Ore 14.00-14.20 **Gestione e opzioni terapeutiche per le infezioni di cute e tessuti molli**
C. Tascini (Udine)

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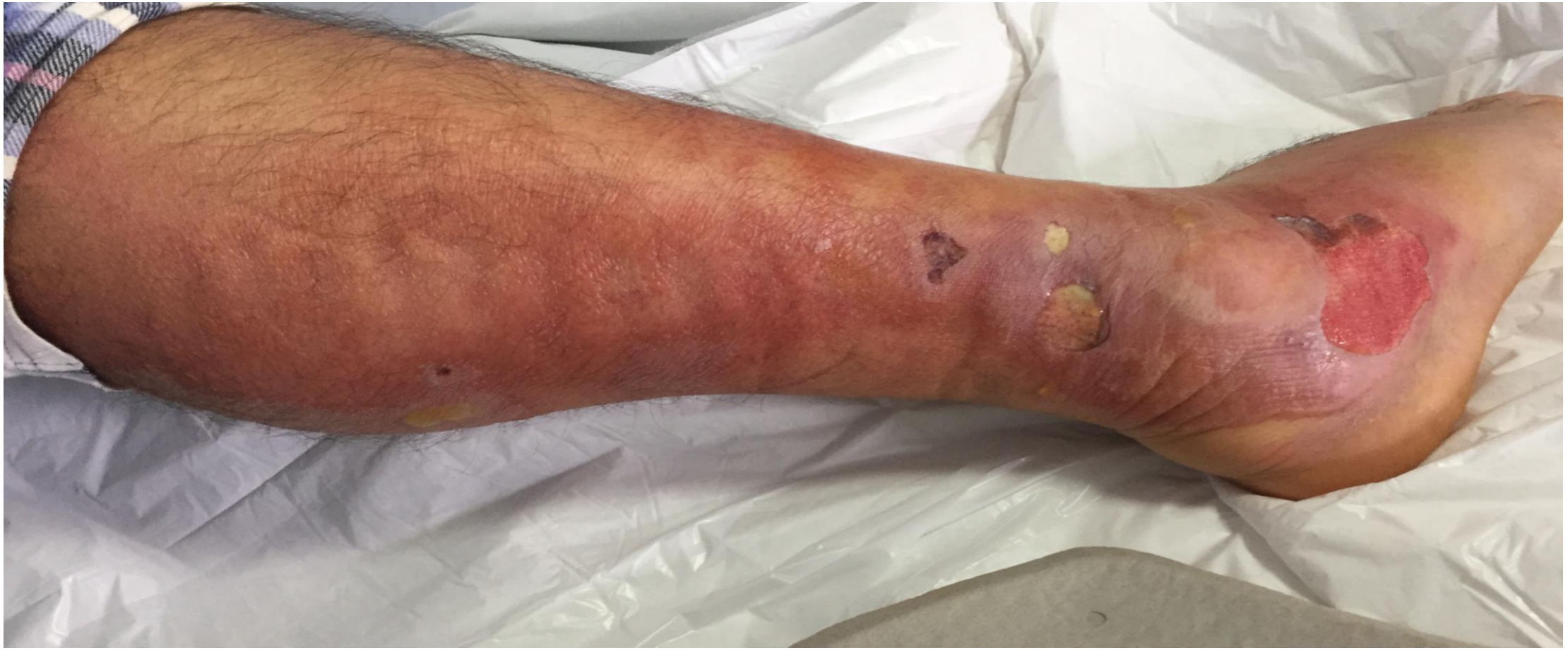
Conflict of interest Disclosure

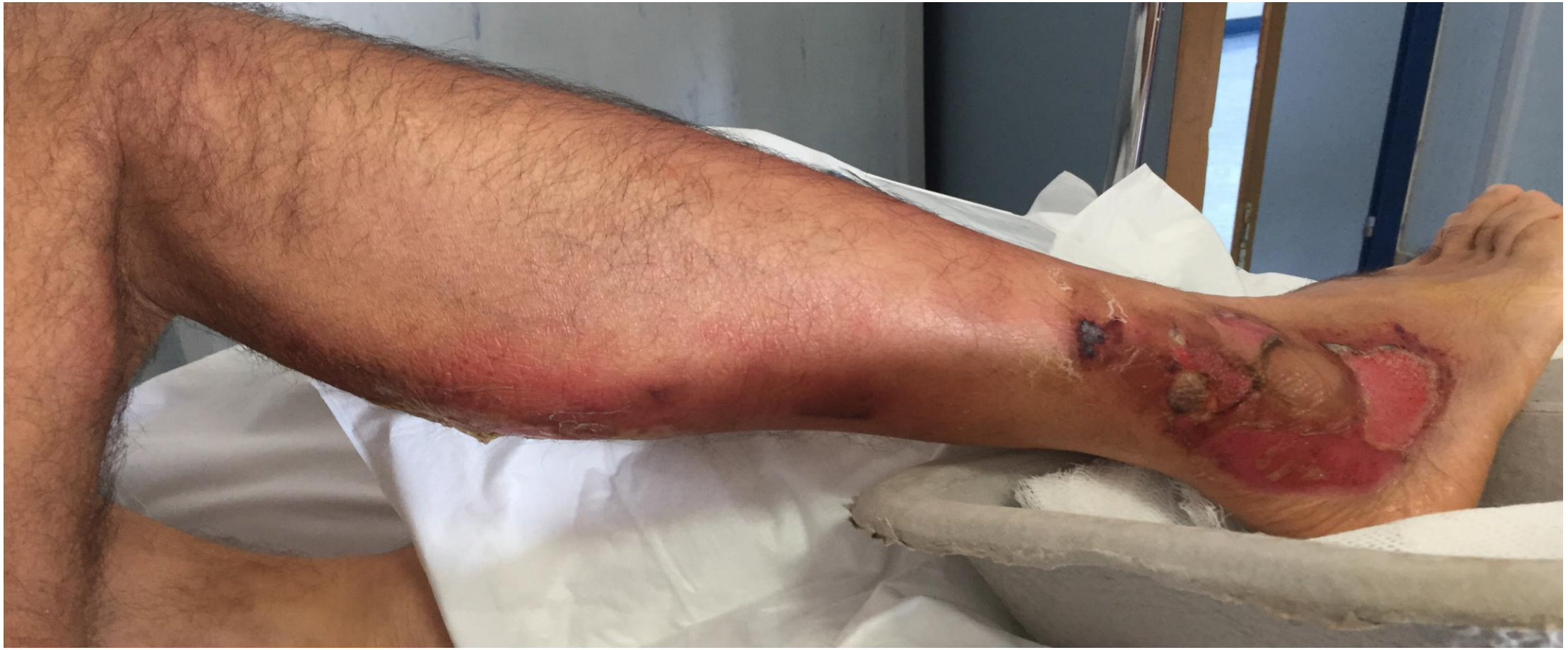
prof. Carlo Tascini has received in the last two years grants as a speaker at symposia from:

- Astrazeneca
- AVIR Pharma
- Merck
- Pfizer
- Astellas
- Angelini
- Gilead
- Novartis
- Biotest
- Thermofischer
- Correvio/Advanz Pharma
- Basilea
- Biomerieux
- Hikma
- Zambon
- Menarini
- Shionogi

Cellulite, MOF sepsi grave: SOFA 3
CPK normale



Dopo terapia con dalbavancina e ceftriaxone: TAOS elevato dopo 15 gg (cellulite da *S. pyogenes*)



SSTI

- Vanno da forme lievi a forme mortali, indicazione molto frequente alla prescrizione di antibiotici, seconda solo alle infezioni polmonari
- Primo giudizio al PS: Ospedalizzazione? Classificazione e parametri di gravità
- Le forme complicate vanno ospedalizzate: a questo punto il medico deve ben descrivere la lesione come estensione e caratteristiche, stabilire gli esami di laboratorio, le eventuali colture, decidere per la consulenza chirurgica e gli esami strumentali (RMN?): iter difficile da impostare (FOTO)
- Una classificazione adeguata può essere utile

Infezioni della cute e tessuti molli

- Patologia orfana di una disciplina di riferimento
- Trattata al PS
- Allo specialista arriva il caso complicato che non rientra nelle ABSSI

Classificazione di Eron

Table 3. Classification of SSTI according to the severity of local and systemic signs, and associated management[7]

Category	Clinical features	Management
Class 1	SSTI but no signs or symptoms of systemic toxicity or co-morbidities	drainage (if required) and oral antibiotics as outpatient
Class 2	either systemically unwell or systemically well but with co-morbidity (e.g. diabetes) that may complicate or delay resolution	oral or outpatient intravenous antibiotic therapy; may require short period of observation in hospital
Class 3	toxic and unwell (fever, tachycardia, tachypnoea and/or hypotension)	likely to require inpatient treatment with parenteral antibiotics
Class 4	sepsis syndrome and life-threatening infection (e.g. necrotizing fasciitis)	likely to require admission to ICU, urgent surgical assessment and treatment with parenteral antibiotics

ICU, intensive care unit.

CLASSIFICAZIONE FDA* DELLE INFEZIONI DELLA CUTE E DEI TESSUTI MOLLI (SSTI)

Non complicate

Infezioni superficiali:

- Foruncoli
- Lesione impetiginizzata
- Celluliti
- Ascesso superficiale

Spesso sufficiente *debridement* locale o incisione chirurgica

Complicate

Coinvolgimento dei tessuti molli profondi

Necessitano di intervento chirurgico, a volte fino alla fasciotomia

- Ulcere infette
- Ustioni infette
- Ascessi profondi, concamerati e di dimensioni maggiori

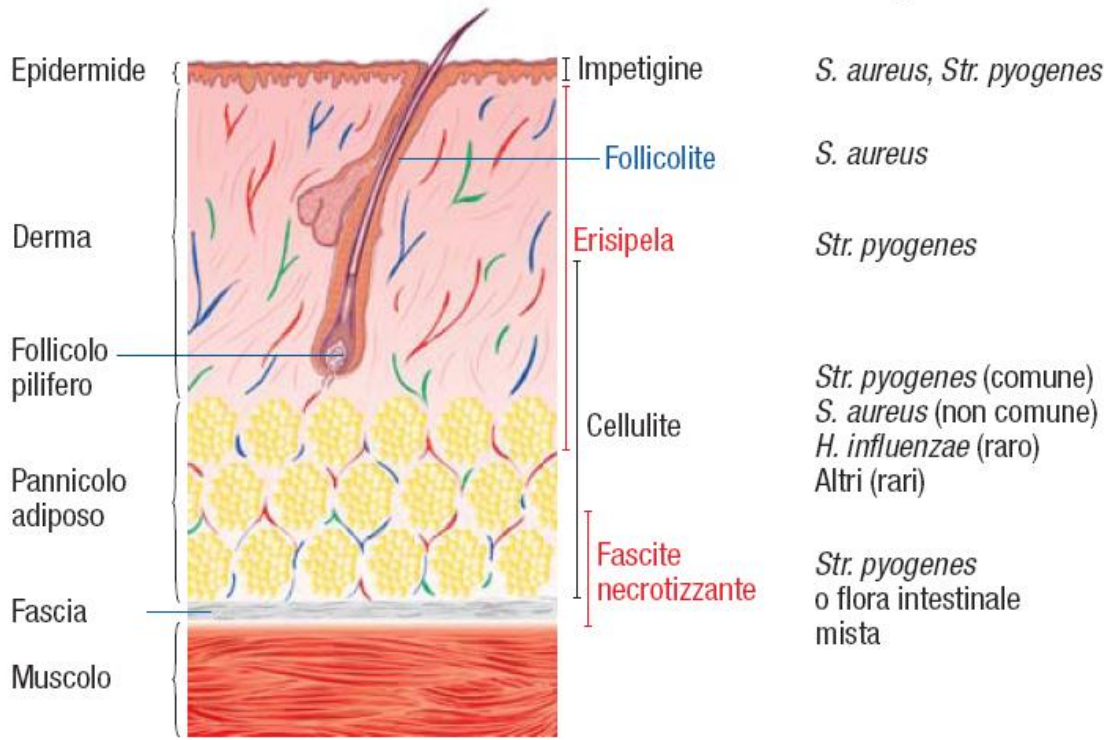
Stato di malattia predisponente, che complica la risposta al trattamento

