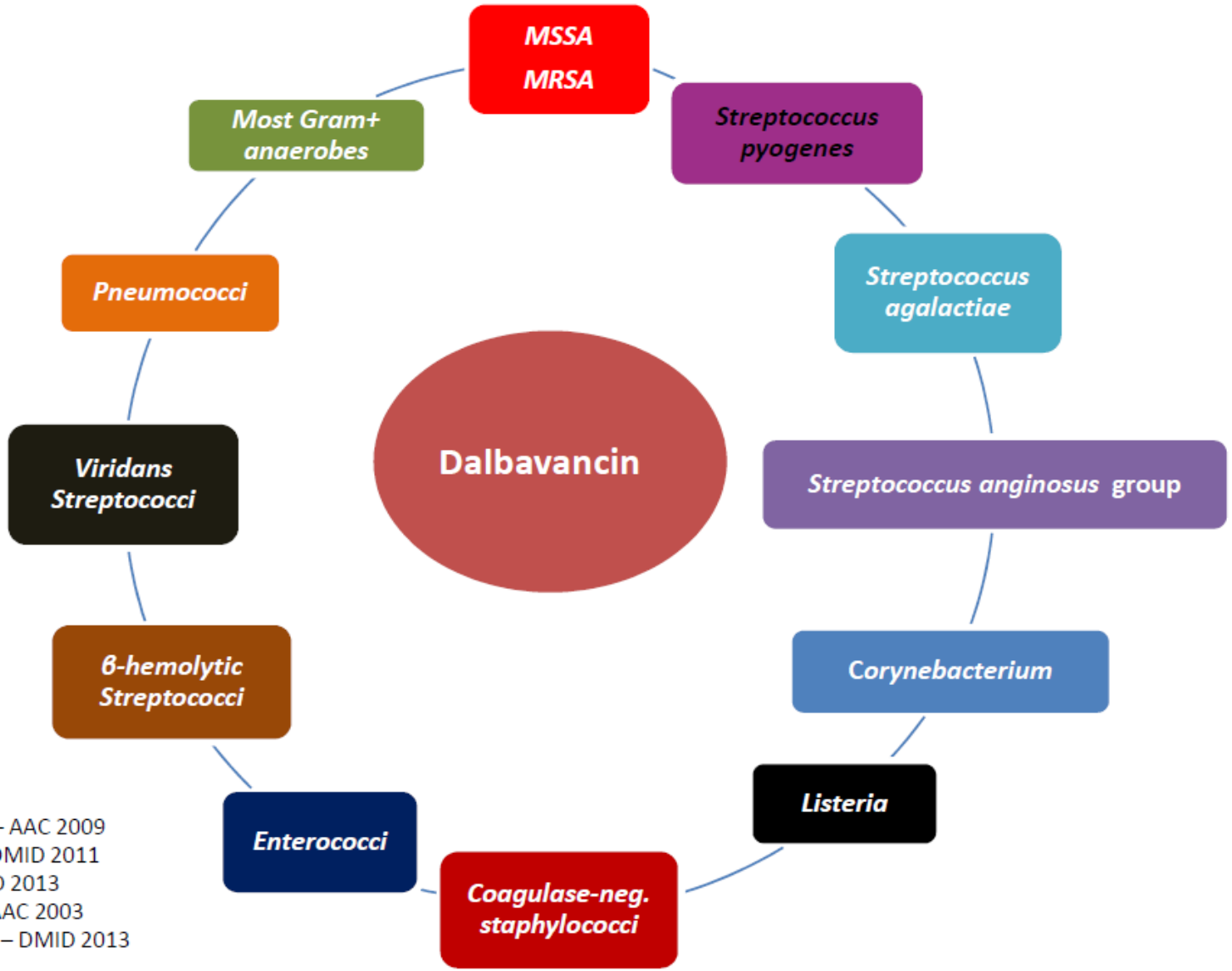
Treatment of complicated skin and soft tissue infections (cSSTI) **non-necrotising care-related infections** (nosocomial or otherwise) such as extensive **cellulitis, abscesses, superinfected wounds or sores** without a history of previous colonisation with *Pseudomonas*. Ceftaroline is well tolerated than vancomycin and does not require monitoring of plasma concentrations and renal function.

