

Ordine dei Medici Chirurghi e Odontoiatri
della Provincia di Udine



**BUON USO DEGLI ANTIBIOTICI NELL'ERA DELLE RESISTENZE.
COME FAR SI CHE IL MIRACOLO CONTINUI**

**Sabato 15 giugno 2019 (dalle 09.00 alle 16.30)
Auditorium Skylevel (ex Hypo Bank) - Tavagnacco**

Le infezioni della cute e dei tessuti molli

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Caso clinico 1

- D.R., M, 70 anni
- APR: ipertensione arteriosa in trattamento, mutazione fattore V Leiden, artroprotesi ginocchio sinistro (2015); esiti di safenectomia destra per insufficienza venosa
- 11/05/19: febbre (T 38,9°C) con brivido; segni di flogosi a livello di arto inferiore destro → accesso in PS, PV stabili



Caso clinico 1

- E.E.: WBC 9400/mmc; PCR 223 mg/l; PCT 2,21 ng/ml; creatinina 1,29 mg/dl; CPK 198 UI/l
- Ecografia: imbibizione tessuti molli, non raccolte; in sede inguinale destra, qualche formazione linfo-nodale con ampio ilo adiposo, la maggiore di circa 25 x 15 mm; doppler negativo
- Emocolture, tampone nasale per *Staphylococcus aureus* meticillino-resistente (MRSA)
- Terapia empirica: amoxicillina/clavulanato + clindamicina
- Comunicazione dalla Microbiologia: emocolture positive per cocci Gram positivi

- Mantenere la terapia in atto?
- *Escalation* per includere nello spettro stafilococchi meticillino-resistenti?

Risk Factors for SSTI by MRSA	Risk factors for CA-MRSA	Risk Factors for SSTI by Gram negatives
Previous colonization or contact with colonized patients	Contact sports	Diabetes mellitus and cirrhosis
Antibiotic treatment or hospitalization in the previous 12 months	Military service	Penetrating injury (<i>Pseudomonas aeruginosa</i>)
Previous infection by MRSA	Incarceration	Intravenous and subcutaneous drug use
Residence in long term care facilities	Overcrowded housing	Injury sustained in fresh water (<i>Vibrio vulnificus</i>)
Previous ICU admission	Poor hygienic conditions	Injury sustained in salt water (<i>Aeromonas hydrophila</i>)
Diabetes mellitus	Intravenous drug use	Human and animal bite
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Chronic wounds		
Peripheral vascular disease		
Immunosuppression		
Chronic renal disease and dialysis		
Farmers – LA-MRSA		

Caso clinico 1

- Emocolture positive per *Streptococcus dysgalactiae* (alfa-emolitico, gruppo Lancefield C)

Ceppo 1	Streptococcus dysgalactiae	
<u>Fenotipo MLSb di Streptococcus.</u>		
Antibiogramma		
	ANTIBIOTICO	Ceppo 1 MIC
	Cefotaxime	S ≤0,0156
	Ceftriaxone	S 0,0312
	Clindamicina	R >0,5
	Eritromicina	R 1
	Levofloxacin	S 1
	Moxifloxacin	S 0.25
	Penicillina G	S ≤0,0078

- 13/05/19: *shift* a **penicillina G** e.v. (4 MU q4h in infusione continua)

Caso clinico 1

- 15/05/19: apiretico, buoni PV
- E.E.: WBC 6250/mmc; PCR 74 mg/l; PCT 0,54 ng/ml; creatinina 1,09 mg/dl; CPK 41 UI/l



- *Early switch* ad **amoxicillina** per os (1g q6h) → fino al 22/05/19
- *Early discharge* (giorni di degenza: 4)

Caso clinico 1

- 22/05/19: fine terapia (10 giorni)



- 27/05/19



Caso clinico 2

- G.L., M, 47 anni, allevatore, addetto alla mungitura
- APR: ndp, non allergie
- APP: ultimi 6 mesi, episodi di infezioni di cute e tessuti molli (piccolo ascesso in sede ascellare, drenato chirurgicamente; cellulite di ginocchio sinistro trattata con antibiotico-terapia; piccolo ascesso cutaneo a livello di coscia sinistra)
- 22/03/19: febbre + segni di flogosi mano destra
- 25/03/19: MMG: amoxicillina/clavulanto per os, 1 g q8h → no risposta clinica

Caso clinico 2

- 29/03/19: accesso in PS, T 38,9°C, PV stabili
- E.E.: WBC 16000/mmc (N 83%), PCR 137 mg/L, PCT 0,04 ng/mL; INR 1.33; funzione epato-renale nella norma; CPK nella norma



Caso clinico 2

- Emocolture, tampone nasale per MRSA
- Ecografia: raccolta diam max 4,5 cm
- Rx mano destra: non segni di osteomielite
- Valutazione ortopedica: incisione e drenaggio



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Farmers – LA-MRSA		



Livestock-associated MRSA (LA-MRSA)



- First described in the beginning of the 2000s in livestock
- it can colonize any animal (cattle, pigs, and poultry are the main reservoirs) – agent of bovine mastitis
- belongs to clonal complex 398 (CC398) - pandemic
- No difference in the pathogenicity of LA-MRSA — compared to the nosocomial- or community-acquired types
- approximately 15% of MRSA SSTI in the community
- 1–2% of MRSA SSTI in the hospital environment