* FDA = Food and Drug Administration

CLASSIFICAZIONE DELLE SSTI

Non complicate (prevalentemente da Gram+)
- Cellulite
- Impetigine
- Erisipela
- Ascesso semplice
- Foruncoli

Complicate (da Gram- e Gram+)
- Ulcere da decubito
- Fascite necrotizzante
- Cellulite
- Ascesso profondo
- Gangrena



FDA: SSTI complicate, serviva per gli studi clinici

- Coinvolge i tessuti profondi
- Necessità di intervento chirurgico
- Coinvolge area peri-anale
- Piede diabetico
- Malattie concomitanti: diabete, obesità immunodepressione

- Per gli studi esclude le fasciti

ABSSSI

- Esclude Piede diabetico
- Ustioni
- Fasciti

SUPPLEMENT ARTICLE

WILEY

Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update)

Benjamin A. Lipsky[1,2] | Éric Senneville[3] | Zulfiqarali G. Abbas[4] | Javier Aragón-Sánchez[5] | Mathew Diggle[6] | John M. Embil[7] | Shigeo Kono[8] | Lawrence A. Lavery[9] | Matthew Malone[10] | Suzanne A. van Asten[11] | Vilma Urbančič-Rovan[12] | Edgar J.G. Peters[13] on behalf of the International Working Group on the Diabetic Foot (IWGDF)

International Working Group on the Diabetic Foot (IWGDF); http://www.iwgdfguidelines.org

Diabetes Metab Res Rev. 2020;36(S1):e3280. https://doi.org/10.1002/dmrr.3280

wileyonlinelibrary.com/journal/dmrr

Recommendation 10:

Treat a person with a DFI with an antibiotic agent that has been shown to be effective in a published randomized controlled trial (RCT) and is appropriate for the individual patient. Some agents to consider include penicillins, cephalosporins, carbapenems, metronidazole (in combination with other antibiotic[s]), clindamycin, linezolid, daptomycin, fluoroquinolones, or vancomycin, but not tigecycline. (Strong; high)

Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update)

Benjamin A. Lipsky[1,2] | Éric Senneville[3] | Zulfiqarali G. Abbas[4] | Javier Aragón-Sánchez[5] | Mathew Diggle[6] | John M. Embil[7] | Shigeo Kono[8] | Lawrence A. Lavery[9] | Matthew Malone[10] | Suzanne A. van Asten[11] | Vilma Urbančič-Rovan[12] | Edgar J.G. Peters[13] on behalf of the International Working Group on the Diabetic Foot (IWGDF)

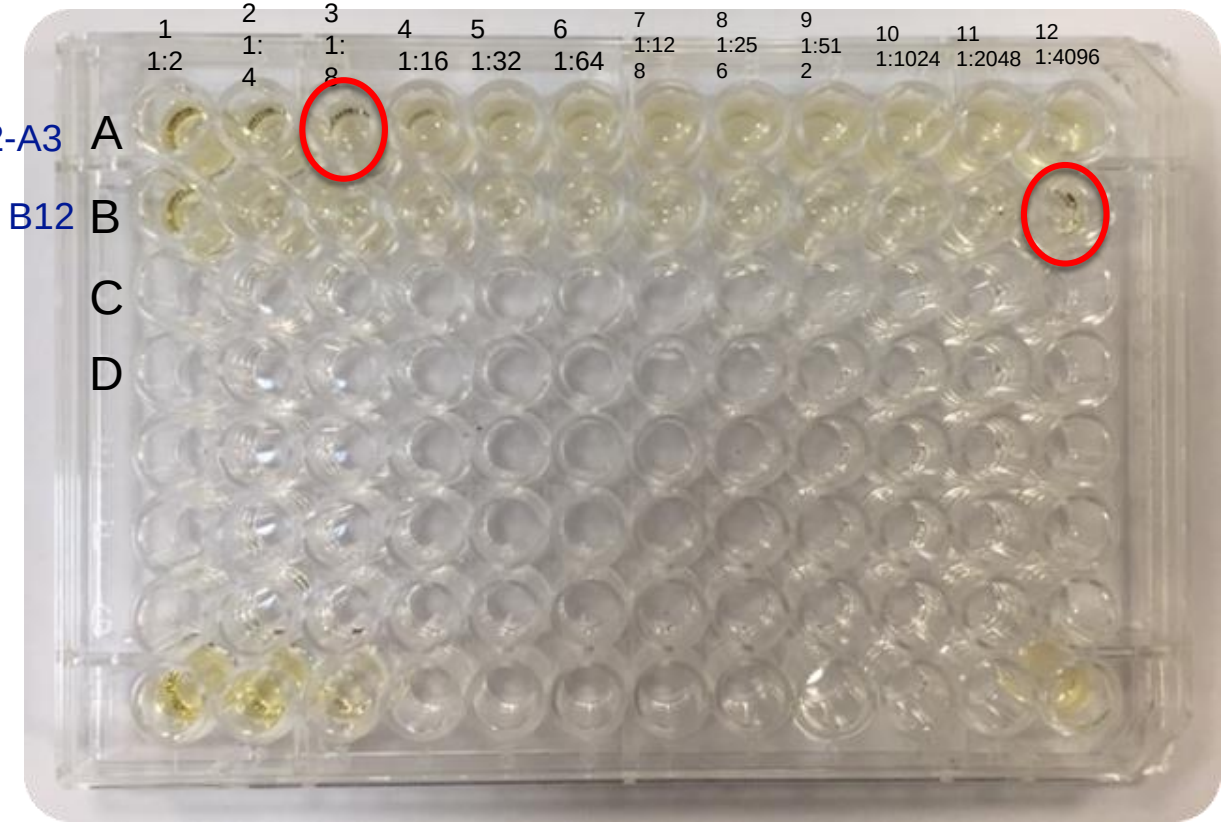
No one antibiotic class or agent has been shown to be superior to others, but tigecycline was found to be clinically inferior to ertapenem (with or without added vancomycin) for treating soft tissue (and, in a small subset, bone) infections in a well-designed clinical trial of over 1000 patients.[132] This study also showed that rates of adverse events were significantly higher in the tigecycline-treated patients. A prospective observational study of 105 patients treated with tigecycline for DFI reported clinical success in only approximately 57% of patients with a moderate or severe infection, significantly lower cure rates in those with peripheral artery disease, and adverse treatment effects in 44%.[133] Other studies have shown high failure rates with long-term treatment with tigecycline, and it is associated with a high rate of nausea.[134] Recent studies suggest that many (perhaps most)

*Serum bacteriostatic/bactericidal activity of **dalbavancin** against a strain of MSSA isolated from a patient with a diabetic foot infection*

inoculum → *< 20*
$2x10^5$ *CFU/well*

Line A, day 1, *linezolid 600mgx2* clear A1-A2-A3

Line B, day 1, *30 minutes* all clear until B12 *after dalbavancin 750 MG (picco)*



1a dose Dalbavancin 750 mg (IRA)

..

*Serum bacteriostatic/bactericidal activity of **dalbavancin** against a strain of MSSA isolated from a patient with diabetic foot infection*

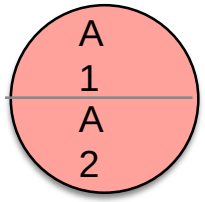
for growth of all three subcultures

inoculum 2x105 → *< 20 CFU*

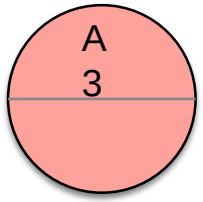
for each subculture 5 CFU (subcultured a quarter of well 50 µl of volume/200 µl