Insufficient for the treatment of community-acquired pneumonias (CAP).

DALBAVANCIN (Xydalba^{R} – Angelini)

- **Long half life (5-7 days)**
- **Weekly drug**
- Protein binding (dalba 93%)
- Only IV
- Potential for OPAT
- Well tolerated
- Potential for many indications

Dalbavancin - The overall spectrum



Biedenbach *et al* – AAC 2009
Karlowski *et al* – DMID 2011
Jones *et al* – DMID 2013
Goldstein *et al* – AAC 2003
Jones and Stilwell – DMID 2013

UPDATE ON DALBAVANCIN ACTIVITY TESTED AGAINST GRAM-POSITIVE CLINICAL ISOLATES RESPONSIBLE FOR DOCUMENTED SSTIs IN US AND EUROPEAN HOSPITALS (2011-13)

Mendes Re et al. *J Antimicrob Chemother* 2015 Advance Access published October 7

ANTIMICROBIAL ACTIVITY OF DALBAVANCIN AGAINST AND MIC DISTRIBUTION OF DALBAVANCIN FOR GRAM-POSITIVE CLINICAL ISOLATES

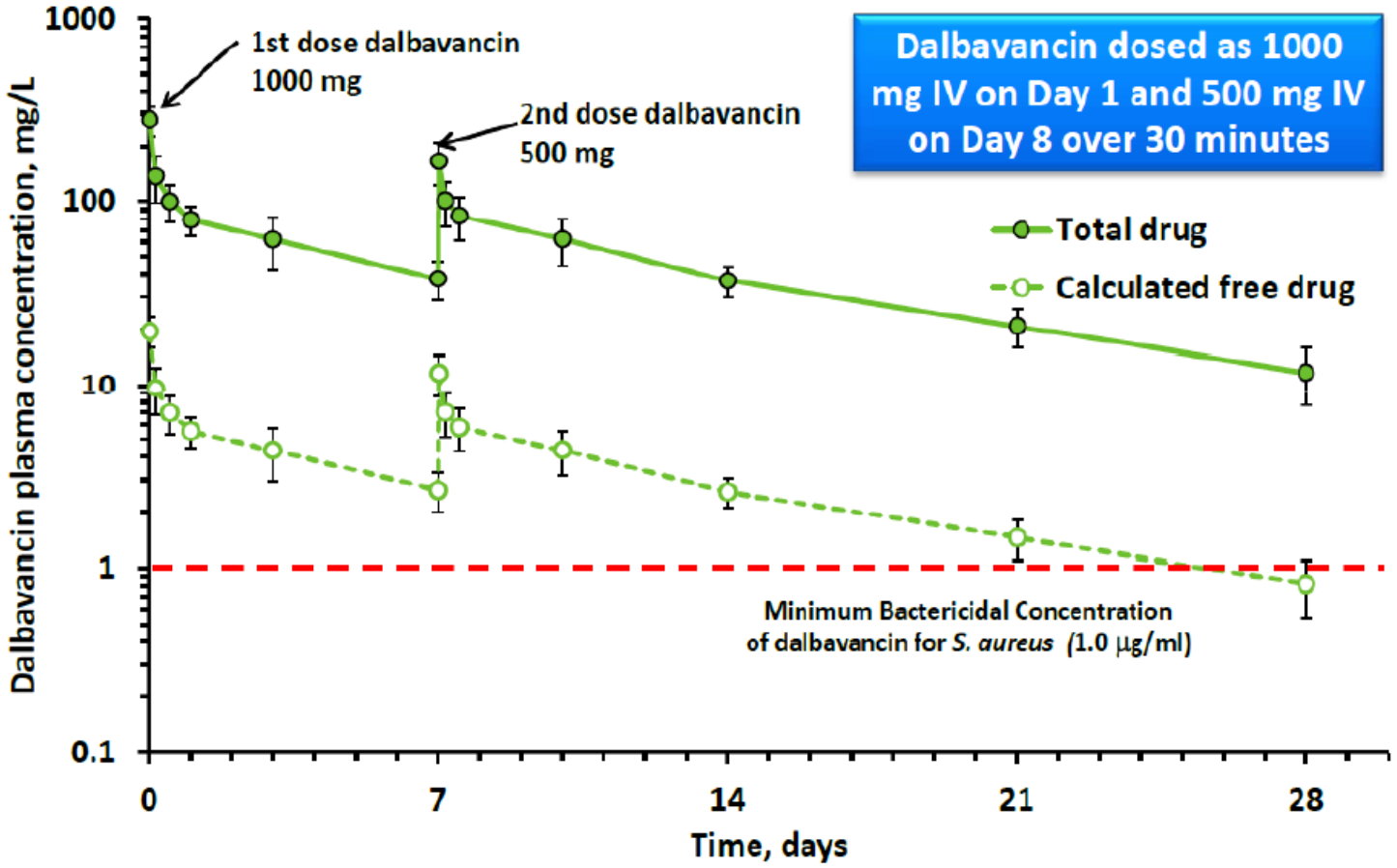
	MIC (mg/L)		Number (cumulative %) inhibited at dalbavancin MIC (mg/L)[a]				
Region, organism (no. tested)	50%	90%	≤0.03	0.06	0.12	0.25	0.5
Europe							
S. aureus (2861)	0.06	0.06	842 (29.4)	**1762 (91.0)**	256 (>99.9)	1 (100.0)	
MSSA (2203)	0.06	0.06	598 (27.1)	**1392 (90.3)**	213 (100.0)		
MRSA (658)	0.06	0.06	244 (37.1)	**370 (93.3)**	43 (99.8)	1 (100.0)	
vancomycin MIC ≤1 mg/L (642)	0.06	0.06	244 (38.0)	**361 (94.2)**	37 (100.0)		