Caso clinico 2

- Ricovero in Clinica di Malattie Infettive
- 29/03/19: avvio **daptomicina** e.v. (10 mg/kg/die)
- 30/03/19: tampone nasale positivo per ***Staphylococcus aureus* meticillino-resistente (MRSA)**
 - decolonizzazione nasale con mupirocina unguento
 - decolonizzazione cutanea con clorexidina gluconato 4%
 - decolonizzazione mucose orali con clorexidina collutorio 0,2%
- Esame colturale su materiale da drenaggio: sviluppo di **MRSA**
- 01/04/19: ecografia: non raccolte residue

Caso clinico 2

Ceppo 1

Staphylococcus aureus

Discreto numero di colonie.

S. aureus meticillino-resistente (MRSA): il risultato di oxacillina predice il risultato di Cefalosporine, Carbapenemi e Betalattamine+inibitori. Si raccomanda di utilizzare le precauzioni standard e da contatto per prevenire la diffusione del microrganismo (Indicazioni per la Sorveglianza dei Microrganismi Sentinella, Direzione centrale salute, integrazione socio sanitaria, politiche sociali e famiglia - Regione FVG Versione n. 0 del 20 Novembre 2014).

Antibiogramma

ANTIBIOTICO	Ceppo 1	
		MIC
Acido fusidico	S	$\leq 0,125$
Ceftarolina	R	1
Clindamicina	S	$\leq 0,125$
Daptomicina	S	0,5
Doxiciclina	R	> 2
Eritromicina	S	≤ 1
Gentamicina	R	> 4
Levofloxacin	S	0,25
Linezolid	S	2
Oxacillina	R	> 2
Rifampicina	S	$\leq 0,062$
Teicoplanina	S	$\leq 0,25$
Tigecyclina	S	0,125
Trimetoprim-sulfametoxazolo	S	$\leq 0,25$
Vancomicina	S	$\leq 0,5$

02/04/19: switch a **linezolid** per os (600 mg q12h) → fino all'08/04/19

Caso clinico 2

- 02/04/19: rimozione drenaggio e dimissione (durata degenza: 6 giorni)
- E.E.: WBC 6230/mmc, Hb 13,2 g/dL, PLT 374.000 mg/L, PCR 7 mg/L.