linezolid 600x2

SBA≥1:2



1:2
1:4



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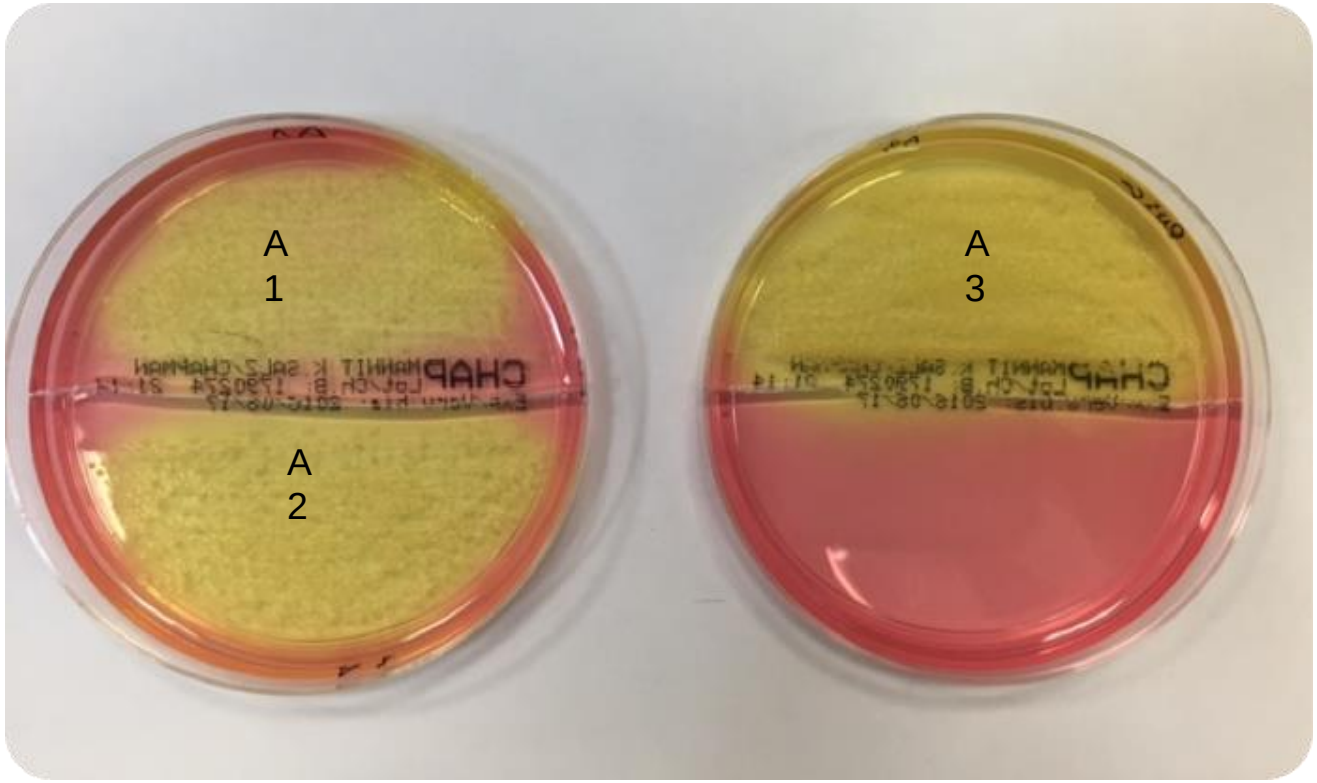
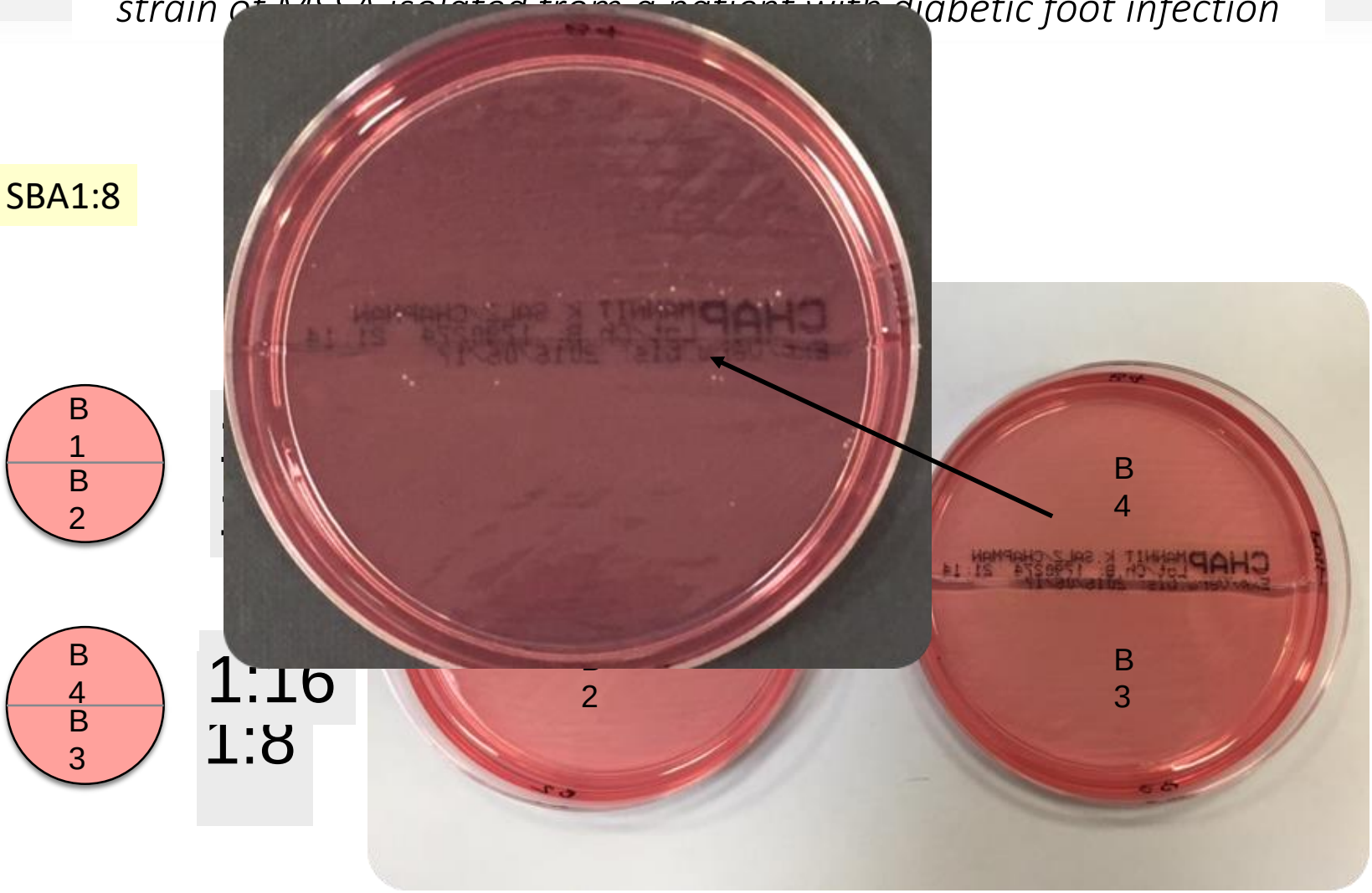


1a dose Dalbavancin 750 mg (IRA)

..

*Serum bacteriostatic/bactericidal activity of **dalbavancin** against a strain of MSSA isolated from a patient with diabetic foot infection*

SBA1:8



positive growth only in B4 > 20 CFU

1a dose Dalbavancin 750 mg (IRA)

*Serum bacteriostatic/bactericidal activity of **dalbavancin** against a strain of MRSA isolated from a patient with a diabetic foot infection without osteomyelitis*

Line A, day 1, *before dalbavancin*

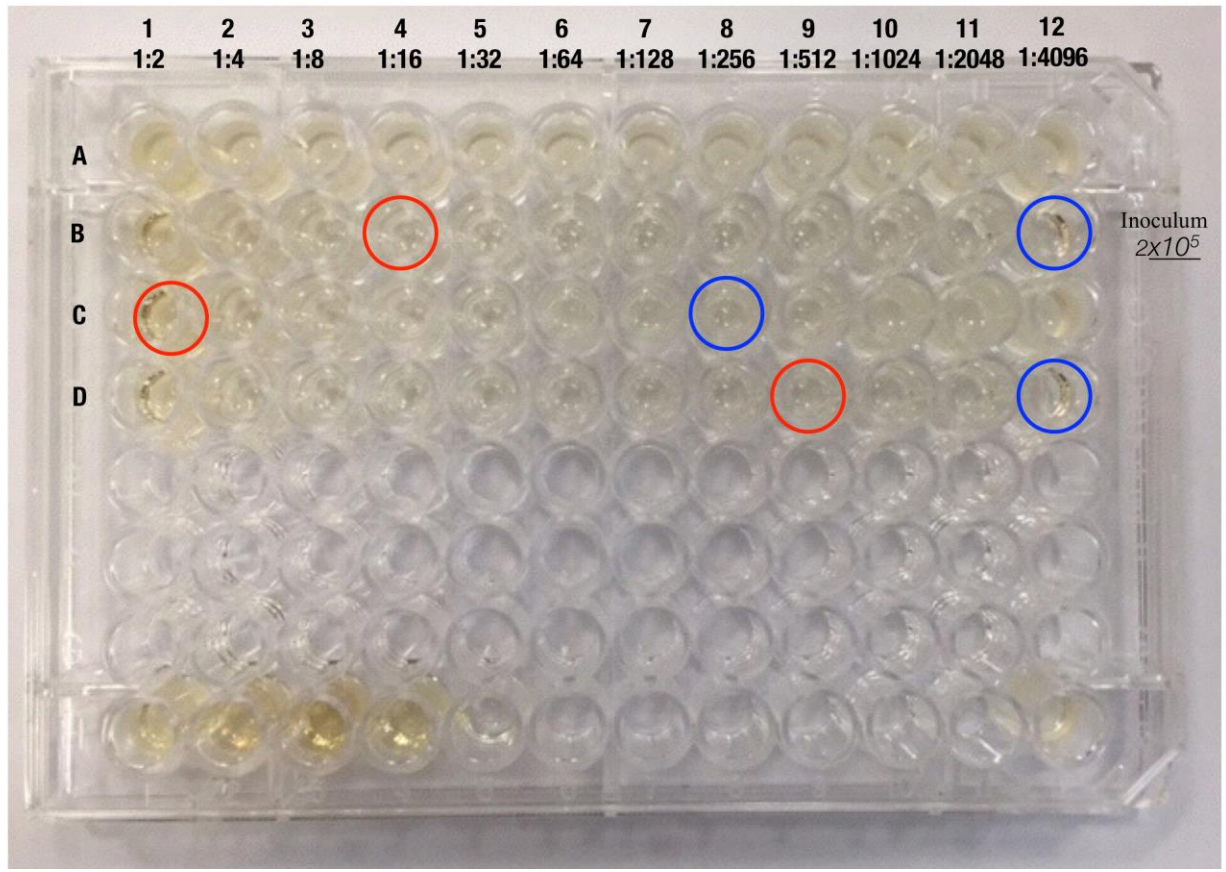
Line B, day 1, *30 minutes after dalbavancin (picco)*

Line C, day 7, *before dalbavancin (valle)*

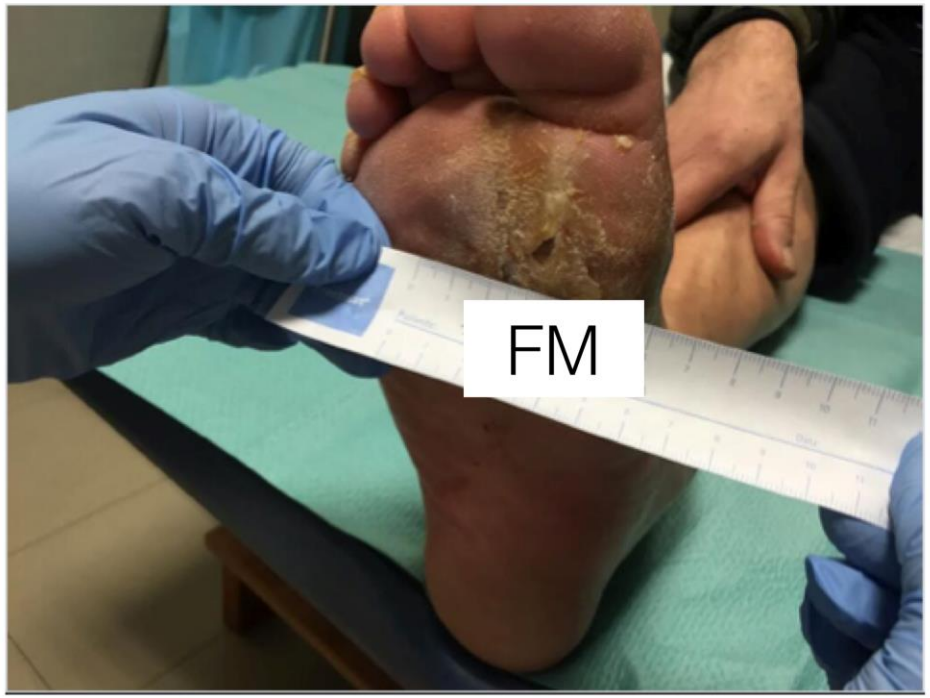
Line D, day 7, *30 minutes after dalbavancin*

