Le infezioni da Gram+ nel trapianto di cellule staminali emopoietiche

Prof. Francesco Menichetti
Università di Pisa
Direttore UOC Malattie Infettive
AOUP, PISA

INFECTIONS & TRANSPLANTATION
VARESE, ATA HOTEL
18 MAGGIO 2017

Infezioni nel paziente con HCT

- Fattori di rischio diversificati per qualità, intensità e durata
- HCT allogenico: tipo di trapianto, fonte, e regime di condizionamento
- GVHD o T-deplezione
- Neutropenia, alt. barriere cutanee e mucose, difetti dell'immunità umorale e cellulare
- Tempi d'insorgenza nel periodo pre-engraftement; epidemiologia locale

Neutropenia ed infezioni

- **Neutropenia post-CHT (<1.000 neutrofili/mm^3) aumenta il rischio di infezioni batteriche e fungine**
- **Neutropenia grave (< 100/mmc): rischio severo di batteriemie/sepsi ad elevata potenziale letalità**
- **Il rischio infettivo incrementa in funzione della rapidità, gravità e durata della neutropenia (leucemia post-CHT, TMO)**
- **Le manifestazioni cliniche e radiologiche possono essere modeste o assenti**
- ***Necessità di adottare una adeguata e tempestiva terapia antibiotica empirica a largo spettro***

Lima et al. Rev Bras Hematol Hemoter. 2013;35:18

Time trend of bacteremias in the neutropenic host

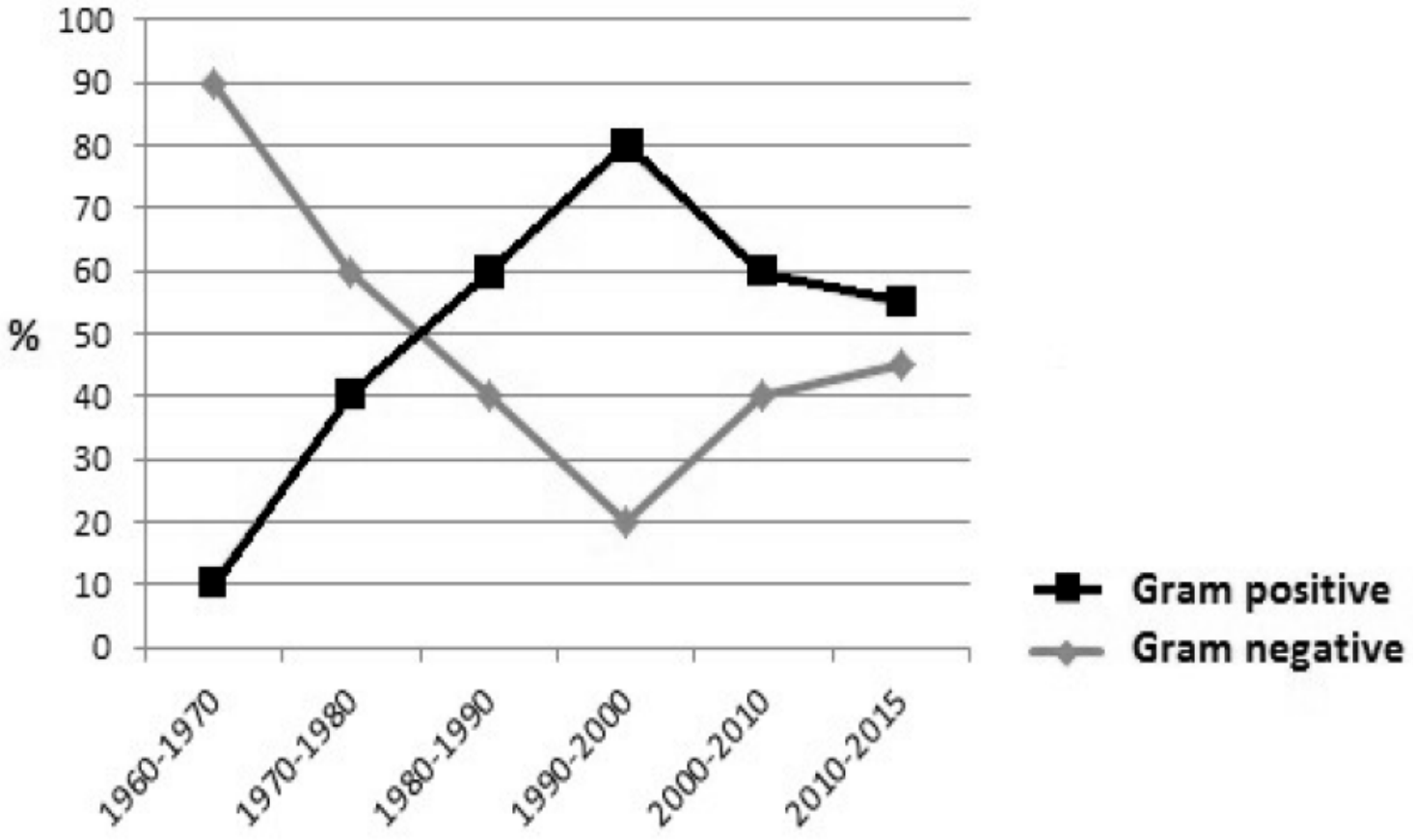
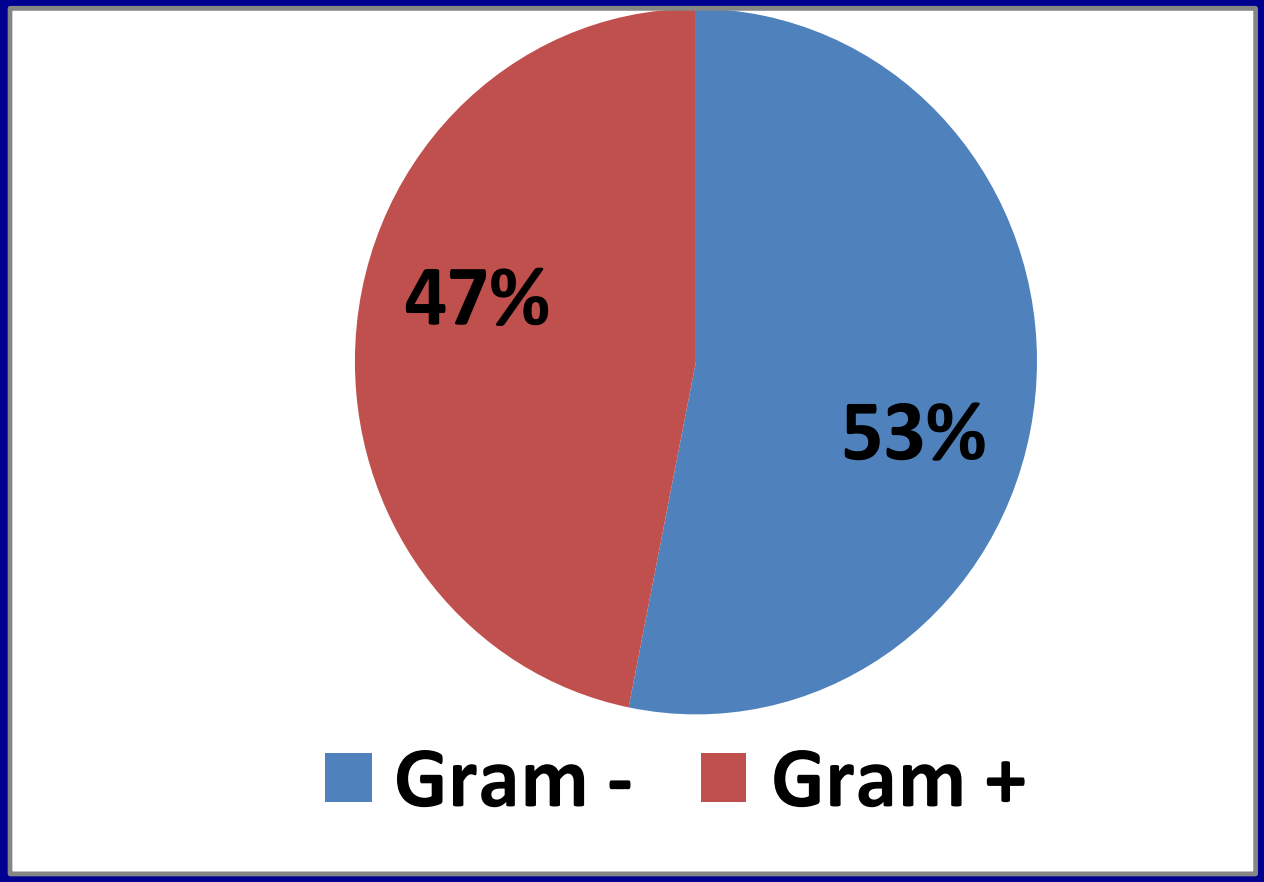