vancomycin MIC 2 mg/L (16)	0.06	0.12	0 (0.0)	**9 (56.3)**	6 (93.8)	1 (100.0)	
VGS[a] (69)	≤0.03	≤0.03	**67 (97.1)**	1 (98.6)	1 (100.0)		
S. anginosus group (48)	≤0.03	≤0.03	**48 (100.0)**				
BHS[b] (466)	≤0.03	≤0.03	**424 (91.0)**	35 (98.5)	7 (100.0)		
S. pyogenes (223)	≤0.03	≤0.03	**207 (92.8)**	12 (98.2)	4 (100.0)		
S. agalactiae (135)	≤0.03	0.06	**120 (88.9)**	13 (98.5)	2 (100.0)		
S. dysgalactiae (47)	≤0.03	≤0.03	**43 (91.5)**	4 (100.0)			
USA							
S. aureus (4611)	0.06	0.06	1253 (27.2)	**2935 (90.8)**	420 (>99.9)	1 (>99.9)	2 (100.0)
MSSA (2292)	0.06	0.06	641 (28.0)	**1425 (90.1)**	225 (>99.9)	1 (100.0)	
MRSA (2319)	0.06	0.06	612 (26.4)	**1510 (91.5)**	195 (>99.9)	0 (>99.9)	2 (100.0)
vancomycin MIC ≤1 mg/L (2289)	0.06	0.06	609 (26.6)	**1490 (91.7)**	190 (100.0)		
vancomycin MIC 2 mg/L (30)	0.06	0.12	3 (10.0)	**20 (76.7)**	5 (93.3)	0 (93.3)	2 (100.0)
VGS[c] (37)	≤0.03	≤0.03	**34 (91.9)**	2 (97.3)	1 (100.0)		
S. anginosus group (25)	≤0.03	≤0.03	**25 (100.0)**				
BHS[d] (483)	≤0.03	≤0.03	**439 (90.9)**	31 (97.3)	13 (100.0)		
S. pyogenes (289)	≤0.03	≤0.03	**273 (94.5)**	14 (99.3)	2 (100.0)		
S. agalactiae (148)	≤0.03	0.06	**121 (81.8)**	17 (93.2)	10 (100.0)		
S. dysgalactiae (11)	≤0.03	≤0.03	**10 (90.9)**	0 (90.9)	1 (100.0)		