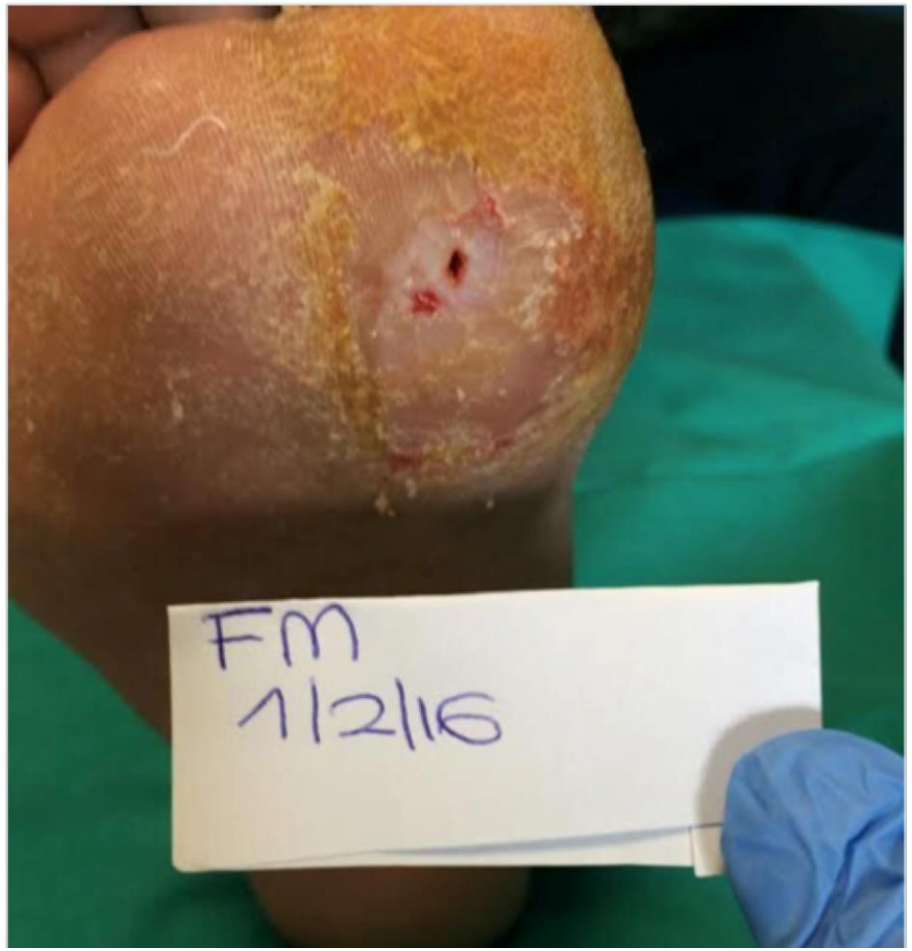
bacteriostatic activity

bactericidal activity



*Serum bacteriostatic/bactericidal activity of **dalbavancin** against a strain of MRSA isolated from a patient with a diabetic foot infection without osteomyelitis*



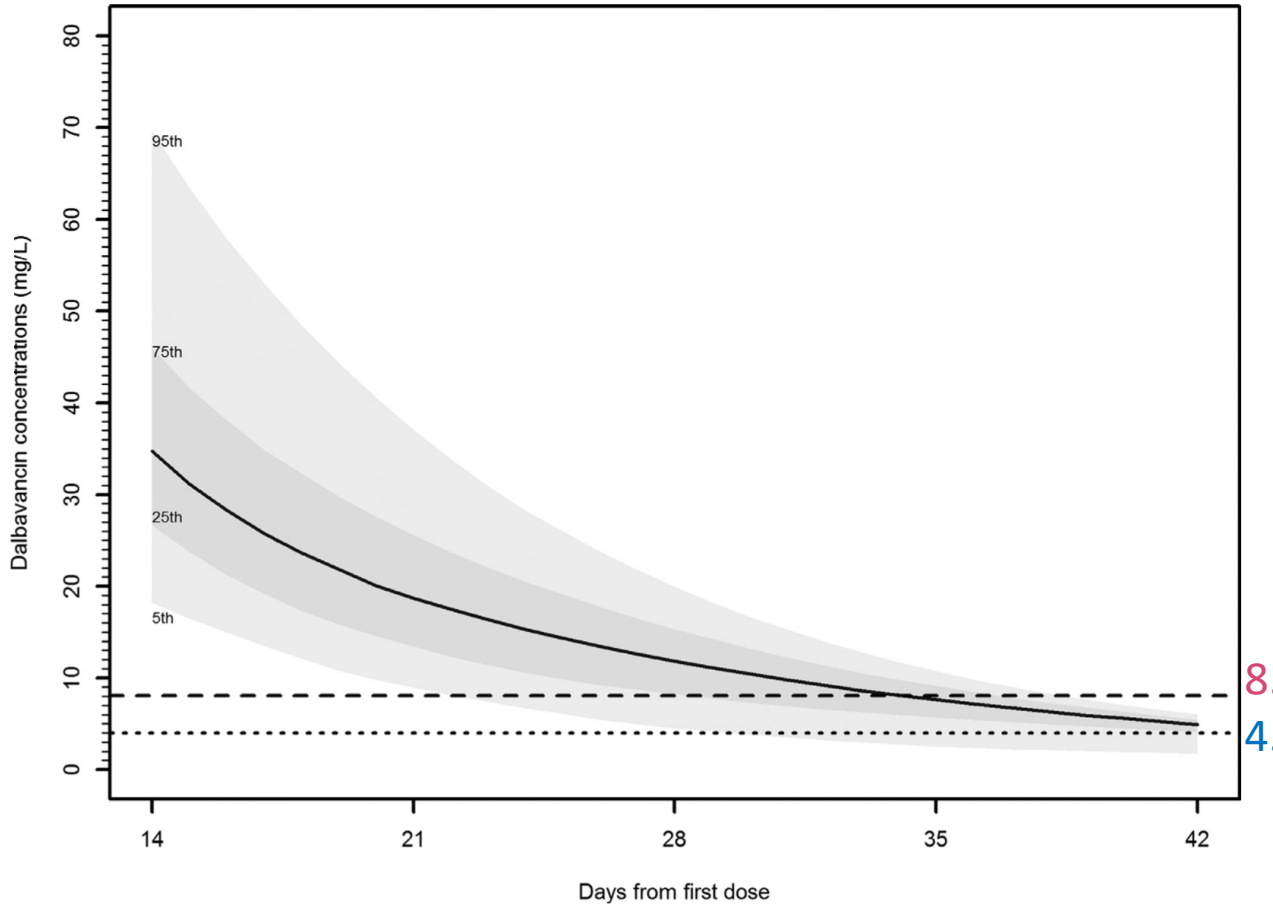


Long term therapy with Dalbavancin, TDM guided

Cojutti PG et al. International Journal of Antimicrobial Agents 58 (2021) 106445

Table 3. Suggested timings (days) for assessing in a timely and cost-effective manner the TDM of dalbavancin in relation to the tested dosing regimens and CLCR classes

Drug dosages	Classes of CL_{CR} (mL/min/1.73m²)			
	≤30	30-59	60-89	90-120
1000 d1 + 1000 d8	28 ± 3	-	-	-
1500 d1 + 1500 d8	-	35 ± 3	28 ± 3	21 ± 3



For dalbavancin there is a reference threshold for re-dosing

Off-label use

cSSSI e ABSSSI

cSSSI

Termine ampio per infezioni della cute e dei tessuti sottostanti che potrebbero essere trattati con incisione chirurgica

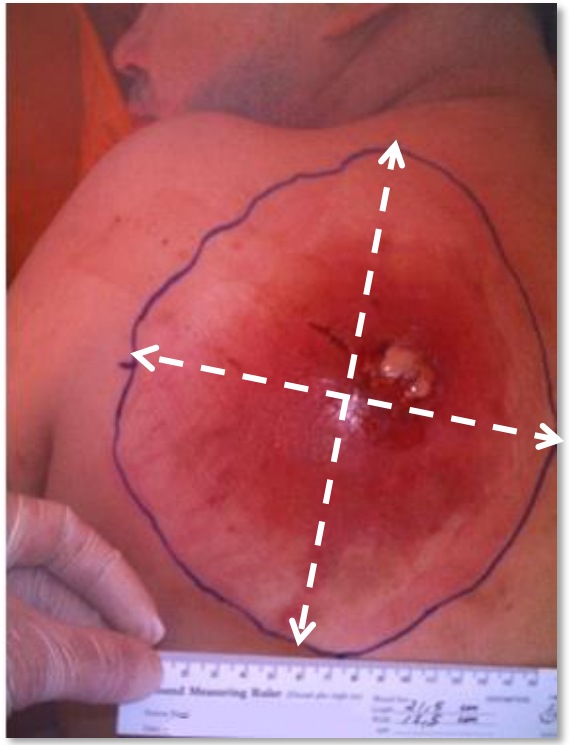
ABSSSI

Definizione FDA: celluliti, erisipela, infezioni di ferita, ascessi maggiori accompagnati da eritema, edema e/o infiltrazione cutanea con un'area di almeno 75 cm^2

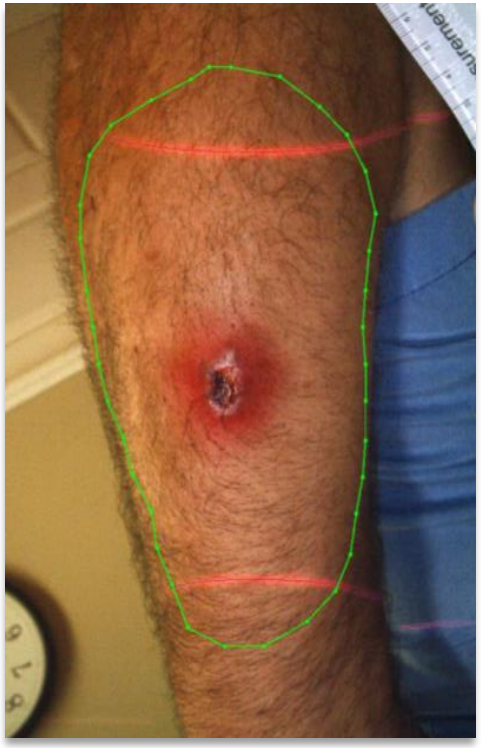
FDA nel 2013 ha rimosso la febbre dai criteri per la diagnosi di ABSSSI.[2]

May AK, et al. *Surg Infect.* 2009;10(5):467-499.
http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071185.pdf.

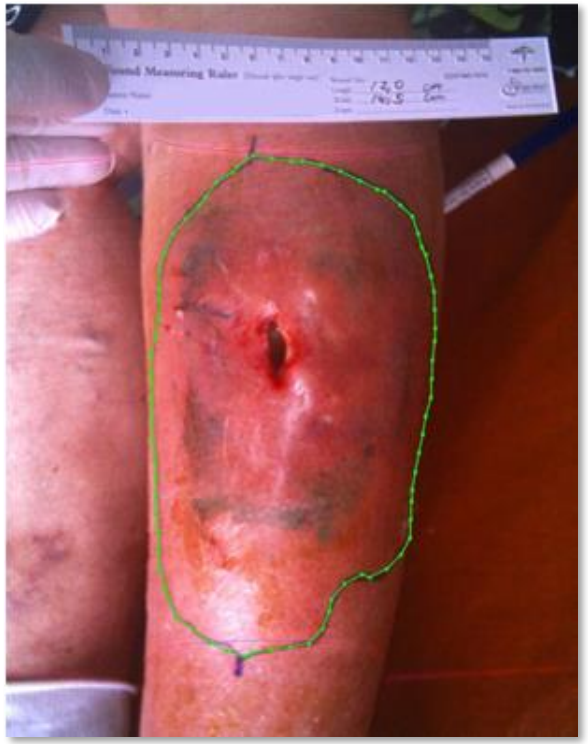
ABSSSI



Regione scapolare sx



Superficie ant di gamba



Avambraccio post sx

Data on file. Chicago, IL: Durata Therapeutics, Inc. 2014. FDA Briefing Presentation. Anti-infective Drugs Advisory Committee Meeting. March 31, 2014. NDA 21-883.