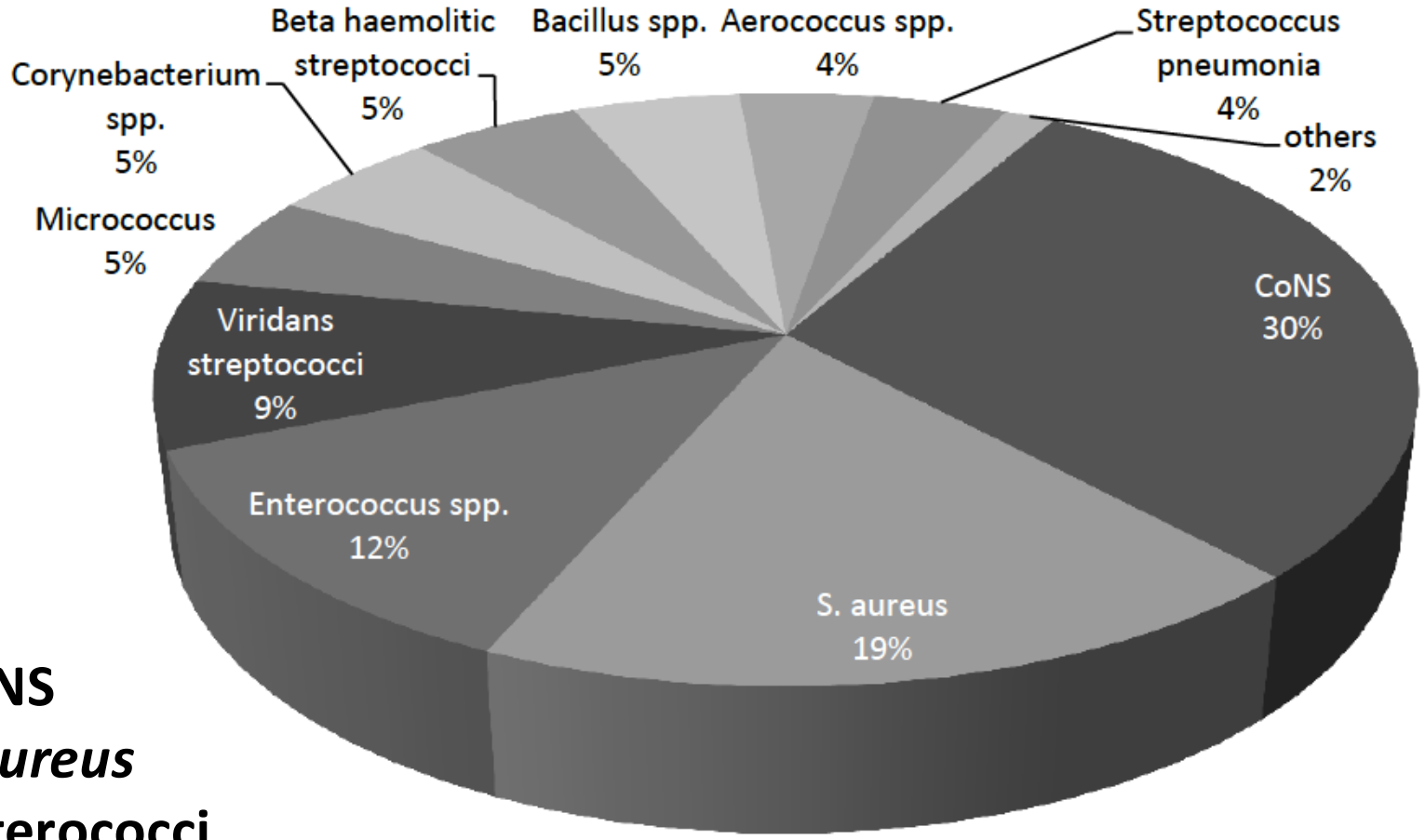
Figure 1. Time trend of bacterial etiology in neutropenic patients BSI.

Current epidemiology of bacterial BSI in patients with HM: an Italian multicentre prospective survey



Trecarichi M et al Clin Microbiol Infect 2015; 21: 337–343

Batteriemie da gram-positivi: isolati



CoNS
S.aureus
Enterococci
Viridans streptococci

Figure 2. Spectrum of gram + bacteremias in patients with cancer (1082 patients) *Modified by Rolston*[44]

Open Forum Infectious Diseases

MAJOR ARTICLE

Infections in Hematopoietic Cell Transplant Recipients: Results From the Organ Transplant Infection Project, a Multicenter, Prospective, Cohort Study

Mindy G. Schuster,[1] Angela A. Cleveland,[2] Erik R. Dubberke,[3] Carol A. Kauffman,[4] Robin K. Avery,[5] Shahid Husain,[6] David L. Paterson,[7] Fernanda P. Silveira,[8] Tom M. Chiller,[2] Kaitlin Benedict,[2] Kathleen Murphy,[1] and Peter G. Pappas[9]

[1]University of Pennsylvania, Philadelphia; [2]Centers for Disease Control and Prevention, Atlanta, Georgia; [3]Washington University, St. Louis, Missouri; [4]VA Medical Center, University of Michigan, Ann Arbor; [5]Johns Hopkins University, Baltimore, Maryland; [6]University of Toronto, Canada; [7]University of Queensland, Brisbane, Australia; [8]University of Pittsburgh, Pennsylvania; and [9]University of Alabama at Birmingham

Prospettico, multicentrico, a coorte, 2006-2011
4 centri trapianto US; 444 pazienti HCT (OTIP)
Età mediana 53 anni
HCT per HM: 87%
osservazione 30 mesi post-HCT
Mortalità cruda: 52%; mortalità infettiva: 21%
Batteriemie 231 (52%); insorgenza precoce (mediana 48 gg.)
Mortalità gram-neg/gram-pos: 45% vs 13% p=0.02

Type of Transplant & Conditioning Regimen

Table 2. Type of Transplant and Conditioning Regimen in 444 Patients

Characteristic	*n*	(%)
Transplant Type		
Matched, unrelated	245	(55)
Matched, related	177	(40)
Mismatched, unrelated	20	(5)
Mismatched, related	2	(1)
Tandem	8	(2)
Transplant Source		
Peripheral blood	386	(87)
Bone marrow	53	(12)
Umbilical cord	5	(1)
T-cell depleted	2	(<1)
Myeloablative conditioning regimen	319	(72)
Immunosuppression[a]		
Tacrolimus	388	(87)
Cyclosporine	90	(20)

[a]At any time posttransplant.