PK PARAMETERS FOR LIPOGLYCOPEPTIDES AT USUAL HUMAN DOSES (HEALTHY VOLUNTEERS)

Parameter	Dalbavancin (1 g day 1, 500 mg day 8)	Telavancin (10 mg/kg od)	Oritavancin (3 mg/kg od)
C_{max} (mg/L)	312	88	29
AUC (mg • h/L)	27 103	858	146
Vd (L/kg)	0.11	0.1	0.65–1.92
Protein binding (%)	93–98	90–93	86–90
Terminal half-life (h)	147–258	7–9	393

Zhanel G et al. *Drugs* 2010; 70 (7): 859-886

Dosing Rationale: Once-Weekly Dosing Regimen of Dalbavancin



This regimen demonstrated no accumulation when dosing was extended to weekly dosing with additional 500 mg doses for up to a total of 8 weeks (Study DUR001-104). A weekly multiple dosing regimen does not substantially affect the PK profile of dalbavancin when extended over 4, 6 or 8 weeks of dosing.

DALBAVANCIN (Xydalba – Angelini)

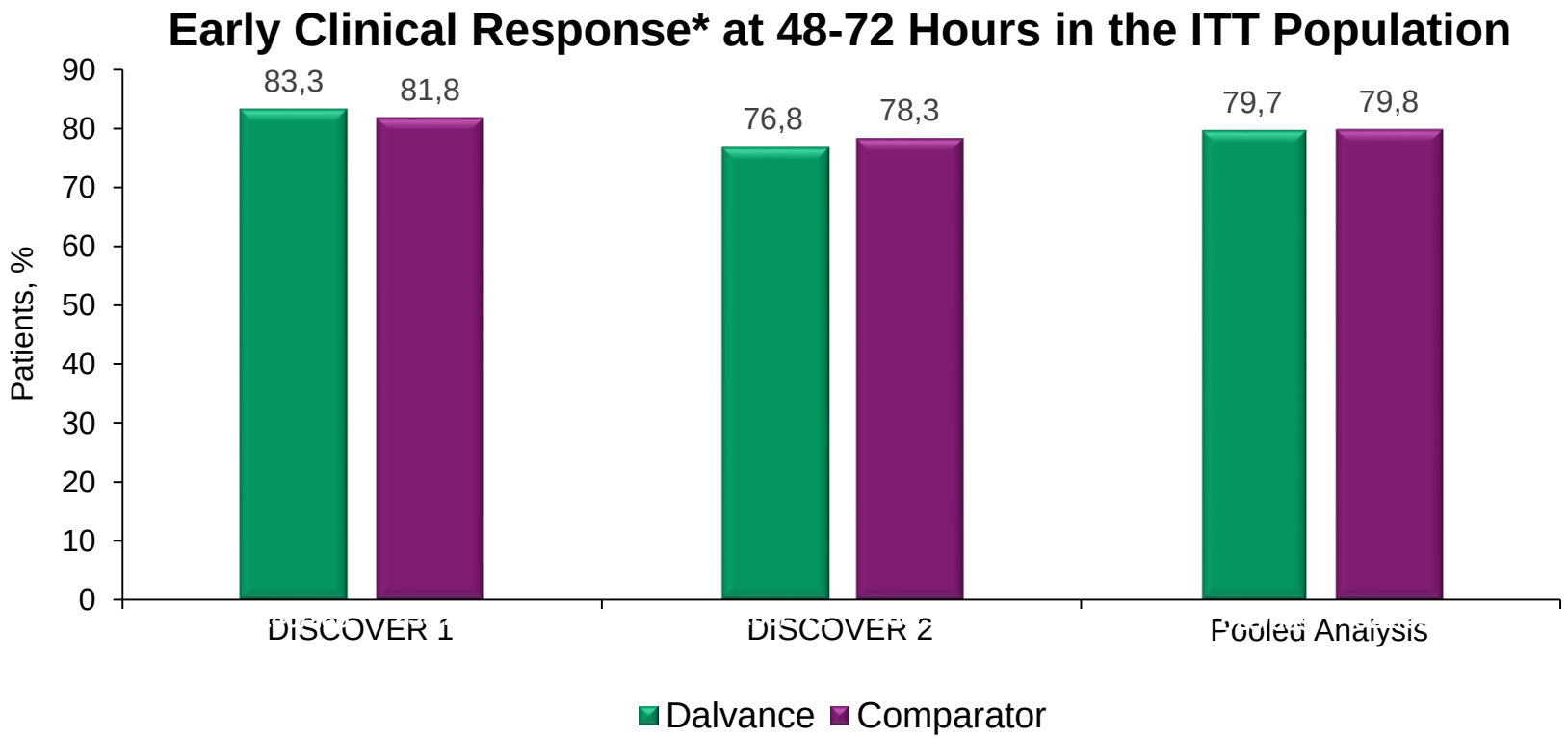
Extended-Duration Dosing and Distribution of Dalbavancin into Bone and Articular Tissue *Dunne MW et al, Antimicrob Agents Chemother 59:1849 –1855*