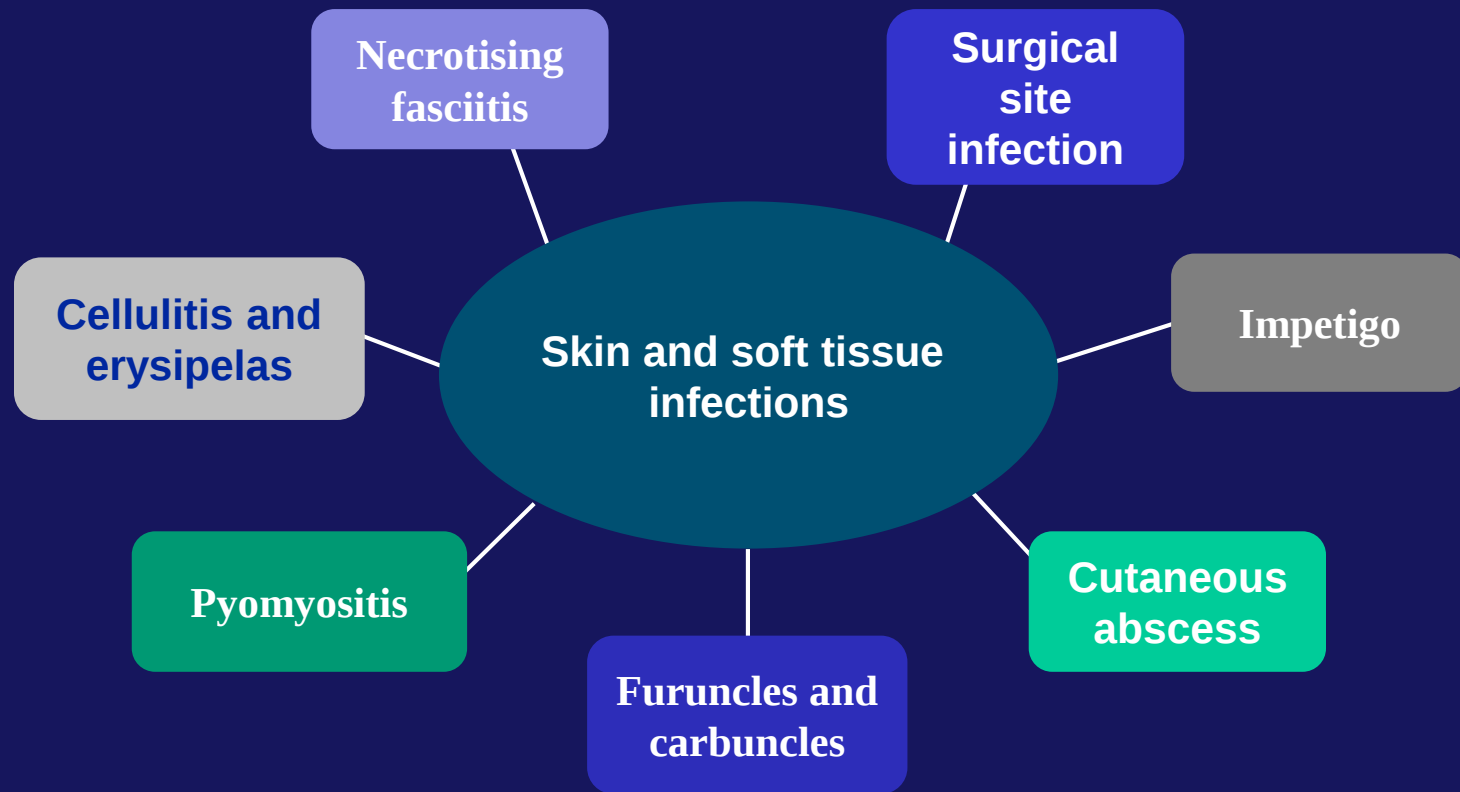
Caso clinico 2

- 08/04/19: fine terapia con linezolid



- Indicazione a screening familiari conviventi per colonizzazione da MRSA
- Contatto con Istituto zooprofilattico per screening bestiame

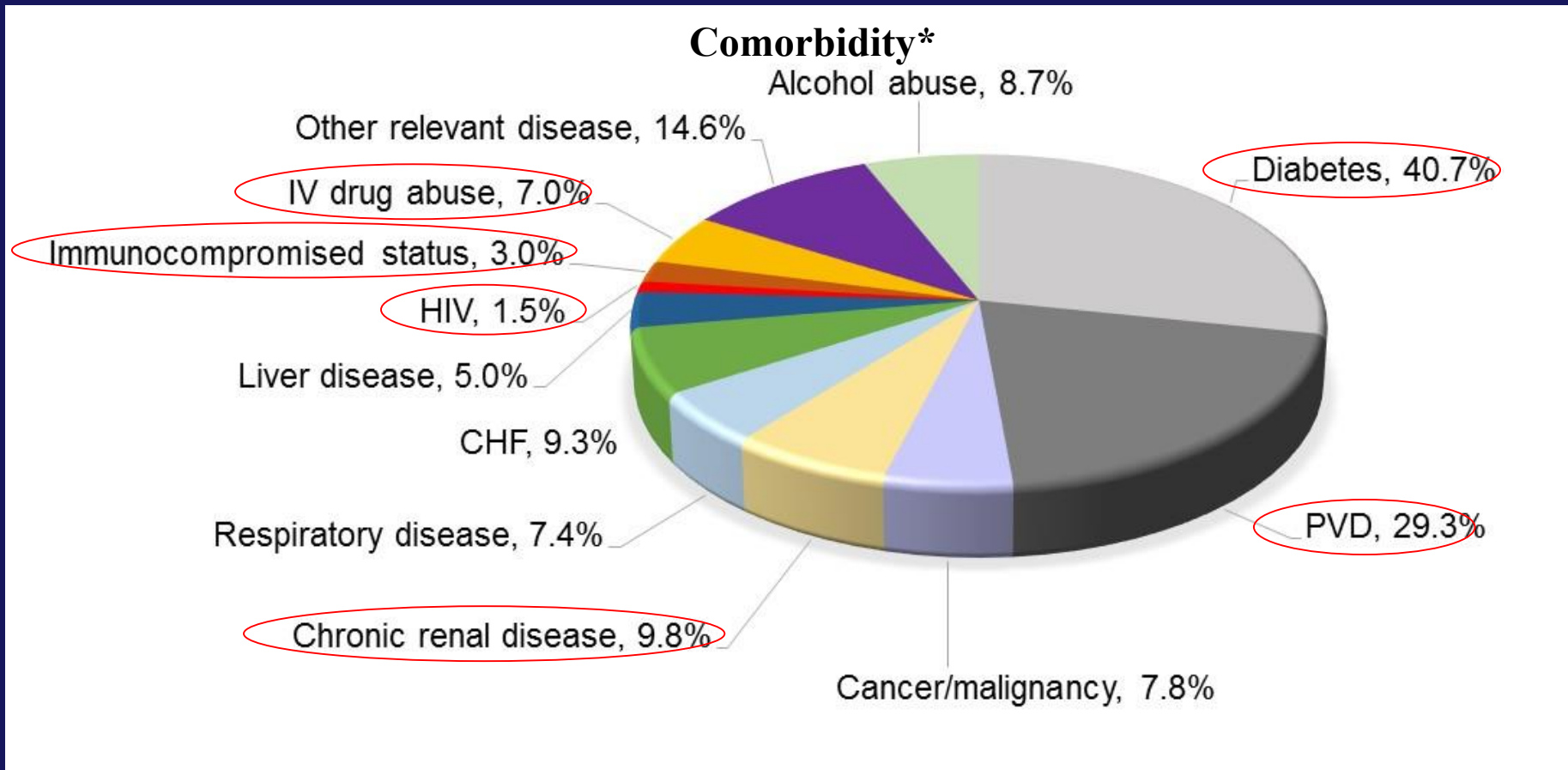
Clinical presentations of Skin and Soft Tissue Infections (SSTIs)