Gram-positive BSI

Table 3. Bacterial Bloodstream Infections in 444 Hematopoietic Cell Transplant Recipients

Characteristic	*N*	(Percent or Range)
Gram positive	244	(56)
Coagulase-negative staphylococci	125	(51)
Vancomycin-resistant *Enterococcus*	41	(17)
Enterococcus faecium	31	(13)
Methicillin-susceptible *Staphylococcus aureus*	17	(7)
Enterococcus faecalis	8	(3)
Methicillin-resistant *S aureus*	7	(3)
β-hemolytic streptococci	4	(2)
Other	8	(3)

Gram-negative BSI

Table 3. Bacterial Bloodstream Infections in 444 Hematopoietic Cell Transplant Recipients

Characteristic	*N*	(Percent or Range)
Gram negative	93	(21)
Pseudomonas aeruginosa	24	(26)
Escherichia coli	20	(22)
Klebsiella pneumonia	20	(22)
Stenotrophomonas maltophilia	6	(7)
Citrobacter freundii	5	(5)
Enterobacter cloacae	5	(5)
Acinetobacter baumanii complex	3	(3)
Burkholderia cepacia	2	(2)
Other	8	(9)
Polymicrobial[b]	50	(12)

Clostridium difficile

Primo tra i patogeni batterici
198 episodi in 148 pazienti (33%)
Singolo episodio in 110 pazienti (74%)
CDI ricorrente in 38 pazienti (26%)
Mediana esordio 27 d. post HCT
Mortalità in CDI: 63% (93) vs. 47% (138) in no CDI
Insorgenza pre–attecchimento; neutropenia, ATBT, immunosoppressione, trasmissione Intra-ospedaliera, GVHD gastrointestinale
Incidenza generale CDI in US nel 2011: 7.4/10.000 gg. paziente 12.1% di tutte le HCAI

Outcomes in 444 HCT pts

Table 6. Outcomes in 444 Hematopoietic Cell Transplant Recipients

Characteristic	*n*	(%)
Median time to engraftment, days	12	(0–101)
Graft-versus-host disease requiring treatment	336	(76)
Death	231	(52)
Death from underlying disease	102	(44)
Death from infection	49	(21)
Autopsy performed	24	(5)
Autopsy evidence of fungal infection	4	(1)

Open Forum Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

Infections in Hematopoietic Cell Transplant Recipients: Results From the Organ Transplant Infection Project, a Multicenter, Prospective, Cohort Study

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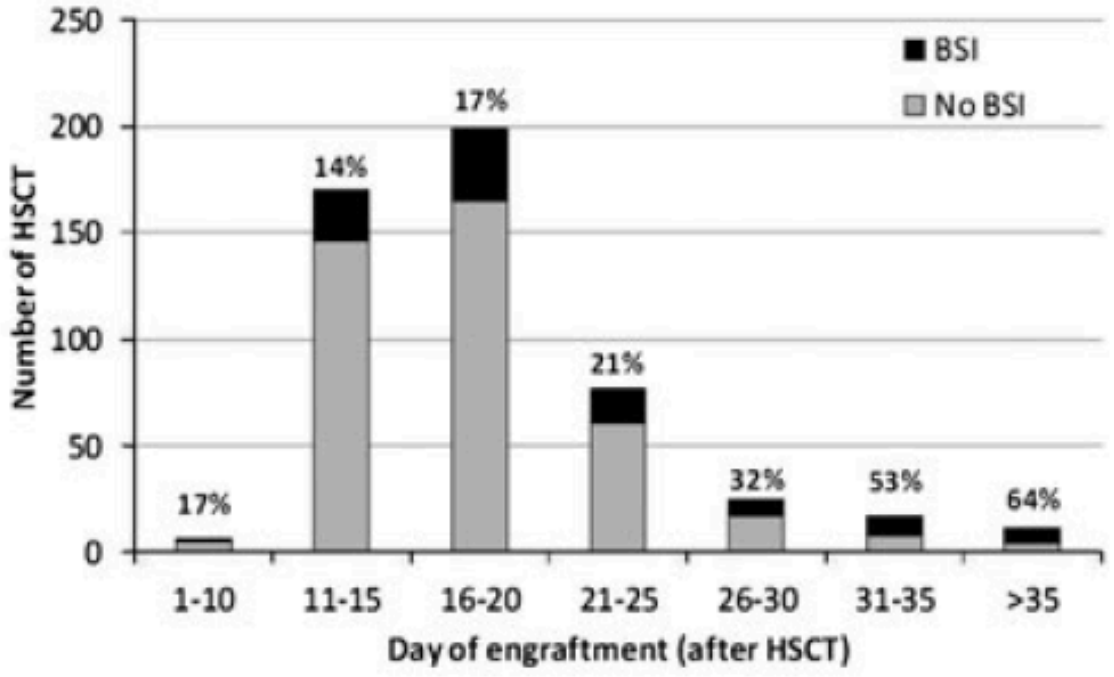
Consistent with previous studies, *Gram-positive bacteremias were more common than Gram-negatives, likely due to the association of Gram positive organisms with central venous catheters.*
Several recent studies suggest that the ratio of Gram-positive to Gram-negative bacteremias has been decreasing.

Incidence, risk factors, and outcome of bloodstream infections during the pre-engraftment phase in 521 allogeneic hematopoietic stem cell transplantations

Transplant Infectious Disease 2014: **16**: 106–114

120 BSI and day of engraftment



GRAM-POSITIVE BSI, KAROLINSKA HOSPITAL

Etiology of bloodstream infection

	2001–2008		1975–1995
Pathogen category	No. of isolates (%)[1]	No. of isolates (%)[2]	No. of isolates (%)[2]
Total bloodstream isolates	126 (100)	169 (100)	164 (100)
Gram-positive bacteria	100 (79)	145 (86)	157 (96)
Viridans streptococci	43 (34)	43 (25)	80 (49)
Coagulase-negative staphylococci	33 (26)	76 (45)	67 (41)
Enterococcus faecalis	9 (7)	9 (5)	ND
Enterococcus faecium	9 (7)	9 (5)	ND
Rothia mucilaginosa	3	3	
Staphylococcus aureus	1	1	
Group B streptococcus	1	1	
Corynebacterium species		3	
Aerococcus urinae	1	1	

Transplant Infectious Disease 2014: **16**: 106–114

RISK FACTORS FOR GRAM-POSITIVE BSI

Multivariate analysis of risk factors for bloodstream infections (BSI)