Dalbavancin tissue concentrations

	Dalbavancin concn (mean [SD]; no. of samples) at hours (days) postdose that samples were collected:					
Tissue	12 (0.5)	24 (1)	72 (3)	168 (7)	240 (10)	336 (14)
Plasma (μg/ml)[a]	85.3 (18.9); 31	ND[b]	ND	ND	ND	15.3 (4.1); 31
Synovium (μg/g)[c]	25.0 (0); 3	17.9 (7.8); 3	19.5 (4.9); 3	19.2 (8.9); 4	25.0 (0); 2	15.9 (7.9); 3
Synovial fluid (μg/ml)[c]	22.9; 1	27.4 (10.8); 4	19.2 (4.9); 3	11.6 (3.3); 2	13.9 (1.0); 3	6.2 (1.7); 2
Bone (μg/g)	6.3 (3.1); 5	5.0 (3.5); 5	4.6 (3.8); 5	3.8 (2.7); 5	3.7 (2.2); 5	4.1 (1.6); 5
Skin (μg/g)[c]	19.4 (7.9); 2	12.5 (6.5); 3	13.8 (1.4); 2	15.7 (1.0); 2	21.6; 1	13.8 (2.1); 2

DISCOVER Trials Results

Two multi-center, randomized, double blind trials of similar design: Dalbavancin 1000 mg + 500 mg vs Vancomycin and Linezolid after day 3. DISCOVER 1 (N=573); DISCOVER 2 (N=739)[1].