Definitions of uncomplicated and complicated Skin and Soft Tissue Infections (SSTI) and Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

Uncomplicated SSTI	Complicated SSTI	ABSSSI
Superficial infections	Deep soft tissue infection	SSTIs with lesions with a minimum surface area of 75 cm ²
Cellulitis	Lesion requiring surgical procedure	Criteria
Erysipelas	Large abscesses	Erythema and/or induration extending ≥ 5 cm from the peripheral margin of the infection
Folliculitis	Infected postoperative wounds	Systemic signs of infection (such as fever)
Furunculosis	Infected burns	(and/or) proximal lymphadenopathy
Ecthyma	Infected chronic ulcers	Types of infections included
Impetigo	Necrotising infections	Cellulitis, erysipelas
Infections that can be treated with surgical incision alone	Rapidly expanding infections	Major cutaneous abscesses
Small abscesses	Bacteremic infections and/or with septic shock	Wound infections
Absence of significant co-morbidities	Significant underlying diseases or co-morbidities compromising treatment outcomes	Excluded : Impetigo and minor cutaneous abscess, animal or human bites, burns, necrotizing fasciitis and myonecrosis, diabetic foot infection, chronic wound infection, ecthyma gangrenosum, underlying osteomyelitis or septic arthritis, concurrent medical conditions that would obscure evaluation of outcome (i. e. neutropenia)

Patients with skin infections frequently have co-morbidities



CHF: congestive heart failure; HIV: human immunodeficiency virus; IV: intravenous; PVD: peripheral vascular disease

Microbiology

	MSSA	MRSA	Gram+	Gram-	Anaer
Impetigo					
Erysipelas					
Cellulitis					
Abscesses					
Furuncles					
Fascitis					
Pyomyositis					
Bites					
DFI					
Decubit Ulcers					

Health care associated (HA-MRSA), community-associated methicillin-resistant (CA-MRSA) and community-associated susceptible (CA-MSSA) *Staphylococcus aureus* characteristics

Characteristic	HA-MRSA	CA-MRSA	CA-MSSA
SCC ¹ <i>mec</i> type	I-II-III	IV-VI	None
Panton-Valentine leukocidin	NO	Common	Rare
Prevalence of lineage	Classic hospital clones	ST8 (USA 300), ST80 (Europe), ST30 (Australia)	Heterogeneous
Age	Adults Elderly	Young adults	Newborn Young adults
Health care exposure	Frequent	Rare	Rare
Comorbidities	Often present	Few	Few
Antibiotic susceptibility	Methicillin resistant	Methicillin resistant	Almost all antibiotic classes

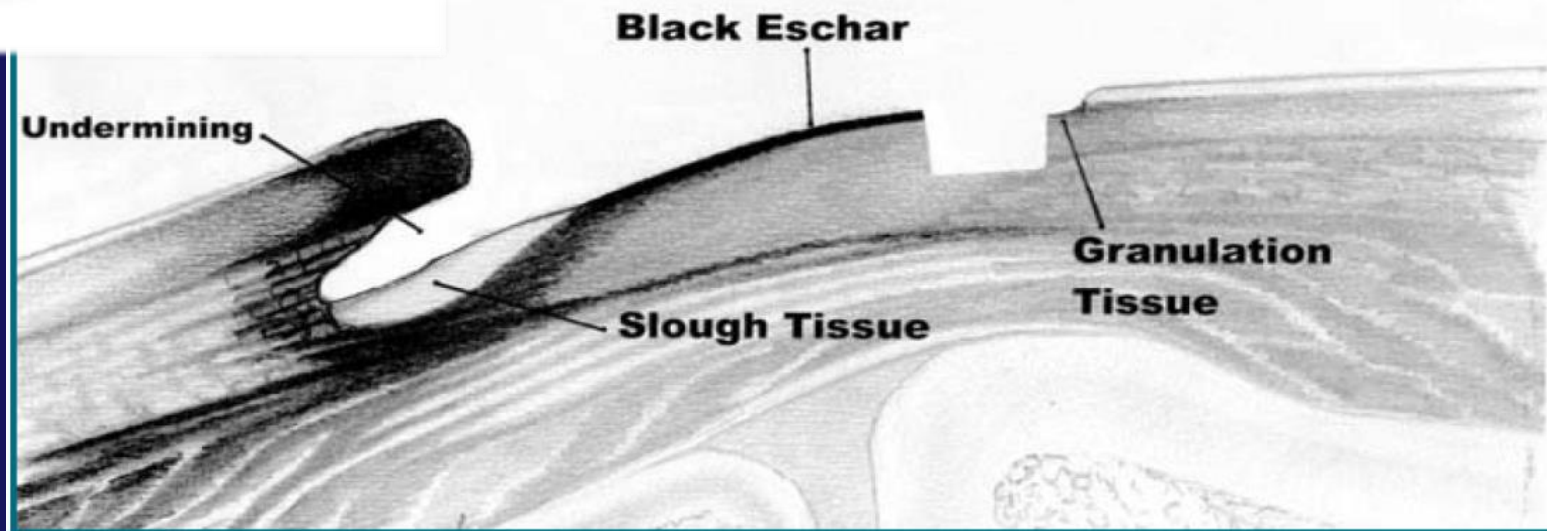
¹SCC, staphylococcal chromosome cassette