Variable	OR	95% CI	*P*-value
Total BSI, *n* = 109			
BSI with viridans-group streptococci, *n* = 43			
MAC	1.00		
RIC **Reduced intensity cond.**	0.25	0.11–0.54	**<0.001**
Related	1.00		
URD **Unrelated donor**	3.66	1.56–8.58	**0.003**
NC dose (cont)	0.91	0.85–0.96	**0.001**
Time to engraftment (cont)	1.03	0.99–1.07	0.10
ABO match	1.00		
ABO mismatch	1.76		0.10
Age (1 year increments)	0.98		0.07

Transplant Infectious Disease 2014: **16**: 106–114

RISK FACTORS FOR GRAM-POSITIVE BSI

Multivariate analysis of risk factors for bloodstream infections (BSI)

Variable	OR	95% CI	*P*-value
Total BSI, *n* = 109			
BSI with coagulase-negative staphylococci, *n* = 32			
BM+PBSC	1.00		
CB **Cord blood**	5.24	2.24–10.5	**<0.001**
BSI with *Enterococcus* species, *n* = 18			
No previous HSCT	1.00		
Previous HSCT	4.07	1.52–10.9	**<0.01**
MAC	1.00		
RIC	2.30		0.15
NC dose (cont)	0.93		0.09

Transplant Infectious Disease 2014: **16**: 106–114

Bold *P*-values are significant.

OR, odds ratio; CI, confidence interval; *n*, number; BM, bone marrow as stem cell source; PBSC, peripheral blood as stem cell source; CB, cord blood as stem cell source; URD, unrelated donor; MAC myeloablative conditioning; RIC, reduced-intensity conditioning; NC dose, nucleated cell dose; cont, continuous variable; HSCT, hematopoietic stem cell transplantation.

Incidence, risk factors, and outcome of bloodstream infections during the pre-engraftment phase in 521 allogeneic hematopoietic stem cell transplantations

- Frequency of BSI during neutropenia 21%
- Attributable mortality: 3.3%
- Declining Viridans streptococci early BSI (49%-34%)
- Reduced Intensity Conditioning: less mucositis (vs. Myeloablative conditioning)
- No VANCO required (??)
- Ciprofloxacin prophylaxis and third-gen. CFSP: enterococcal late BSI

Transplant Infectious Disease 2014: **16**: 106–114

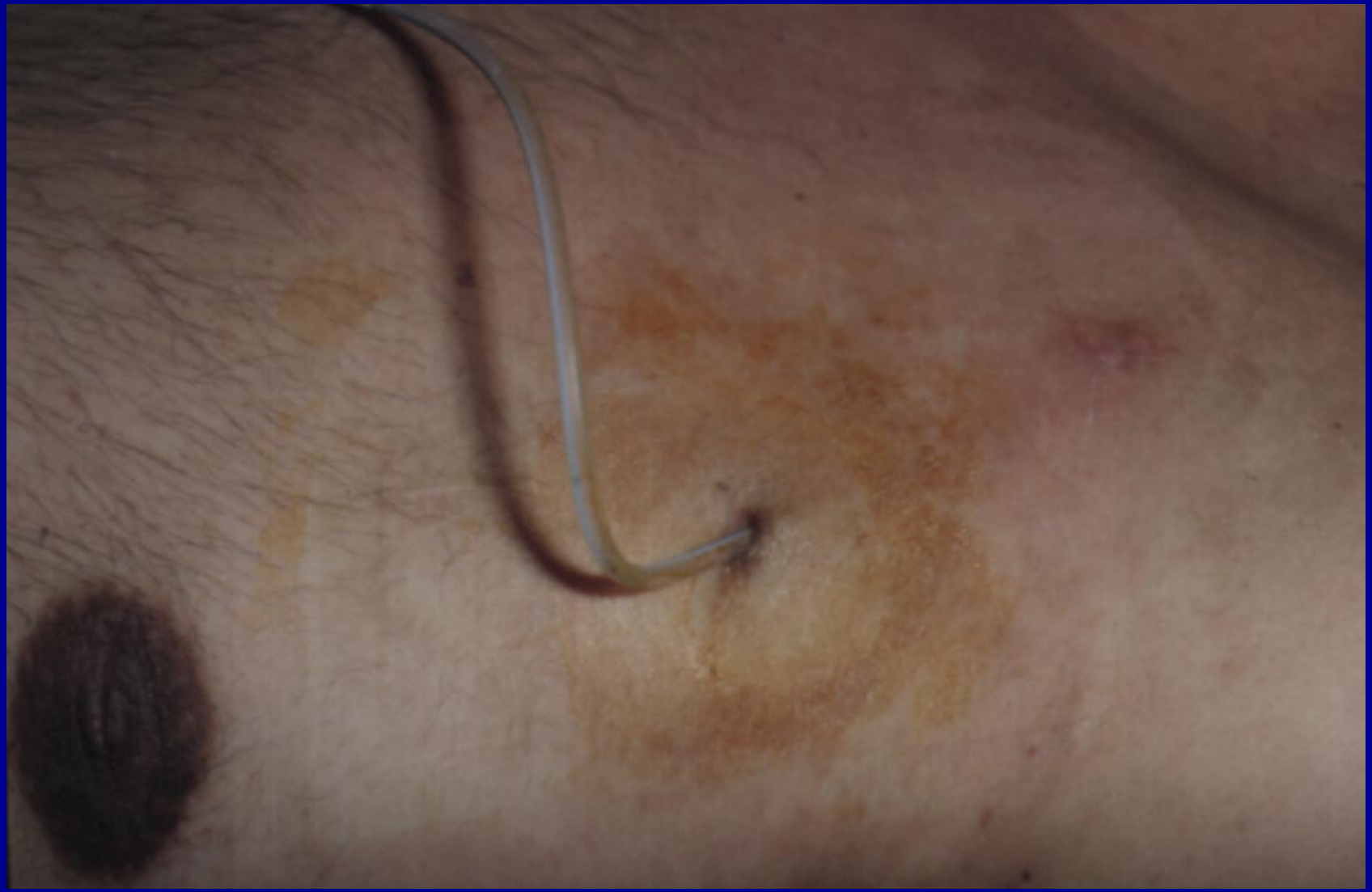
Breakthrough viridans streptococcal bacteremia in allogeneic hematopoietic stem cell transplant recipients receiving levofloxacin prophylaxis in a Japanese hospital

Fluoroquinolone prophylaxis should be considered for high-risk patients Allo-HSCT recipients with prolonged and profound neutropenia. Breakthrough blood stream infection (BSI) on fluoroquinolone prophylaxis has been reported. **Some allo-HSCT recipients have also been reported to have breakthrough BSI on levofloxacin prophylaxis, and viridans group streptococcus (VGS) is one of the causative organisms.**