Punti critici

- Un numero considerevole di raccomandazioni sulle infezioni della cute e tessuti molli sono state pubblicate negli ultimi anni.
- La terapia ottimale è un “Source control” tempestivo ed aggressivo
- Bisogna distinguere tra patologie necrotizzanti e non necrotizzanti
- La terapia empirica deve tener conto la gravità del paziente, la diffusione dell’infezione ed i fattori di rischio per germi MDR

Table 1. Topics addressed in recent guidelines for the management of skin and soft tissues infections

	SEQ/SEMI 2006 [2]	SIS 2009 [3]	ISID/ISC 2011 [4]	JSC/JAID 2011 [5]	WSES 2014 [6▪▪]	IDSA 2014 [7▪▪]
Clinical diagnosis						
Nonnecrotizing superficial infections						
Abscesses		+	+		+	+
Impetigo	+	+	+		+	+
Erysipelas	+	+	+		+	+
Cellulitis	+	+	+		+	+
Pyomyositis	+					+
Necrotizing infections	+	+	+	+	+	+
Clostridial gas gangrene	+		+	+		+
Nonclostridial gas gangrene	+			+		
Myonecrosis			+		+	+
Necrotizing fasciitis	+		+		+	+
Synergistic gangrene	+		+			
Fournier's gangrene			+		+	+
Bites	+		+			+
Immunosuppressed patients					+	+
Surgical infection	+	+	+		+	+
Diagnosis and management						
Imaging procedures		+	+	+	+	+
Antibiotic therapy	+	+	+	+	+	+
Nutrition					+	
Surgical techniques		+			+	+
Dressing and postoperative care					+	+
Hyperbaric oxygen	+	+	+	+	+	+
Immunoglobulins		+	+		+	+

IDSA, Infectious Diseases Society of America; ISID/ISC, Italian Society of Infectious Diseases/International Society of Chemotherapy; JSC/JAID, Japanese Society of Chemotherapy/Japanese Association for Infectious Diseases; SEQ/SEMI, Sociedad Espanola de Quimioterapia:Sociedad Espanola de Medicina Interna; SIS, Surgical Infection Society; WSES, World Society of Emergency Surgery.

Gravità

- Valgono i criteri per la diagnosi di sepsi e shock settico
- MEWS e SEWS e LRINEC non vengono presi in considerazione dalle linee guida
- CPK e fascite?
- TAOS
- Dolore spropositato rispetto all’obiettività clinica

Value of Standard Laboratory Tests for the Early Recognition of Group A β-Hemolytic Streptococcal Necrotizing Fasciitis

Thierry Simonart,[1] Jean-Marie Simonart,[2] Inge Derdelinckx,[7] Gilbert De Dobbeleer,[1] Ann Verleysen,[4] Sylvie Verraes,[7] Josianne de Maubeuge,[3] Jean-Paul Van Vooren,[1] Jean-Marie Naeyaert,[4] Michel de la Brassine,[6] Willy E. Peetermans,[5] and Michel Heenen[1]

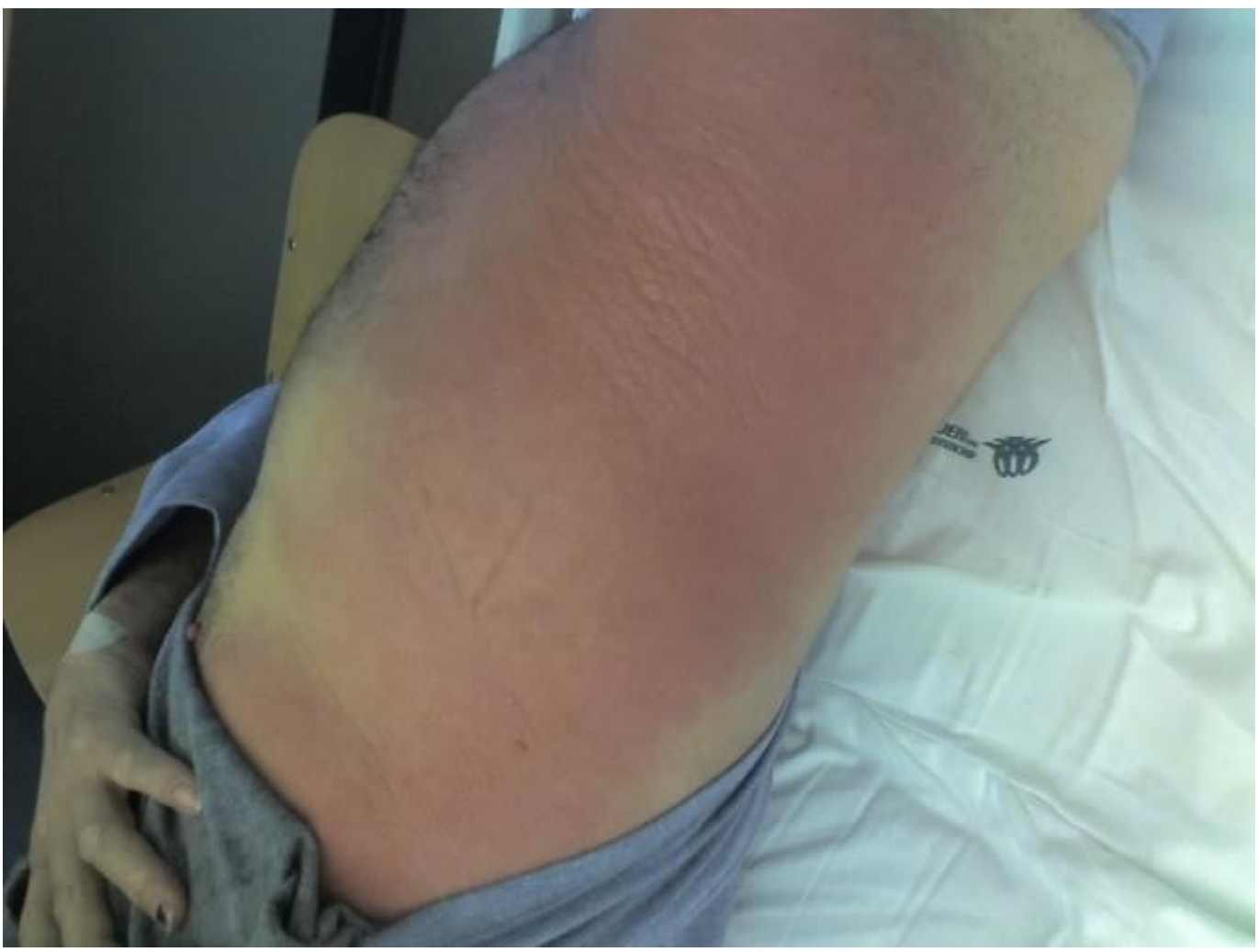
[1]Department of Dermatology and Infectious Diseases, Hôpital Universitaire Erasme, [2]Department of Medicine, Centre Hospitalier Etterbeek-Ixelles, [3]Department of Dermatology, Centre Hospitalier Universitaire Saint-Pierre, Brussels; [4]Department of Dermatology, Universitair Ziekenhuis Gent, Gent; [5]Department of Internal Medicine, University Hospital Leuven, Leuven; [6]Department of Dermatology, Centre Hospitalier Universitaire Liège, Liège, Belgium; [7]Department of Dermatology, Centre Hospitalier Universitaire Reims, France

Table 1. Risk factors associated with group A β-hemolytic *Streptococcus* necrotizing fasciitis (GAS NF) and cellulitis.

Risk factor	Patients with GAS NF (n = 17)	Patients with Cellulitis (n = 145)	OR (95% CI)	P
Host factor				
Age	54 ± 18	59 ± 22	—	—
Sex, M/F	12/5	85/60	1.6 (0.5–5.0)	—
Diabetes mellitus	4 (23)	20 (13)	1.9 (0.5–6.3)	—
Chronic alcoholism	4 (23)	14 (9)	2.8 (0.8–9.5)	<.01
Corticosteroid therapy	4 (23)	19 (13)	2.0 (0.6–6.7)	
Peripheral vascular disease	2 (12)	25 (17)	0.6 (0.1–2.9)	—
Chronic cardiac disease	1 (6)	9 (6)	0.9 (0.1–7.9)	—
Obesity	1 (6)	12 (8)	0.6 (0.1–5.6)	—
Affected site				
Extremities	12 (70)	122 (84)	0.5 (0.1–1.4)	—
Trunk	4 (23)	2 (1)	22.0 (5.8–82.7)	<.001
Head and neck	1 (6)	14 (31)	0.5 (0.1–4.6)	—

Mortalità 53%

Note. Data are no. (%) of patients, unless otherwise indicated.



Diagnosi di laboratorio della NF

Table 2. Initial laboratory results for patients with group A β-hemolytic *Streptococcus* necrotizing fasciitis (GAS NF) or cellulitis.

Laboratory result	Patients with GAS NF	Patients with Cellulitis	*P*
Hemoglobin, g/dL	10.9 ± 1.0 (15)	11.6 ± 1.5 (118)	—
Leukocyte count, 1000 cells/mm^3	13,600 ± 6900 (12)	12,100 ± 4800 (15)	—
Glucose, mg/dL	154 ± 33 (13)	139 ± 28 (110)	—
Creatinine, mg/dL	2.0 ± 1.0 (14)	1.5 ± 0.5 (115)	<.01
Aspartate aminotransferase, U/L	52 ± 40 (14)	39 ± 26 (111)	—
C-reactive protein, mg/dL	27.0 ± 10.2 (9)	9.3 ± 7.4 (104)	<.001
Creatine kinase, U/L	1892 ± 2422 (12)	139 ± 298 (101)	<.001

Note. Values are expressed as mean ± SD (no. of patients).

Esami ematici

- PCT non viene considerata (pro-adrenomedullina?)
- Emocolture nelle forme non necrotizzanti sono positive in meno del 5% dei casi

Usefulness of Serum Procalcitonin for Early Discrimination Between Necrotizing Fasciitis and Cellulitis

Takeshi KATO[#], Noriki FUJIMOTO[#], Shinichiro HONDA, Norikazu FUJII, Masae SHIRAI, Takeshi NAKANISHI, Gen NAKANISHI and Toshihiro TANAKA

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[#]These authors contributed equally to this work.

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Table I. Summary of clinical and laboratory characteristics in necrotizing fasciitis, and in cellulitis with LRINEC scores of ≥6 and <6

	Necrotizing fasciitis ($n=3$)	Cellulitis ($n=5$) (LRINEC score ≥6)	Cellulitis ($n=16$) (LRINEC score <6)
Sex, *n*			
Male	1	0	5
Female	2	5	11
Age, years, mean±SD	46±17.6	68.6±15.3	66.7±14.4
White blood cell/μl, mean±SD	12,067±5,020	14,700±2,753	13,819±4,678
C-reactive protein, mg/dl, mean±SD	20.8±15.0	21.3±5.3	11.0±7.5
Creatine kinase, U/l, mean±SD	5,147±8,004.7	443.4±791.2	95.3±123.2
LRINEC score, mean±SD	7.3±1.2	7.8±1.8	2.3±1.5
PCT, ng/ml, mean±SD	89.8±78.7	3.6±2.1	0.9±1.5
Past history	1 patient had diabetes mellitus	3 patients had diabetes mellitus	4 patients had diabetes mellitus
Affected sites, *n*	Arm (1), leg (2)	Lower leg (all cases)	Upper limb (5), lower limb (11)