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Farmers – LA-MRSA		

Diagnosi - Campioni Da Evitare

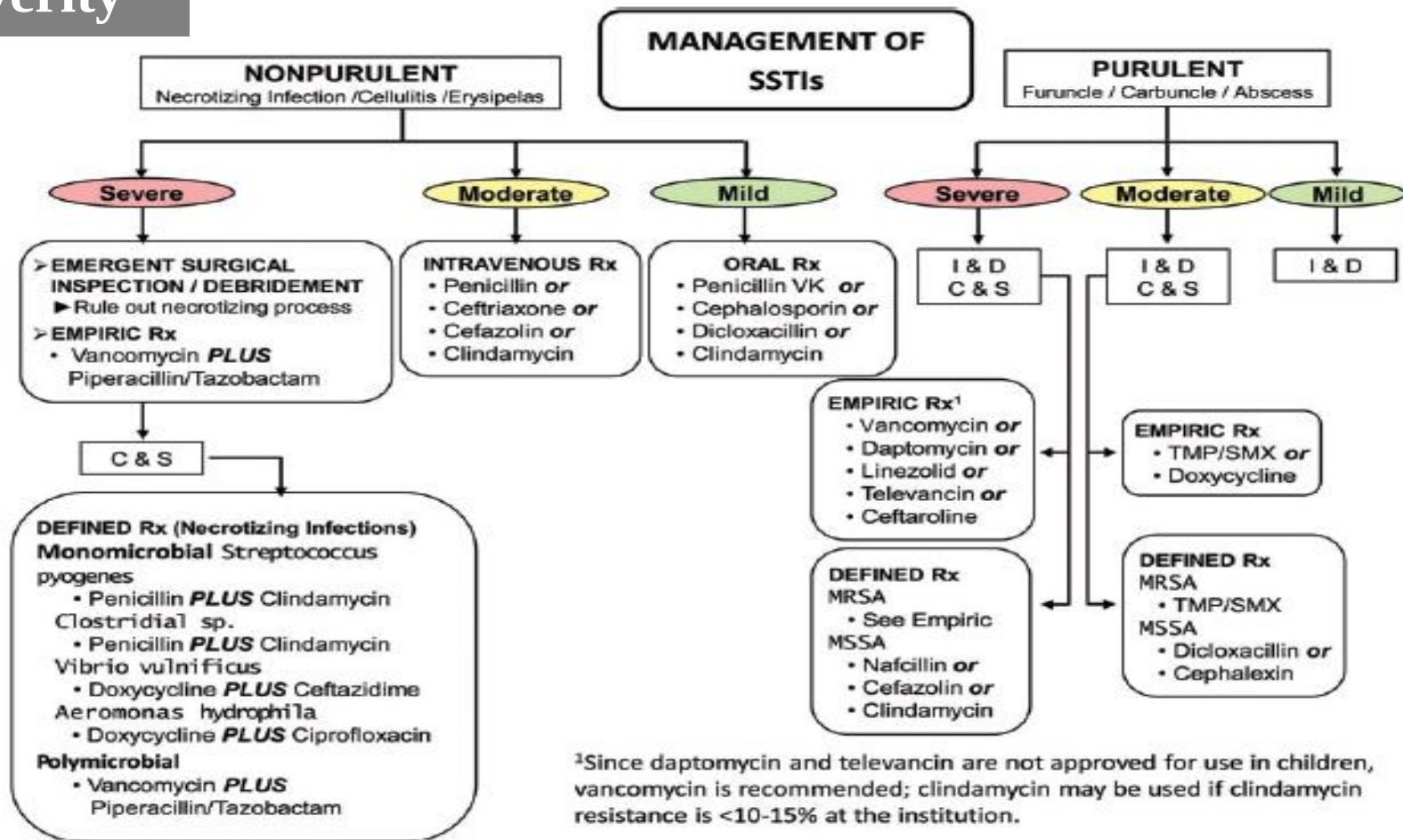
- Emocolture nelle infezioni non complicate (< 5% positive in paziente apiretico)
- tamponi di ulcere da decubito
- tamponi da fistole/ascessi perirettali
- tamponi superficiali di ulcere ai piedi e di escare
- ogni materiale adiacente mucose non ben decontaminate

Biopsia profunda/punch biopsy (gold standard)