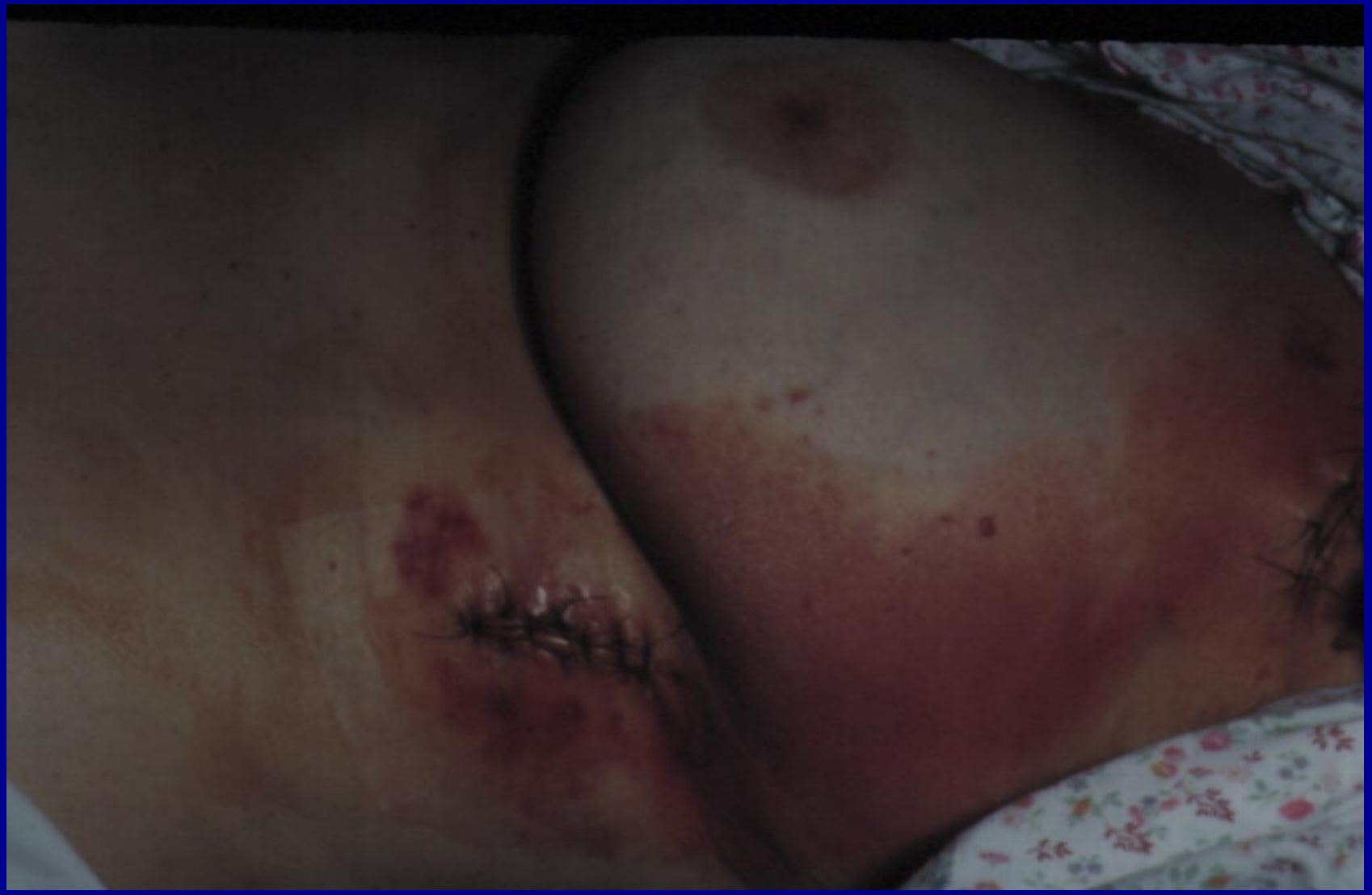
Batteriemie da gram-positivi

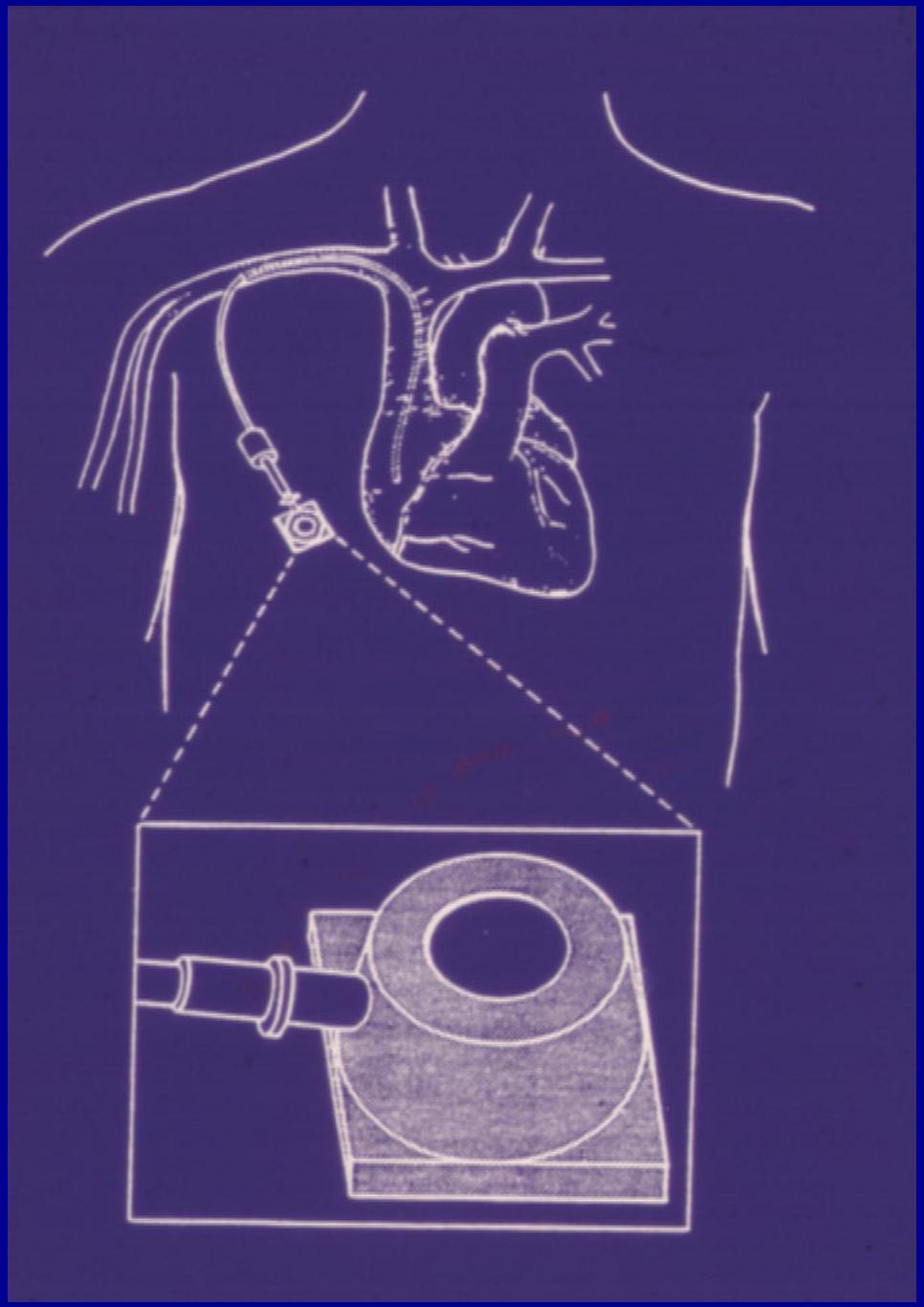
- Stafilococchi coagulasi-negativi: CVC-relate
- *Staph. aureus*: meno frequente, meno invasivo se neutropenia
- Streptococchi del gruppo viridans: mucosite orale; quadri polmonari gravi
- Enterococchi: mucosite gastrointestinale