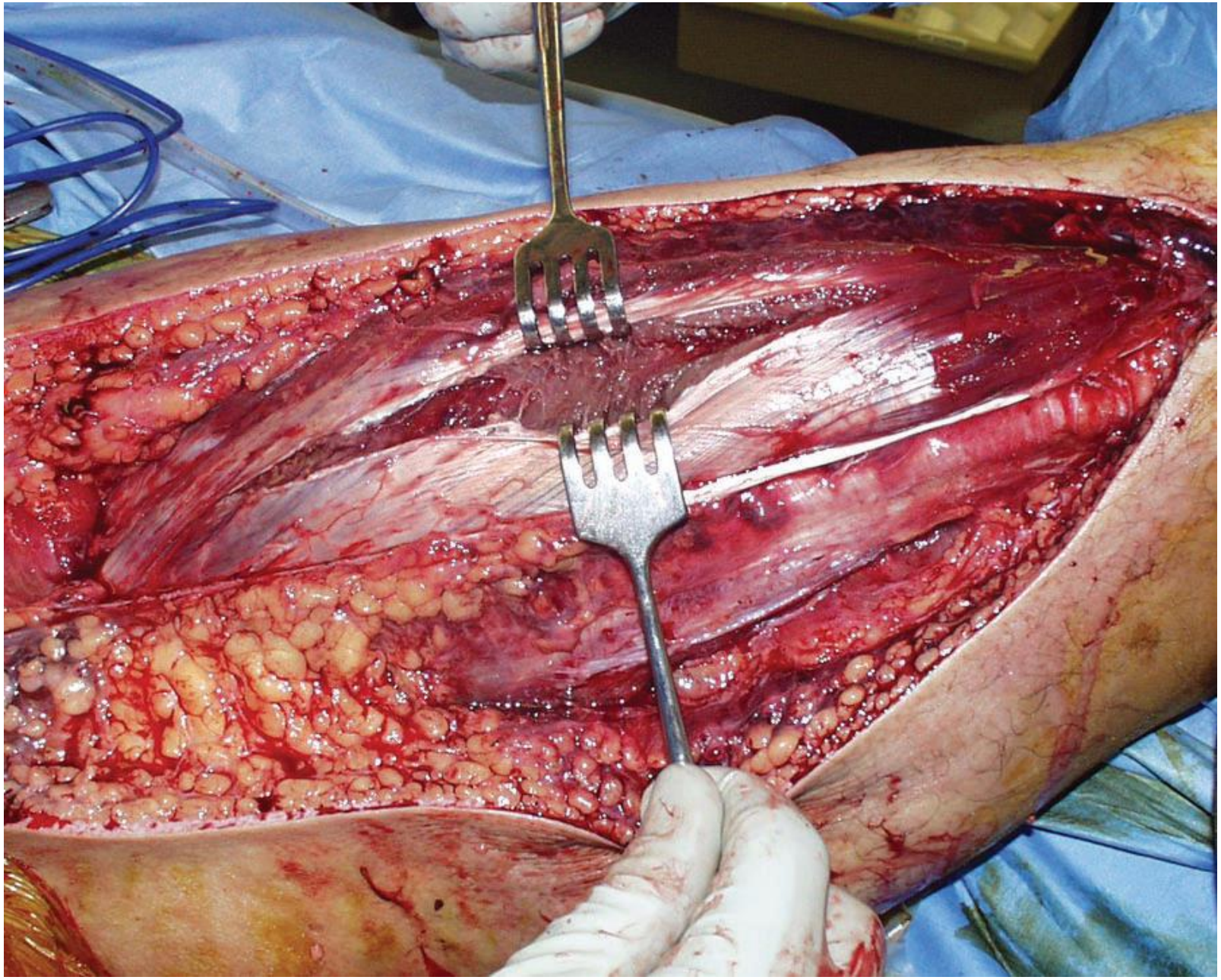
LRINEC: Laboratory Risk Indicator for Necrotizing Fasciitis.

Diagnosi

- La TAC e RMN possono dimostrare un edema della fascia e gas
- Ecografia può dimostrare un interessamento dei tessuti sotto-fasciali
- Non ritardare l'esplorazione chirurgica o la biopsia se non si riesce a fare l'esame radiologico

Source control

- Non fare la chirurgia nella fascite può portare a mortalità di quasi il 100%
- Non viene data indicazione sul tipo di chirurgia
- Nessuna indicazione sulla gestione infermieristica delle ferite
- Solo IDSA racomanda ispezione quotidiana
- Solo GISIG si sbilancia sulla VAC therapy



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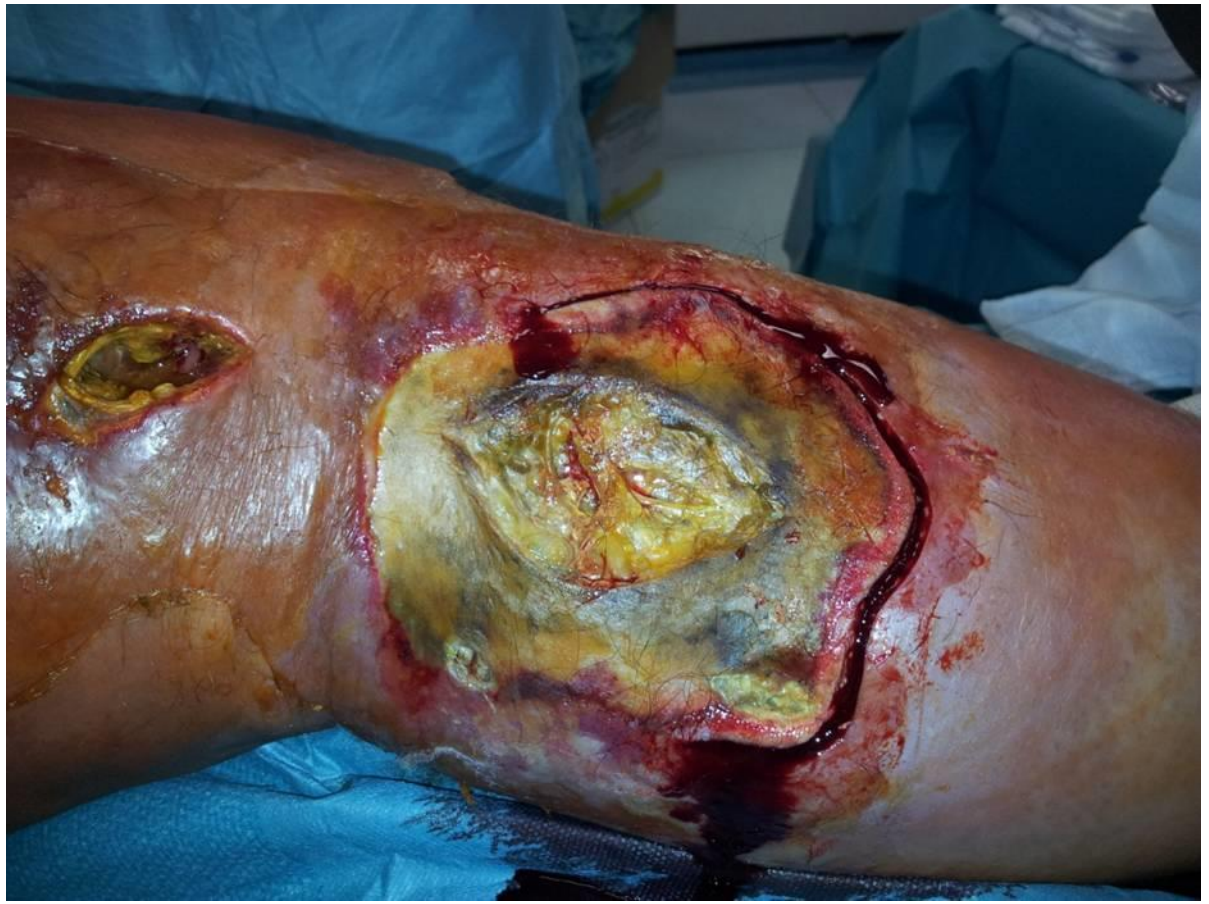
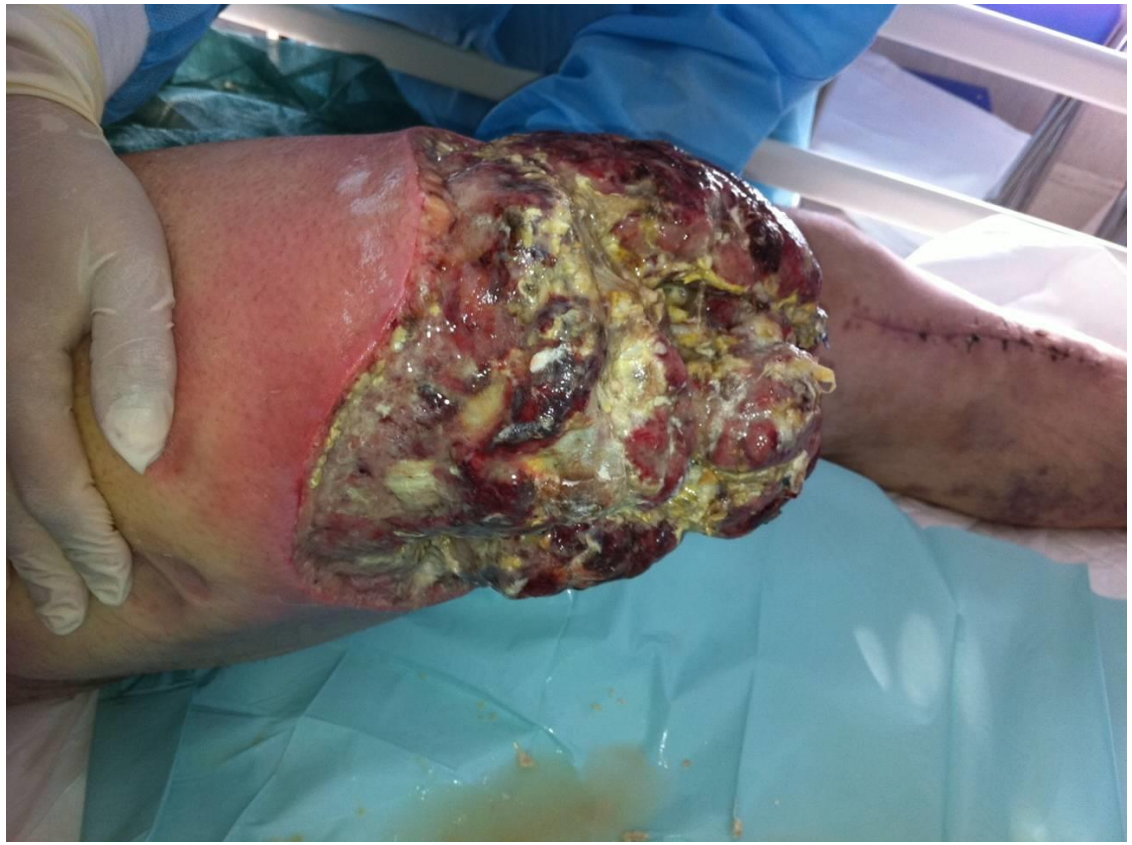