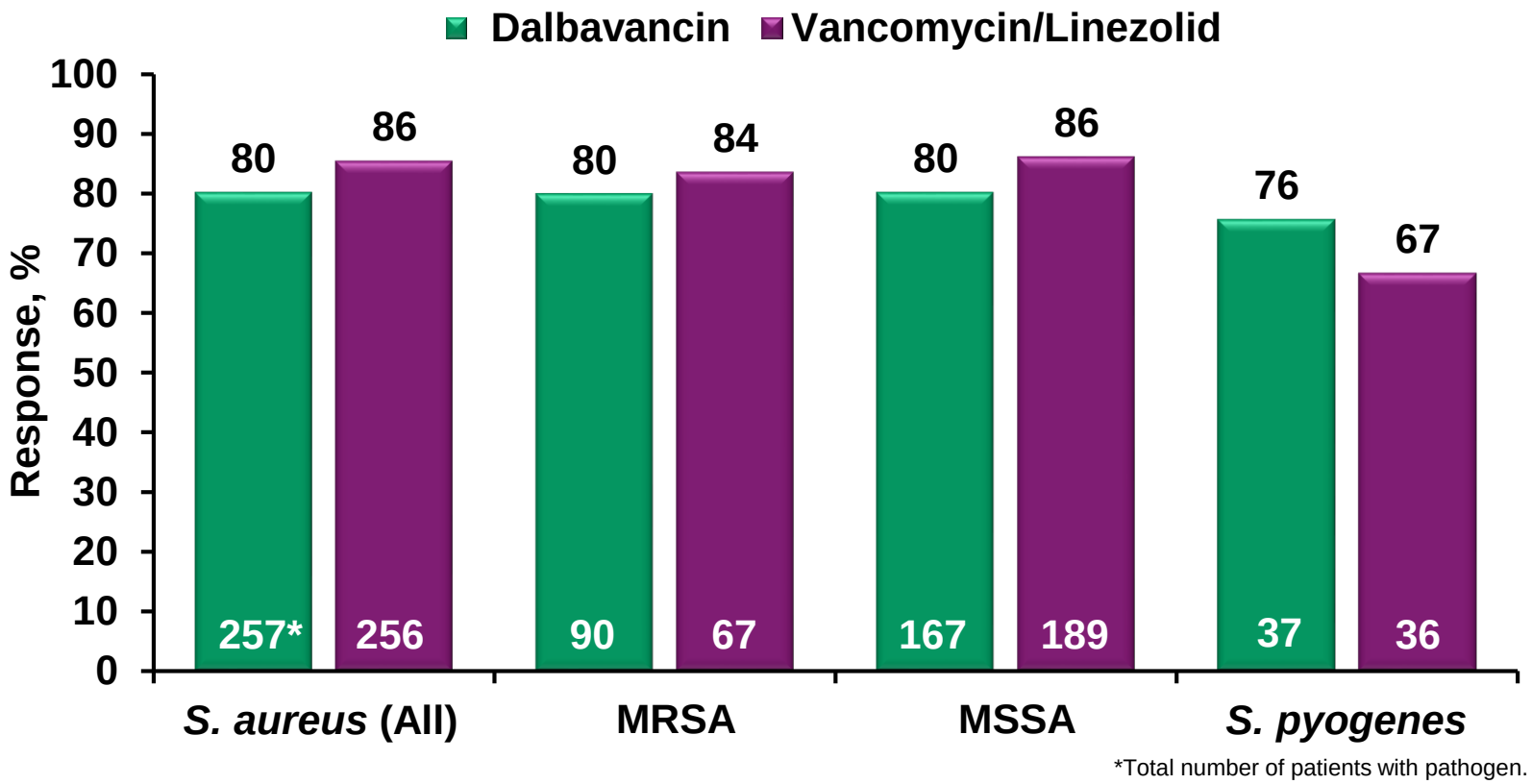
DISCOVER 1 Absolute Difference (95% CI) Percentage Points [1.5 (–4.6 to 7.9)]. DISCOVER 2 Absolute Difference (95% CI) Percentage Points [-1.5 (–7.4, 4.6)] Pooled Analysis Absolute Difference (95% CI) Percentage Points [-0.1 (–4.5 to 4.2)].

*Early clinical response was defined as both cessation of spread of the erythema associated with the infection and a temperature of 37.6°C or lower at three consecutive readings performed 6 hours apart. ITT, intent-to-treat

1. Boucher HW, et al. *N Engl J Med*. 2014;370:2169-79.

Outcomes by Baseline Pathogen
Early Response at 48-72 Hours

Pooled Analysis of DISCOVER 1 and DISCOVER 2
Micro ITT Population



*Total number of patients with pathogen.

There were 2 patients in the dalbavancin arm with methicillin-susceptible *S. aureus* at baseline who did not receive treatment and were counted as non-responders/failures.