CNS exit-site infection



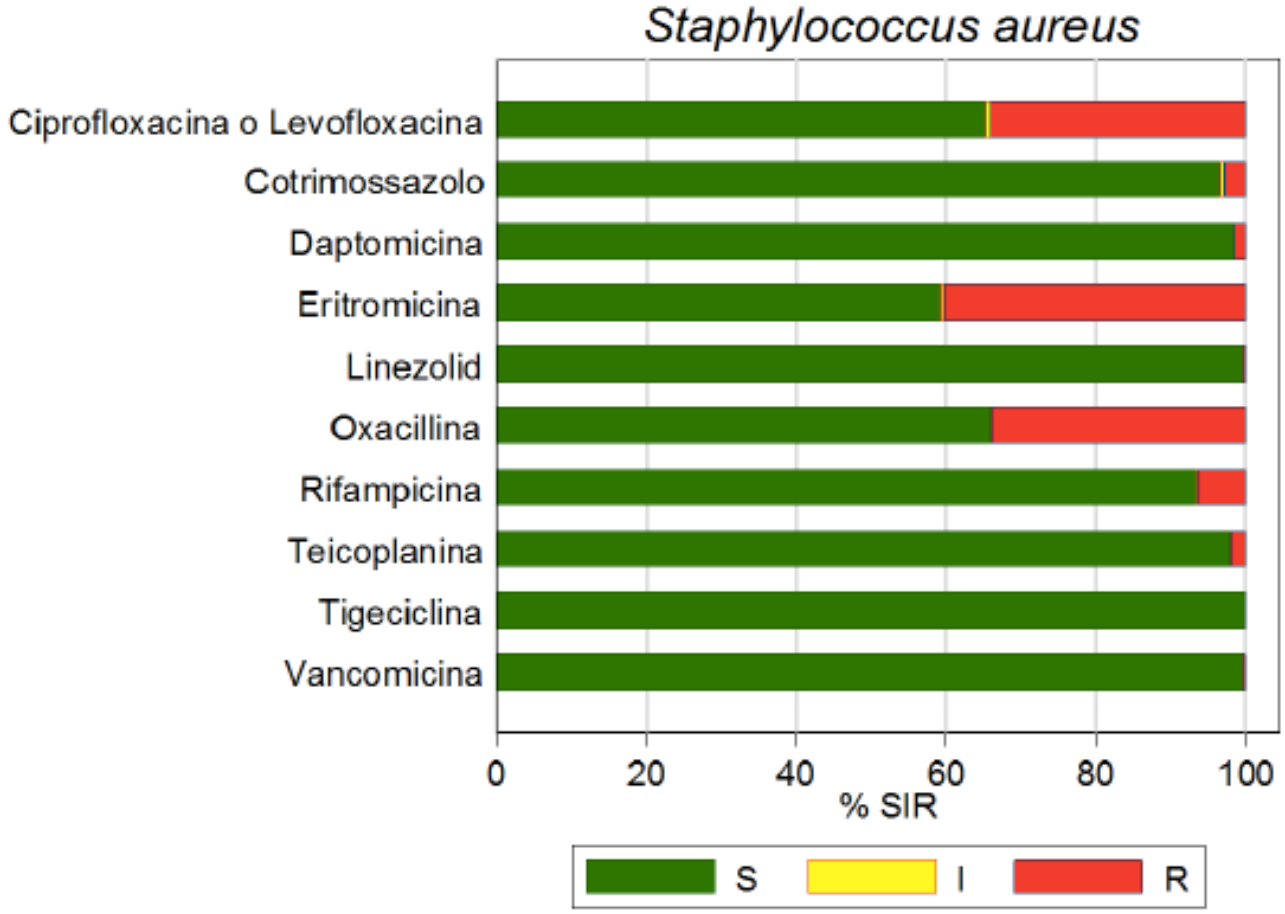
MRSA periport infection





Staphylococcus aureus:

fenotipi di resistenza: Toscana 2015



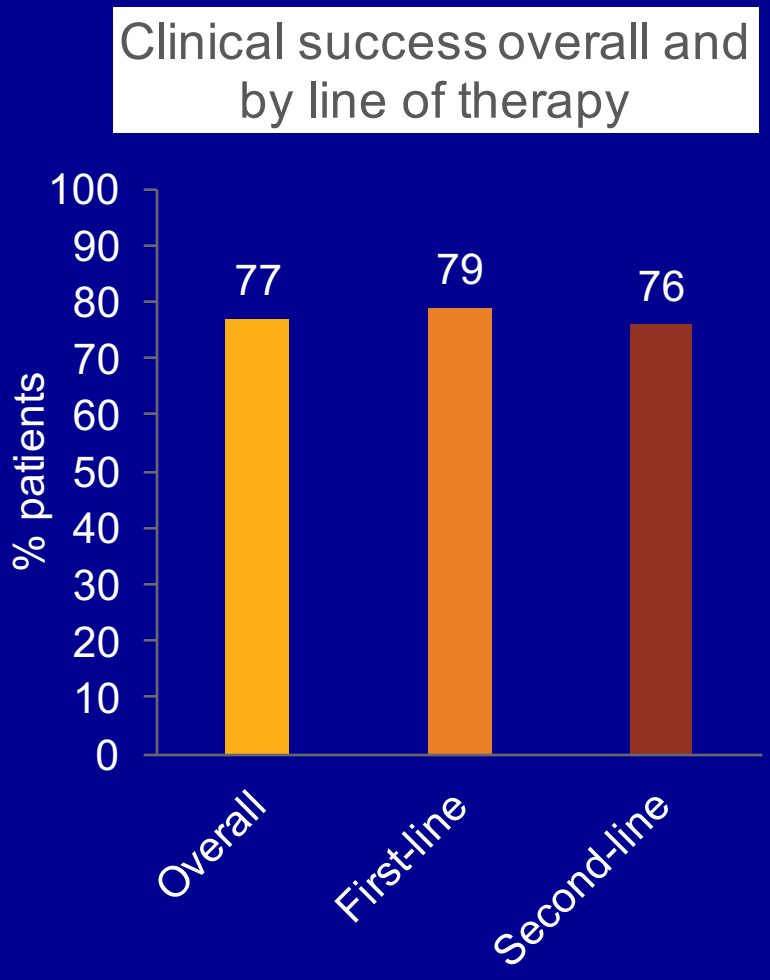
MRSA: 34%

Recommendations for the treatment of MRSA

Indication	Vancomycin	Linezolid	Daptomycin
Complicated SSTI	AI	AI	AI
Osteomyelitis Septic arthritis	BII	BII	BII
Pneumonia	AII	AII	-
CNS infections	BII (+RFP)	BII	-
Bacteremia & IE, NV	AII	-	AI
PVE	BIII (GM+RFP)	-	-

IDSA Guidelines for MRSA; CID 2011; 52 (3) e18-e55

Daptomycin in 446 pts with febrile neutropenia



Clinical success, % patients	
By primary infection	
Bacteremia	74
cSSTI	81
uSSTI	73
By pathogen	
CoNS	86
S. aureus	
Overall	77
MRSA	78

c/uSSTI, complicated/uncomplicated skin and soft tissue infection;
CoNS, coagulase-negative staphylococci;
MRSA, methicillin resistant *Staphylococcus aureus*