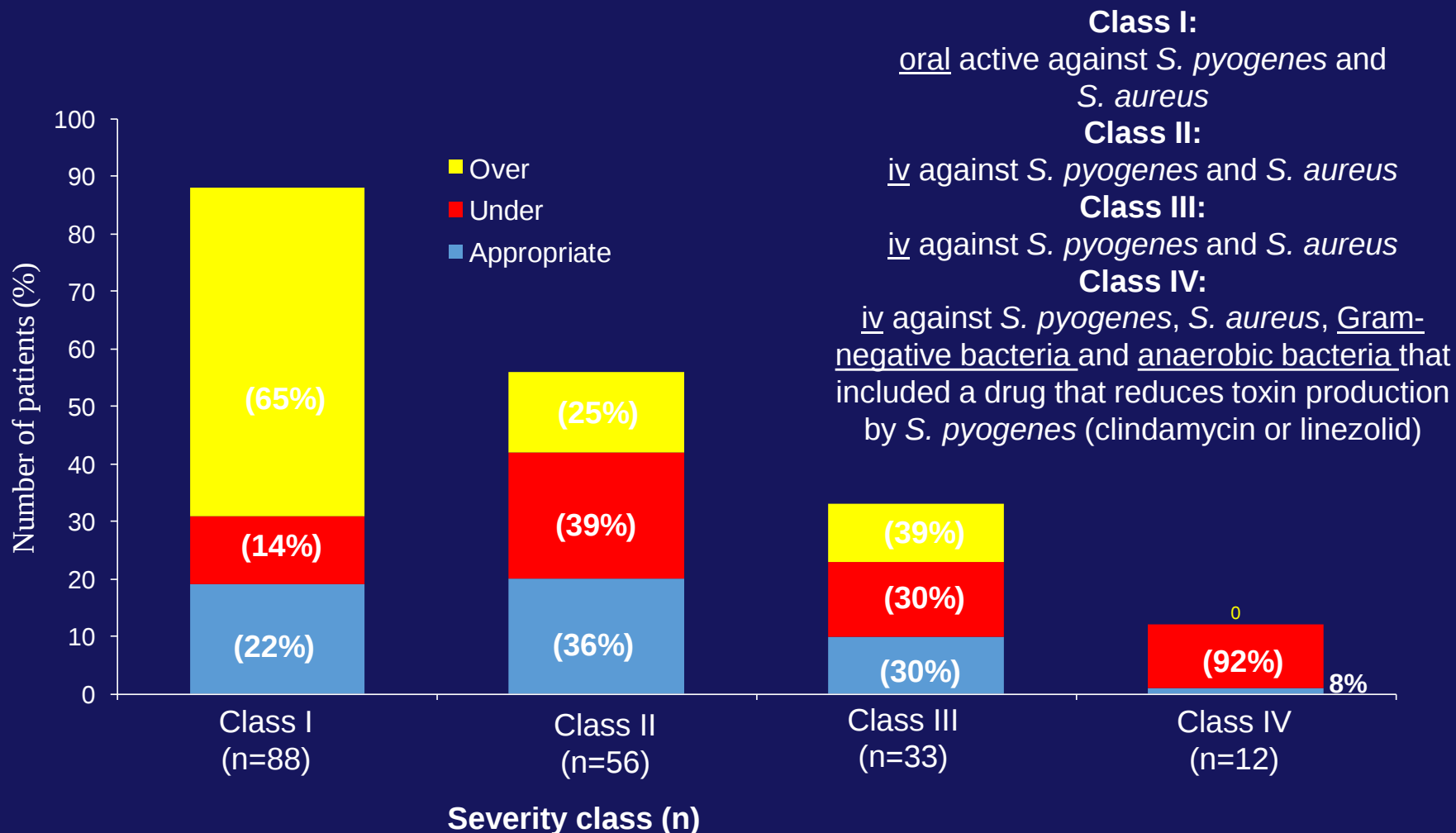
One treatment does not fit all

Purulent Severity



Empirical treatment

189 hospitalized patients with SSTI



Appropriateness of antibiotic treatment duration and selection

Variable	AGH (n = 120)	WPH (n = 43)	Total Cohort (n = 163)	p value
Appropriate treatment duration, n (%)				.74
Less than 10 days	22 (18.3)	11 (25.6)	33 (20.2)	
Inappropriate treatment duration, n (%)				.99
10 to 14 days	63 (52.5)	21 (41.9)	84 (51.5)	
More than 14 days	35 (29.2)	11 (25.6)	46 (28.2)	
Inappropriate broad spectrum antibiotics for > 24 h, n (%)				
Gram-negative coverage	52 (43.3)	21 (48.8)	73 (44.8)	.59
Anaerobic coverage	46 (38.3)	19 (44.2)	65 (39.9)	.59
Anti-pseudomonal coverage	21 (17.5)	7 (16.3)	28 (17.2)	.99

AGH Allegheny General Hospital, WPH Western Pennsylvania Hospital
p value represents comparison between study sites

- 163 episodes of uncomplicated SSTIs
- Mean duration of total antibiotic therapy: 12.6 days
- Nearly half of the patients received inappropriate therapy with extended Gram-negative coverage
- Blood cultures were collected in greater than three-quarters of patients

Dalbavancin

- Intravenous lipoglycopeptide with activity against Gram-positive pathogens and an MIC₉₀ for *S. aureus* of 0.06 µg/ml
- Half-life of > 14 day (once-weekly administration)
- Dosing regimen: 1000 mg i.v. over 30 min followed 1 week later by a 500-mg infusion (or 1500 mg i.v. as a single infusion)

TABLE 4 Dalbavancin tissue concentrations (safety population)

Tissue	Dalbavancin concn (mean [SD]; no. of samples) at hours (days) postdose that samples were collected:					
	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