1.dalbavancin for injection Full Prescribing Information. Chicago, IL: Durata Therapeutics, Inc. 2014

Summary of Adverse Events

Pooled Analysis of DISCOVER 1 and DISCOVER 2

Variable	Dalbavancin (N=652) No. of patients (%)	Vancomycin/Linezolid (N=651) No. of patients (%)	P Value*
Treatment-emergent AE	214 (32.8)	247 (37.9)	0.05
Treatment-related AE†	80 (12.3)	89 (13.7)	0.45
Serious AE			
Any event	17 (2.6)	26 (4.0)	0.16
Treatment-related serious event†	2 (0.3)	4 (0.6)	0.41
Premature discontinuation due to TEAE	14 (2.1)	13 (2.0)	0.85
Death	1 (0.2)	7 (1.1)	0.03
Most common treatment-related adverse event‡			
Nausea	16 (2.5)	19 (2.9)	0.62
Diarrhea	5 (0.8)	16 (2.5)	0.02
Pruritus	4 (0.6)	15 (2.3)	0.01

*The P value was calculated with the use of the Cochran-Mantel-Haneszel test, with adjustment for study. The P values for the total number of adverse events and total number of drug-related adverse events were calculated by means of Poisson regression.
†The investigator, who was unaware of the treatment assignment, assessed whether the adverse event was related to treatment.
‡The most common adverse events were defined as those that occurred in more than 2% of the patients in either treatment group. A patient may have had more than one event.
1. Boucher HW, et al. *N Engl J Med*. 2014;370:2169-79.

PLACE IN THERAPY: DALBAVANCIN

- **Label:**
- cSSTIs: one-two shots!
- ABSSSI with high risk of MRSA involvement
  - **Erysipelas, cellulitis, abscess, skin ulcers, nosocomial cellulitis**
  - Surgical wound infections with high risk of MR Staph involvement
- **Non-label:**
- CBSIs: empiric and targeted use
  - One shot could be enough for S.epi MR
- **Bone and joint infections: osteomyelitis**
- Endocarditis

Vantaggi dei farmaci long-acting

- Riduzione dei costi del farmaco di preparazione, acquisto e somministrazione
- Riduzione dei tempi di ospedalizzazione
- Riduzione dei cosiddetti costi intangibili
- Riduzione dei rischi di complicanze da infusione (sepsi, flebiti, tromboflebiti)
- Riduzione dell'assistenza infermieristica durante la degenza in ospedale
- Riduzione del rischio di infezioni nosocomiali per la rapida dimissione