Source: Keil et al., ECCMID 2015 poster presentation

New anti gram-positives antibiotics

		ABSSSI	CAP	HAP	VAP	note
Ceftaroline Zinforo	Astra Zeneca	X	X			No VAP 600 mg bid
Ceftobiprole Mabelio	Basilea		X	X		No VAP 500 mg bid
Telavancina * Vibativ	Astellas	X		X	X	Once-daily 10 mg/Kg No IR
Dalbavancin Xydalba	Angelini	X				Once-weekly IV 1500mg
Oritavancin Orbactiv	The Medicines Company	X				IV Single dose 1200 mg
Tedizolid Sivextro	MSD	X				200 mg IV/OS X 6 days

* When alternative treatment is not suitable

5th Generation Cephalosporins

Ceftaroline

- ❑ Broad-spectrum cephalosporin
- ❑ Sp… E…
- ❑ C…
- ❑ B…
- ❑ IV
- ❑ t_1…
- ❑ El…
- ❑ MIC range 0.5 – 2 mg/L
- ❑ 600 mg BID

Ceftobiprole

- ❑ **Broad-spectrum cephalosporin**
- ❑ **…VISA, and**
- ❑ **Elimination: renal**
- ❑ **MIC range 0.5 – 2 mg/L**
- ❑ **500 mg TID**

Potential role in bacteremia & endocarditis (evidence pending)

Dalbavancin (Xydalba)

- Activity vs most G+
- Bactericidal for 15 days !! (1500 mg)
- Good PK profile (high concentrations, long half-life)
  - 63% in bone similar to linezolid (60%)
- Good safety proflie
- Role in CVC related bacteremia ?
- Step-down from daptomycin ?

Comparative Activity vs Staphylococci

Organism (N) Antibiotic	MIC_{90} (mg/L) MSSA (2834)	MRSA (1119)	MS CoNS (353)	MR CoNS (1129)
Dalbavancin	0.06	0.06	0.06	0.12
Teicoplanin	1	4	4	4
Vancomycin	1	2	2	2

Jones. ICAAC 2004. Abstract E-2009.

Eravacycline & Omadacycline

pros

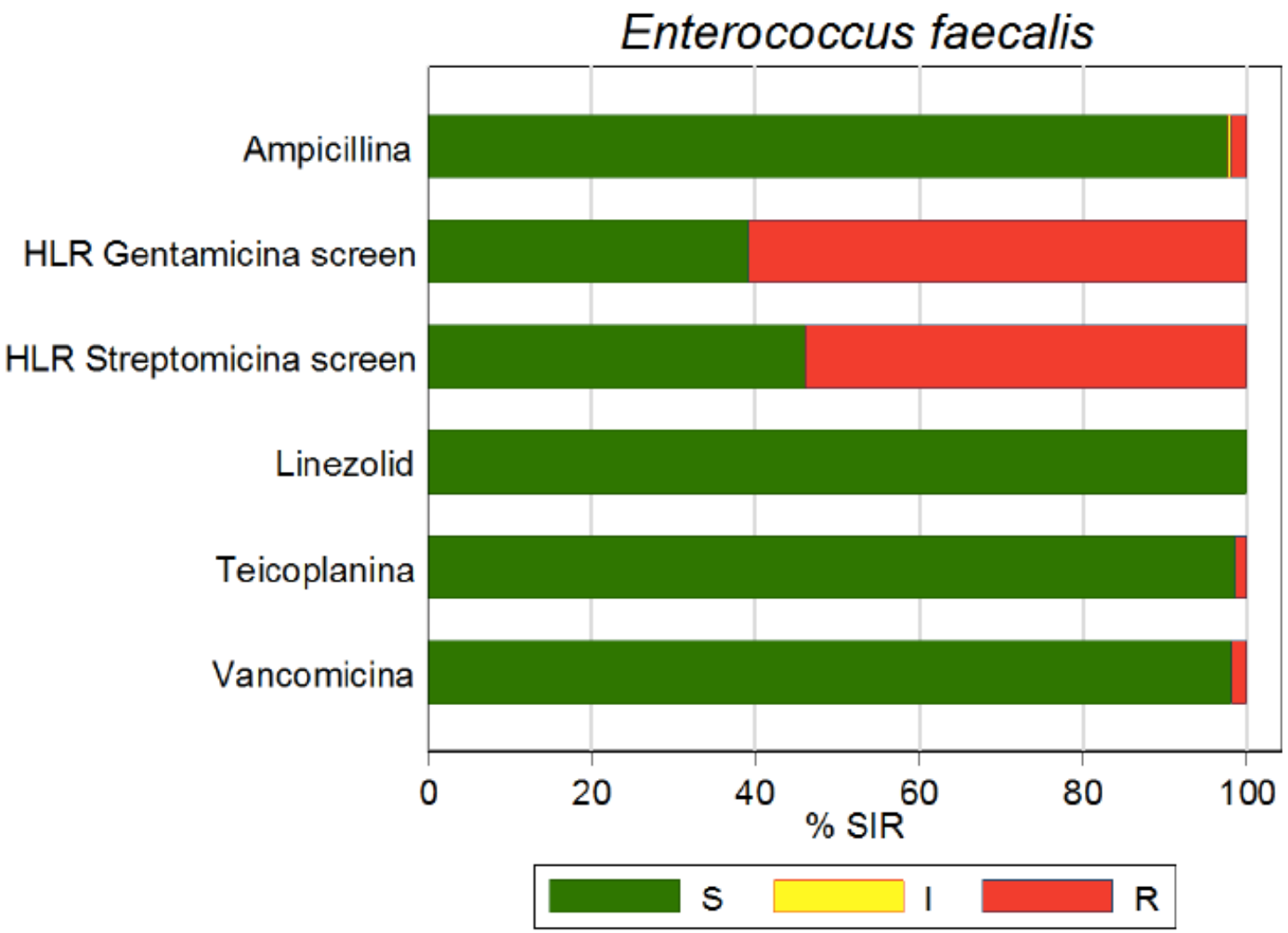
- Broad spectrum (Gram+[MRSA], Gram-[including *Acinetobacter*, ESBLs, KPC, NDMs], anaerobes)
- Favorable safety and
- tolerability profile
- Q12-Q24 interval
- Oral dosing
- Good lung/intra-abdominal/skin penetration
- OK for cSSTIs, IAIs (eravacycline)