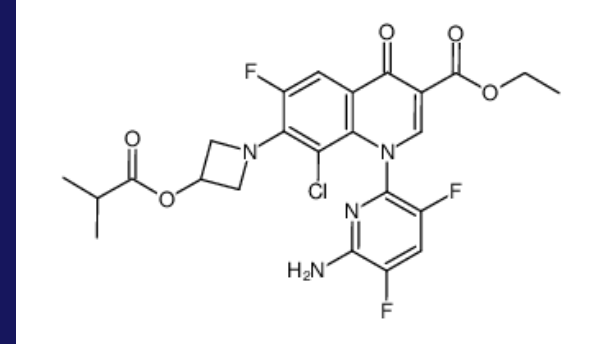
^a Mean (SD) plasma concentrations in 31 subjects at 772 and 1,080 h were 6.2 (2.4) and 3.4 (1.7), respectively.

^b ND, not detected.

^c Concentrations above the upper limit of quantification are reported as 25 µg/unit.

Delafloxacin

- New compound in the class of quinolones, approved by the FDA on June 19, 2017 for the treatment of acute bacterial skin and skin structure infections (ABSSSI)
- Very low MICs for Gram-positive (**including MRSA**) and anaerobic bacteria and a wide spectrum of activity against Gram-negative organisms
- Improved activity in acidic environments
- Low potential for drug-drug interactions
- No evidence of QT interval prolongation or phototoxicity
- Injectable/oral (300 mg bid/450 mg bid for 5-14 days)

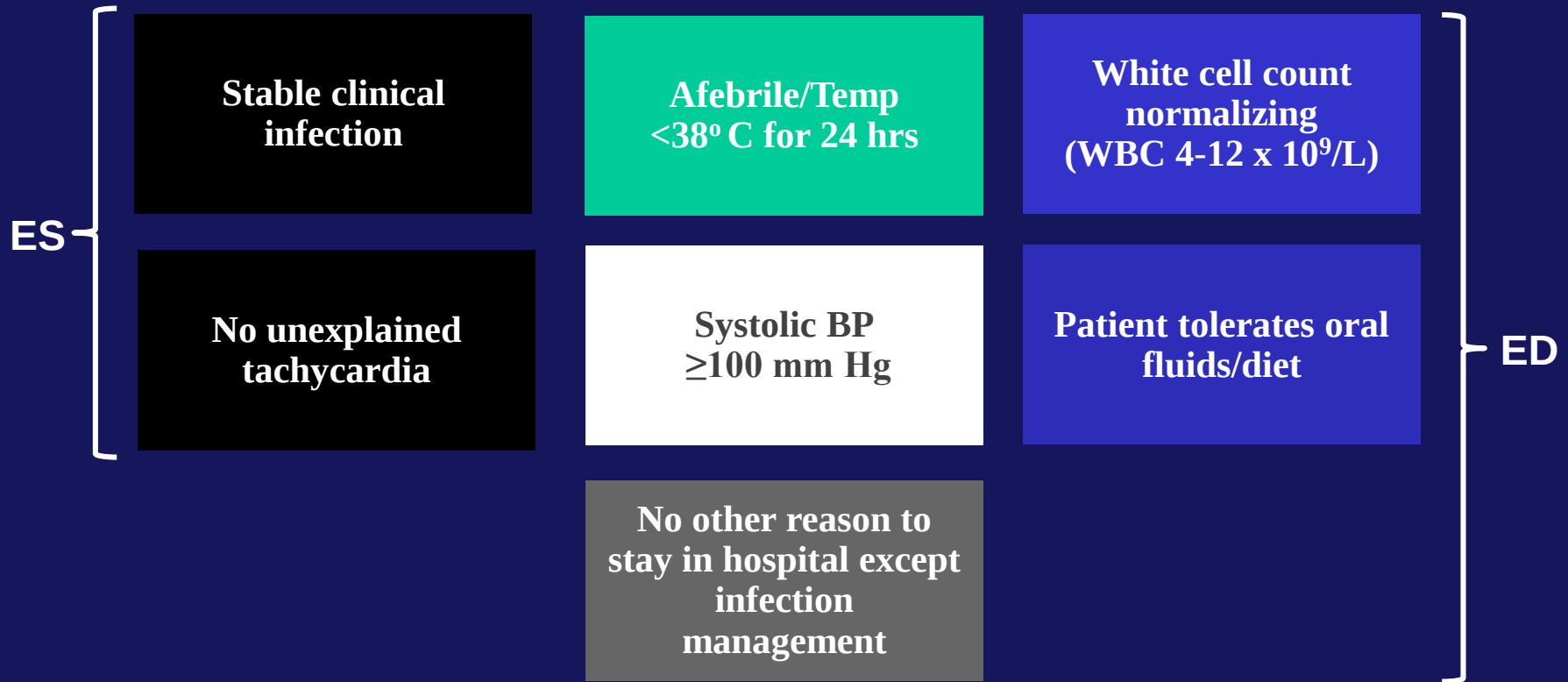


Tedizolid

- New oxazolidinone, PO and IV formulation
- Tedizolid 200 mg taken once daily demonstrated non-inferior efficacy and a good safety profile in patients with acute bacterial skin and skin structure infections
- 6 days of 200 mg tedizolid PO or sequential intravenous (IV)/PO once-daily treatment non-inferior to 10 days of 600 mg linezolid PO or sequential IV/PO twice-daily treatment
- Less myelotoxicity compared to linezolid
- Less drug-drug interactions
- Once daily