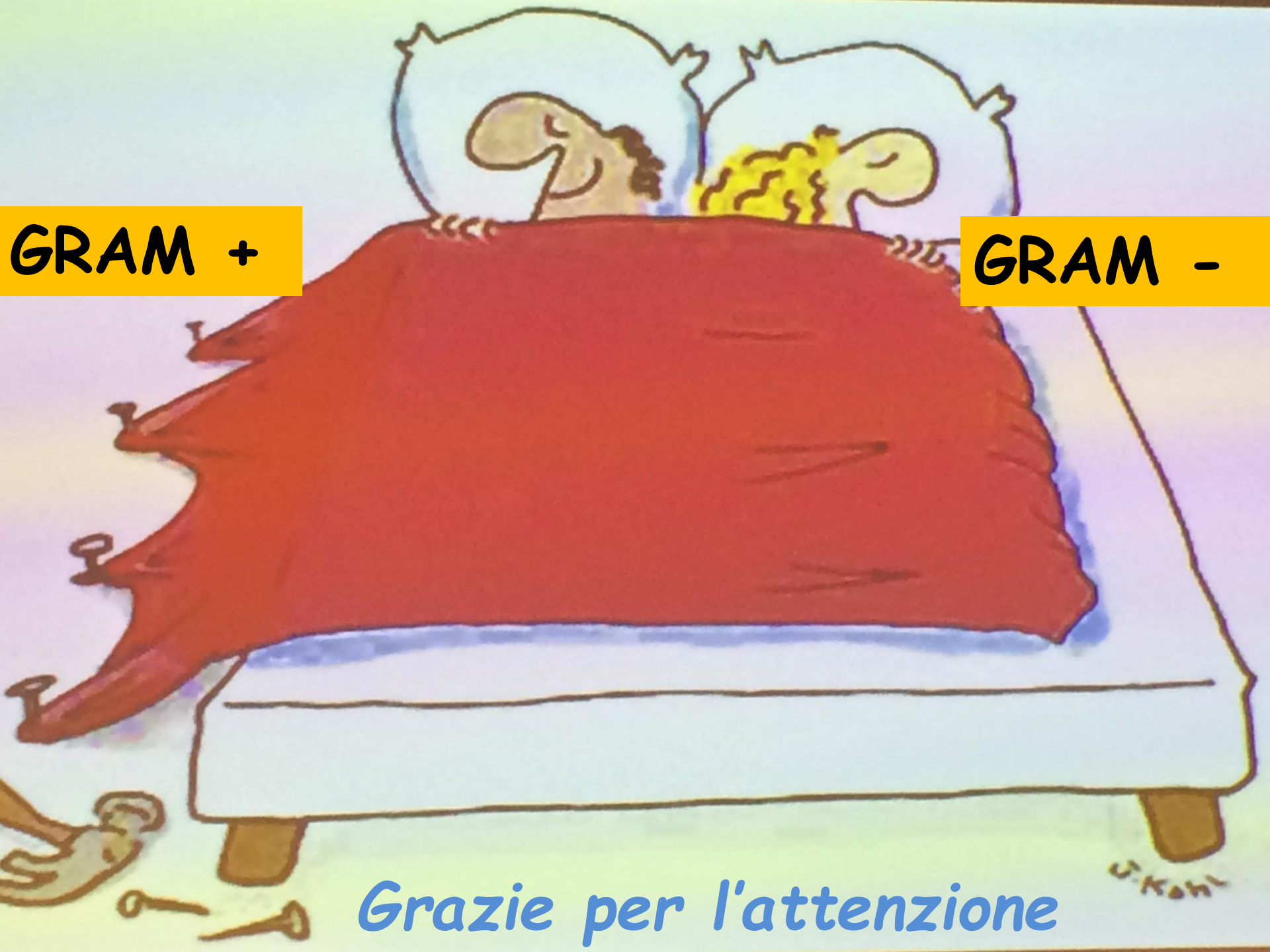
Pros and cons of new antimicrobial for cSSTI

Drug	Pros	Cons
Daptomycin	Rapid bactericidal activity Antibiofilm activity Good tolerability profile	Only intravenous Spectrum limited to Gram positives
Tigecycline	Broad spectrum of activity	Only intravenous Bacteriostatic
Linezolid	Oral formulation allows treatment of outpatients and early oral-switch	Bacteriostatic Spectrum limited to Gram positives Drug–drug interactions Important adverse effects
Tedizolid	Oral formulation allows treatment of outpatients early oral-switch Once-daily administration Low drug interactions Low myelotoxicity	Bacteriostatic Spectrum limited to Gram positives
Dalbavancin	Once-weekly administration Good penetration into cortical bone and articular tissues Good tolerability profile	Spectrum limited to Gram positives Only intravenous Bactericidal
Oritavancin	Single-dose treatment Good tolerability profile	Spectrum limited to Gram positives Only intravenous Bactericidal
Ceftaroline	Broad-spectrum activity Good tolerability profile	Only intravenous

Curr Opin Infect Dis 2016, 29:99–108

Take home messages

- Skin and soft tissue infections caused by MRSA are increasing, and new therapeutic options have recently become available
- Novel antibiotics with oral formulation or once-weekly administration may allow early discharge and may reduce hospitalization-related complications and overall health-care costs
- Novel antibiotics with reduced toxicity represent good options for patients with comorbidities
- Studies assessing both the cost efficacy of these new therapeutic options in real life and the potential role of these new drugs in specific clinical setting are needed



Grazie per l'attenzione