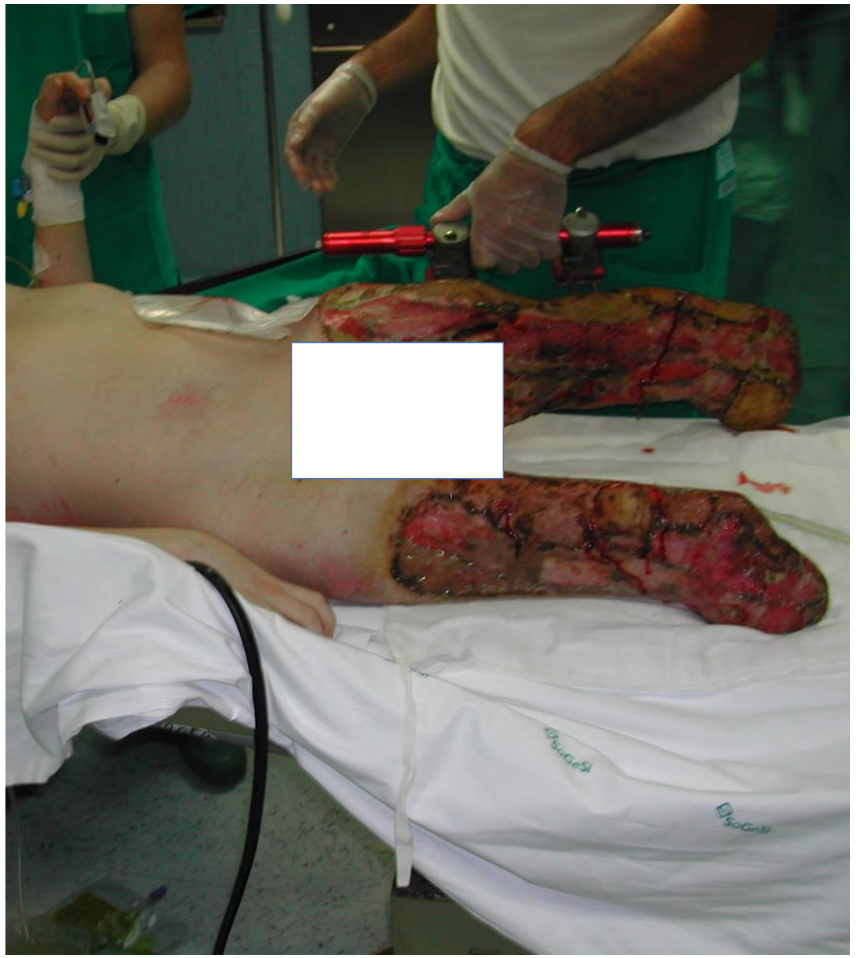
Cortesia del Dr G. Riccio

Fascite da *A. baumannii*



Cortesia del Dr G. Riccio

Fascite da *A. baumannii*



CASE REPORT

Colistin, meropenem and rifampin in a combination therapy for multi-drug-resistant *Acinetobacter baumannii* multifocal infection

A case report

G. BIANCOFIORE, C. TASCINI [1], M. BISÀ, G. GEMIGNANI [1], M. L. BINDI, A. LEONILDI [1]
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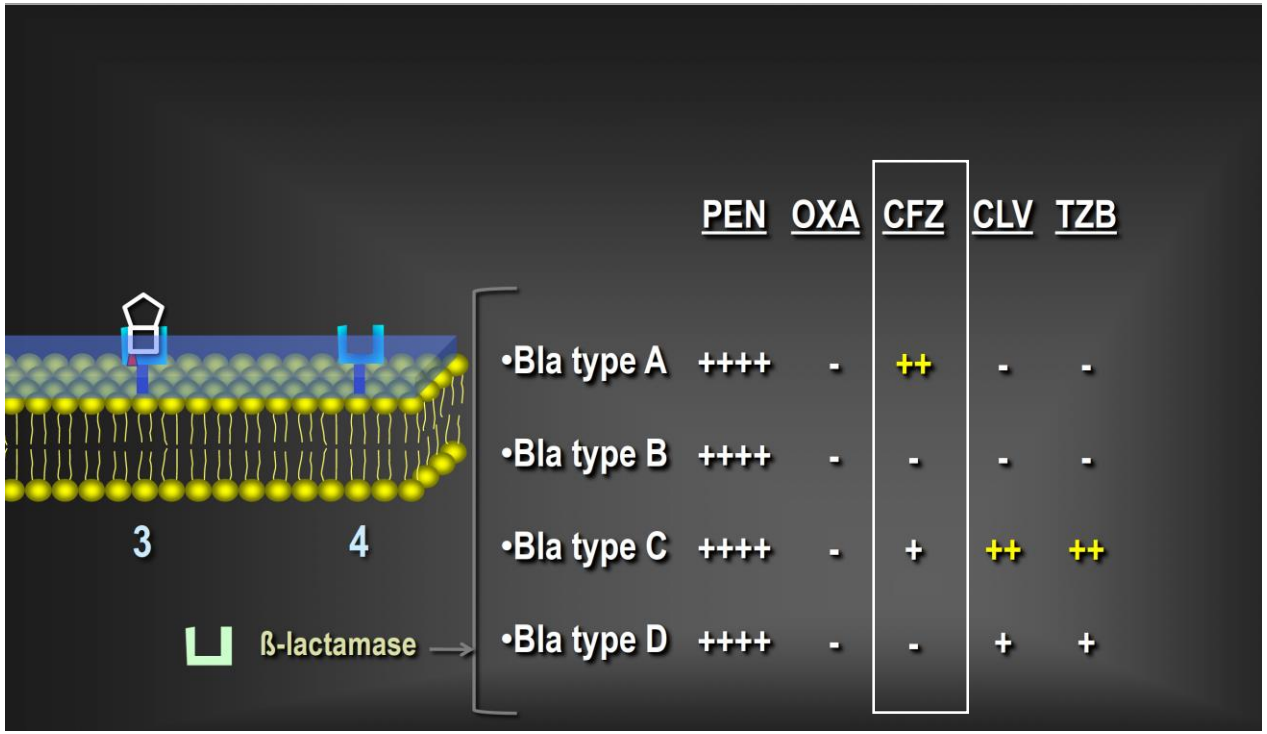
MINERVA ANESTESIOL 2007;73:181-5

Morsi	Eziologia (Spesso polimicrobiche)	Concia	IDSA	WSES	ISID	SIS
Uomo	Streptococchi, S. aureus, eikenella, fusobacterium, peptostreptococcus, prevotella, pophyromonas spp	Amoxi/clav Pip/tazo TMP/SMX+ clindamicina	Amoxi/clav Ampi/sulbactam Ertapenem	Non specificata terapia ad ampio spettro vs aerobi e anaerobi	Amoxi/clav Alternative os Cefalosporine II + Clinda/metronid Doxiciclina + Clinda/metronid Fluorochinolone+ Clinda/metronid TMP/SMX + Clinda/metronid Moxifloxacina Infezioni severe Terapia ev: Amoxi/clav Pip/tazo Cefoxitina carbapenemi	Antibiotico che copra la flora orale dell'animale o dell'uomo
Cane Gatto	Non purulenti: Cocchi Purulenti: aerobi e Anaerobi (bacteroides, fusobaterium) Pasteurella Capnocytophaga canimorsus (sepsi)	Amoxi/clav Fluorochinolone + Clindamicina TMP/SMX + clindamicina	Amoxi/clav Cefalosporine II/III + Clinda/metronid Carbapenemi Doxiciclina Moxifloxacina Fluorochinolone+ Clinda/metronid TMP/SMX + Clinda/metronid			
Ratto	Spirillium minus, streptobacillus monoliformis	Amoxi/clav Doxiciclina				
Maiale	Cocchi gram + Bacilli gram- Anaerobi Pasteurella spp	Amoxi/clav Cefal III Carbapenemi				
Scimmia	Herpes virus simiae	Acyclovir				

Cefazolin (CFZ) inoculum effect and susceptibility to beta-lactamases in *S. aureus*



Singh KV, et al. Efficacy of Ceftaroline in a Rat Model of Endocarditis Against MSSA Exhibiting the Cefazolin High Inoculum Effect. ***Antimicrob Agents Chemother 2017***

Strains	MICs (mcg/ml)[a] Standard inocula 10^5 CFU/ml			High inocula 10^7 CFU/ml		
	CFZ	NAF	CPT	CFZ	NAF	CPT
S. aureus ATCC 29213[b] ßla type A producer	0.5	0.5	0.25	8	1	0.25
S. aureus ßla negative ATCC 25923[c]	0.5	0.5	0.125	0.5	1	0.125
TX0117 (MSSA, Bla type A)	1	0.5	0.25	32	2	1
TX0117c (Bla cured)	0.5	0.5	0.25	0.5	2	0.5

Clinical Infectious Diseases
SUPPLEMENT ARTICLE

Current Treatment Options for Acute Skin and Skin-structure Infections

Yoav Golan
Department of Internal Medicine, Division of Infectious Diseases, Tufts Medical Center, Boston, Massachusetts

Table 3. 2014 Infectious Diseases Society of America Recommendations for Antibiotic Treatment of Acute Bacterial Skin and Structure Infection Caused by Methicillin-resistant *Staphylococcus aureus* [6]

Antibiotic	Route	Recommended Dosing in Adults
Vancomycin	IV	15 mg/kg every 12 hours
Linezolid	IV/oral	IV: 600 mg every 12 hours Oral: 600 mg twice a day
Clindamycin	IV/oral	IV: 600 mg every 8 hours Oral: 300–450 mg 4 times a day
Daptomycin	IV	4 mg/kg daily
Ceftaroline	IV	600 mg every 12 hours
Doxycycline, minocycline	Oral	100 mg twice a day
Trimethoprim-sulfamethoxazole	Oral	1–2 double strength tablets twice a day

Abbreviations: IV, intravenous.

Clinical Infectious Diseases
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Table 2. Summary of Recently Approved Antibiotics for the Treatment of Acute Bacterial Skin and Structure Infection [8–12]

Product Characteristics	Dalbavancin	Oritavancin	Tedizolid	Delafloxacin
Indications	ABSSSI caused by susceptible strains of gram-positive microorganisms	ABSSSI caused by susceptible strains of gram-positive microorganisms	ABSSSI caused by susceptible strains of gram-positive microorganisms	ABSSSI caused by susceptible strains of gram-positive and gram-negative microorganisms
Microbiology	In vitro and clinical activity against the following aerobic and facultative gram-positive bacteria: • *Staphylococcus aureus* (including MRSA) • *Streptococcus pyogenes* • *Streptococcus agalactiae* • *Staphylococcus dysgalactiae* • *Staphylococcus anginosus* group (including *Staphylococcus anginosus, Staphylococcus intermedius, Staphylococcus constellatus*) • *Enterococcus faecalis* (vancomycin-susceptible isolates only)	In vitro and clinical activity against: • *S. aureus*, (including MRSA) • *S. pyogenes* • *S. agalactiae* • *S. anginosus* group (including *S. anginosus, S. intermedius, S. constellatus*) • *E. faecalis*	In vitro and clinical activity against gram-positive bacteria including: • *S. aureus* (including MRSA) • *S. agalactiae* • *S. anginosus* group (including *S. anginosus, S. intermedius, S. constellatus*) • *S. dysgalactiae* • *S. pyogenes* • *E. faecalis* (vancomycin-susceptible isolates only)	In vitro and clinical activity against the following aerobic gram-positive and gram-negative bacteria: • *S. aureus* (including MRSA) • *Staphylococcus haemolyticus* • *Staphylococcus lugdunensis* • *S. pyogenes* • *S. agalactiae* • *S. dysgalactiae* • *S. anginosus* group *(including S. anginosus, S. intermedius, S. constellatus)* • *E. faecalis* • *Escherichia coli* • *Klebsiella pneumonia* • *Enterobacter cloacae* • *Pseudomonas aeruginosa*
Formulations	IV	IV	IV/oral	IV/oral
Dosing	Single-dose regimen: 1500 mg IV over 30 min Two-dose regimen: 1000 mg IV over 30 min followed 1 week later by 500 mg IV over 30 min	Single-dose regimen: 1200 mg IV over 3 hours	200 mg IV/oral tablet daily for 6 days; IV infusion over 1 hour	300 mg IV over 60 min every 12 hours for 5–14 days OR 450 mg oral tablet every 12 hours for 5–14 days

Abbreviations: ABSSSI, acute bacterial skin and skin-structure infection; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.