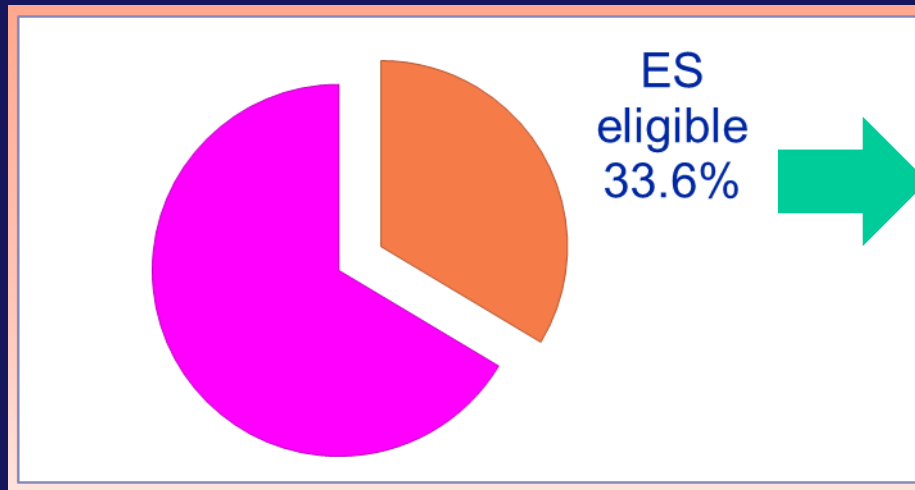
Pan-European early switch/early discharge opportunities exist for hospitalized patients with MRSA cSSTI

- Literature review with expert validation formed the basis for 14 criteria used in the study; inclusive of Desai & Parodi criteria



Possibility of Early Switch to Oral Antibiotics for Patients With MRSA cSSTI in a Pan-EU Study

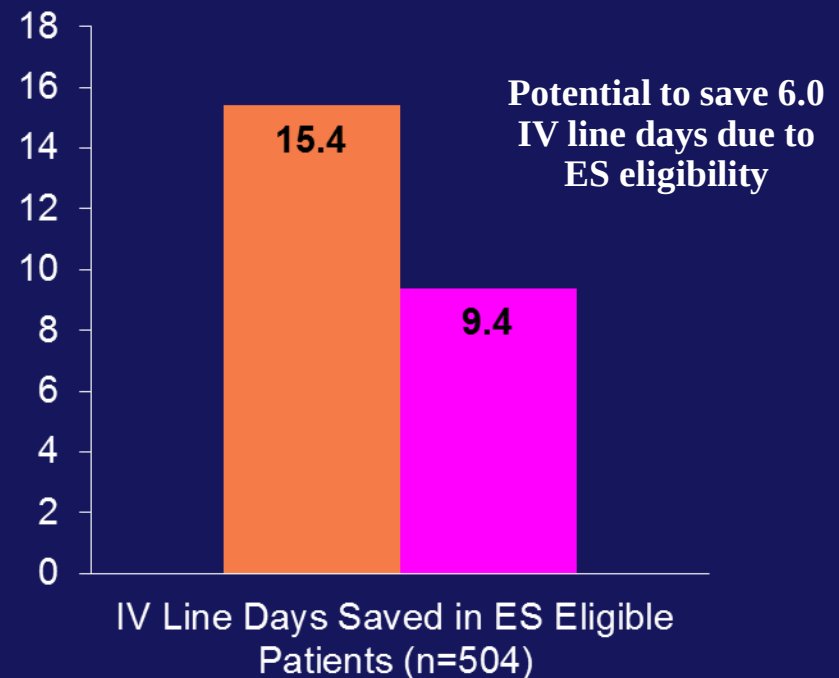
- 33.6% of MRSA cSSTI patients treated with IV antibiotics met ES criteria and potentially could have discontinued IV therapy 6.0 ± 5.5 days sooner; 37.9% met ED criteria and could have been discharged 6.2 ± 8.2 days earlier



1502 patients hospitalized with MRSA cSSTI

ES eligible patients, $n=504/1502$

■ Actual ■ Hypothetical



Take home message

1. La gestione delle infezioni non complicate di cute e tessuti molli rappresenta una significativa opportunità di *antimicrobial stewardship*
2. I pazienti con infezioni non complicate possono essere trattati con cicli brevi di terapia antibiotica (5-7 giorni)
3. E' necessario conoscere i fattori di rischio per MRSA e Gram negativi
4. Per i medici ospedalieri, vanno considerate alcune peculiarità specifiche degli antibiotici (disponibilità di formulazioni endovenose e orali che consentano l'*early switch*, molecole *long acting*, molecole a basso potenziale di interazioni farmacologiche)
5. Potenziamento dell'OPAT (*Outpatient Parenteral Antibiotic Therapy*) e necessità di centri per la terapia infusiva



Grazie