Cons

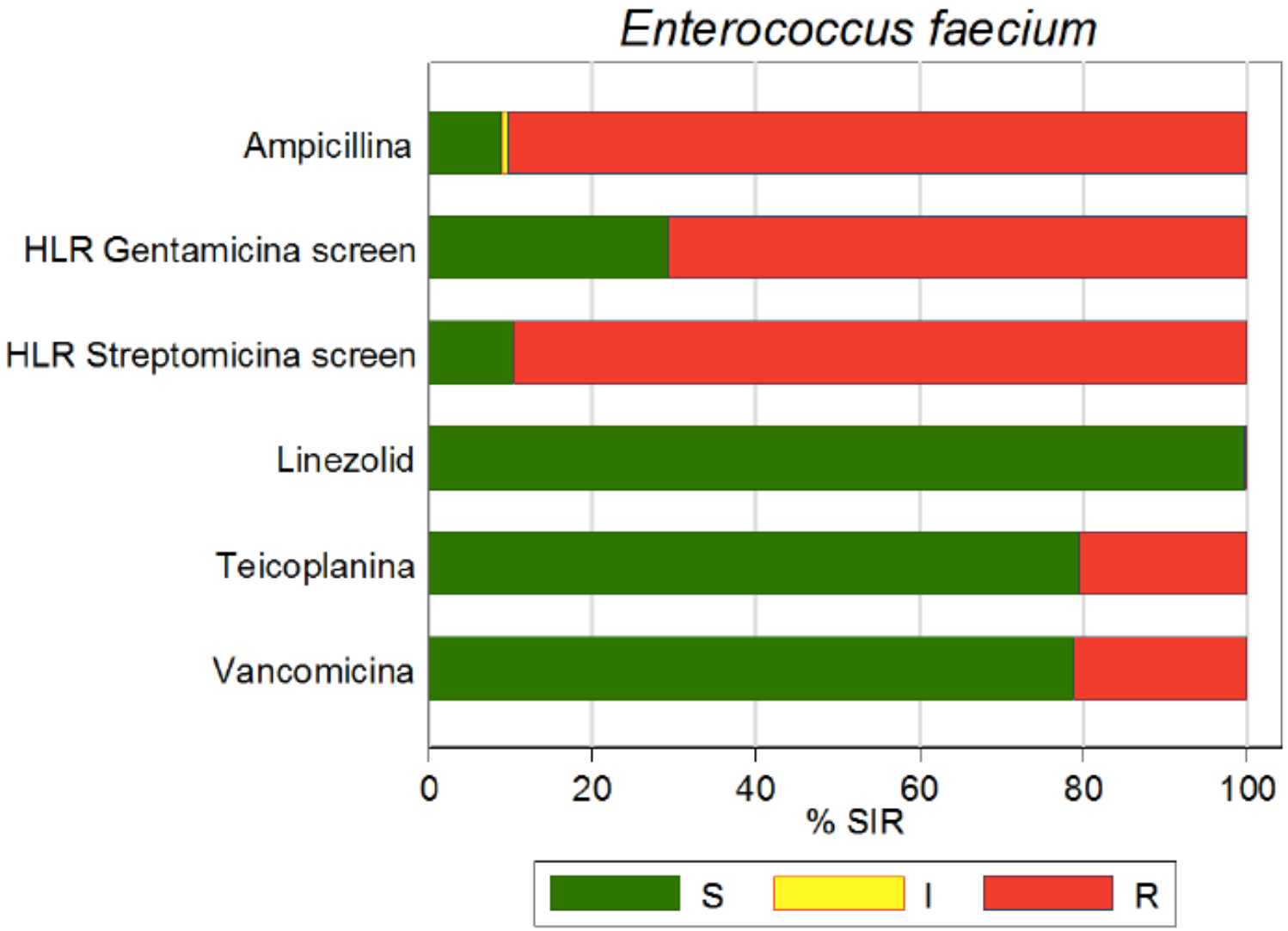
- Contraindicated in pregnancy and in children
- Failed in cUTI P3 trial (eravacycline)
- Oral formulation: low avialability (eravacycline)

Relative to tigecycline: 2-4~ more potent; 2~ higher AUC

Batteriemie da *E. faecalis*: Toscana 2015



Batteriemie da *E. faecium*: Toscana 2015



Chlorhexidine bathing for the prevention of colonization and infection with multidrug-resistant microorganisms in a hematopoietic stem cell transplantation unit over a 9-year period

Impact on chlorhexidine susceptibility

Abstract

Health care associated infections (HAIs) are currently among the major challenges to the care of hematopoietic stem cell transplantation (HSCT) patients. The objective of the present study was to evaluate the impact of 2% chlorhexidine (CHG) bathing on the incidence of colonization and infection with vancomycin-resistant *Enterococcus* (VRE), multidrug-resistant (MDR) gram-negative pathogens, and to evaluate their CHG minimum inhibitory concentration (MIC) after the intervention.

A quasi-experimental study with duration of 9 years was conducted. VRE colonization and infection, HAI rates, and MDR gram-negative infection were evaluated by interrupted time series analysis. The antibacterial susceptibility profile and mechanism of resistance to CHG were analyzed in both periods by the agar dilution method in the presence or absence of the efflux pump inhibitor carbonyl cyanide-m-chlorophenyl hydrazone (CCCP) and presence of efflux pumps (qacA/E, qacA, qacE, cepA, AdeA, AdeB, and AdeC) by polymerase chain reaction (PCR).

The VRE colonization and infection rates were significantly reduced in the postintervention period ($P = 0.001$). However, gram-negative MDR rates in the unit increased in the last years of the study. The CHG MICs for VRE increased during the period of exposure to the antiseptic. A higher MIC at baseline period was observed in MDR gram-negative strains. The emergence of a monoclonal *Pseudomonas aeruginosa* clone was observed in the second period.

Concluding, CHG bathing was efficient regarding VRE colonization and infection, whereas no similar results were found with MDR gram-negative bacteria.

Medicine (2016) 95:46(e5271)

Batteri gram-pos MDR vecchi e nuovi

Vecchi

- MRSA & MRSE
- HLGR/HLSR *E faecalis* & *E faecium*
- *E casseliflavus*
- *Pediococcus* & *Leuconostoc*
- *Erysipelothrix rusiopathiae*
- *Lactobacillus* spp

Nuovi

- *Corynebacterium striatum, C. jeikeium, C. urealyticum*
- *Staphylococcus haemolyticus*
- VISA & VRE
- Lin R/MRSA

Empiric antimicrobial regimens in the neutropenic patient

- Should be based on local epidemiology
- Infections due to Gram-positive cocci (CNS, MRSA/MSSA, streptococci) are prevalent today
- Increase of infection due to MDR/XDR GNB (i.e. ESBL + enterobacteriaceae; CR *P. aeruginosa, A. baumannii, K. pneumoniae*)
- Monotherapy (piperacillin/tazobactam or meropenem)
- An anti-Gram-positive agent may be added
- Empiric approach tailored according to specific local epidemiology/patient risk factors

When to add antibiotics vs resistant Gram-positive bacteria to the initial empiric therapy

- Haemodynamic instability, or other evidence of severe sepsis, septic shock or pneumonia
- Colonization with MRSA, VRE or P-R *S. pneumoniae*
- Suspicion of serious catheter-related infection
  - E.g. chills or rigors with infusion through catheter, and cellulitis around the catheter exit site
- Skin or soft-tissue infection at any site

Cometta et al. 41st ICAAC - Abs 774
Freifeld et al. Clin Infect Dis. 2011;52:e56

Is antibiotic de-escalation better than escalation in febrile neutropenia ?

- Defining de-escalation
  - Initial empirical regimen is very broad, with coverage of multi-resistant Gram-positive and -negative pathogens (e.g. ESBL-producers)
    - E.g. carbapenem + anti-MRSA agent
  - Therapy is de-escalated to a simpler or narrower spectrum ('targeted') regimen, once the microbiology lab does not report the presence of resistant pathogens

Conclusioni

- Infezioni da gram-pos nel paziente HCT
- Fattori di rischio molteplici
- Epidemiologia locale
- Infection-control
- Screening dei colonizzati intestinali (VRE)
- Terapia empirica/targeted in funzione gravità
- Ruolo dei nuovi antibiotici
- PROGRAMMI DI STEWARDSHIP ANTIMICROBICA

G.I.S.A.

GRUPPO ITALIANO PER LA STEWARDSHIP ANTIMICROBICA

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