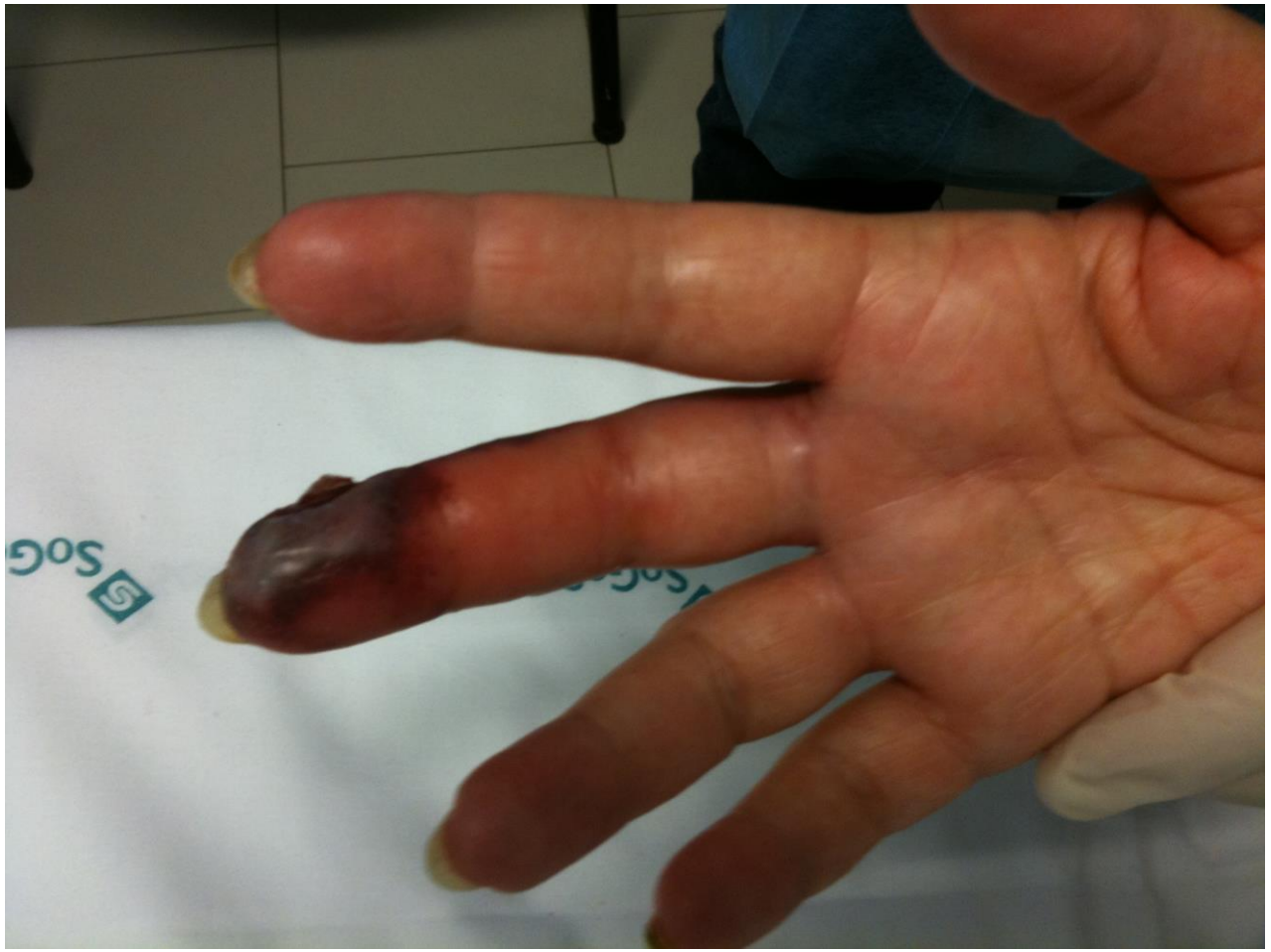
Terapia antitossina

- Linezolid e clindamicina sono consigliate in quanto capaci di bloccare il rilascio e la produzione delle tossine (basso livello di evidenza)
- Nessun cenno ad altri farmaci inibitori della sintesi proteica come tetracicline e macrolidi

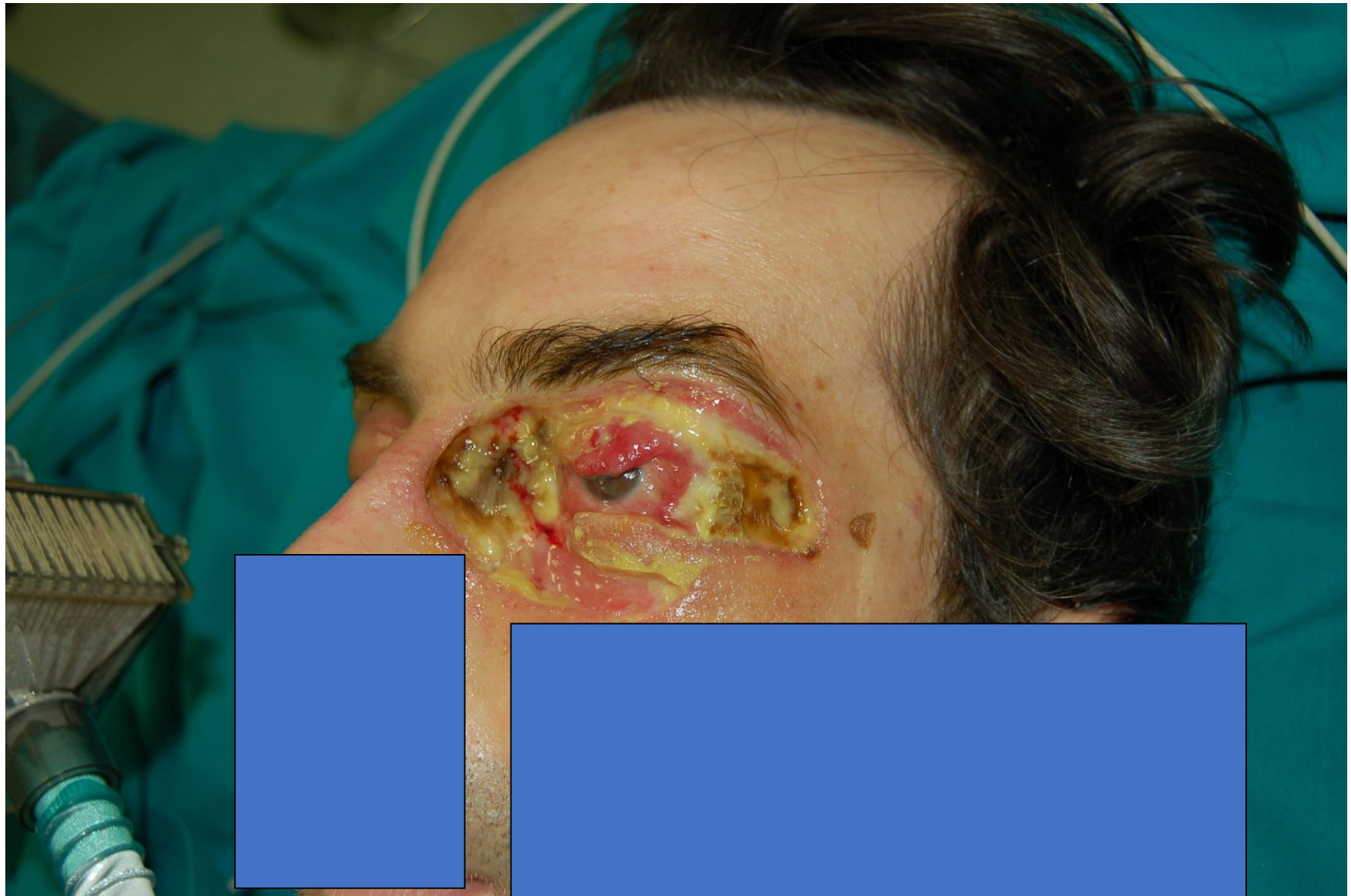
Neutropenico

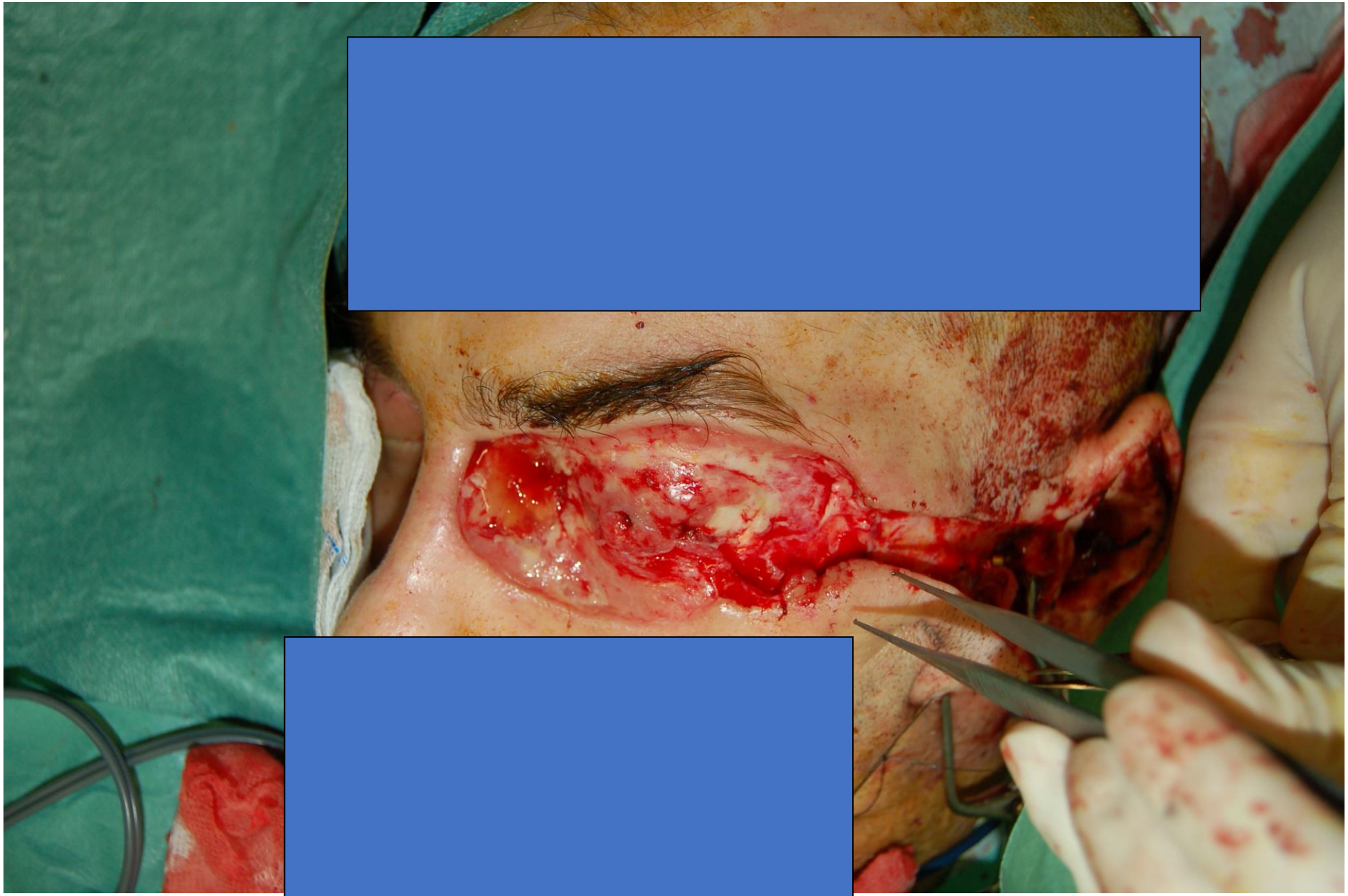
- Attenzione ai gram negativi
- Anti MRSA più antipseudomonas

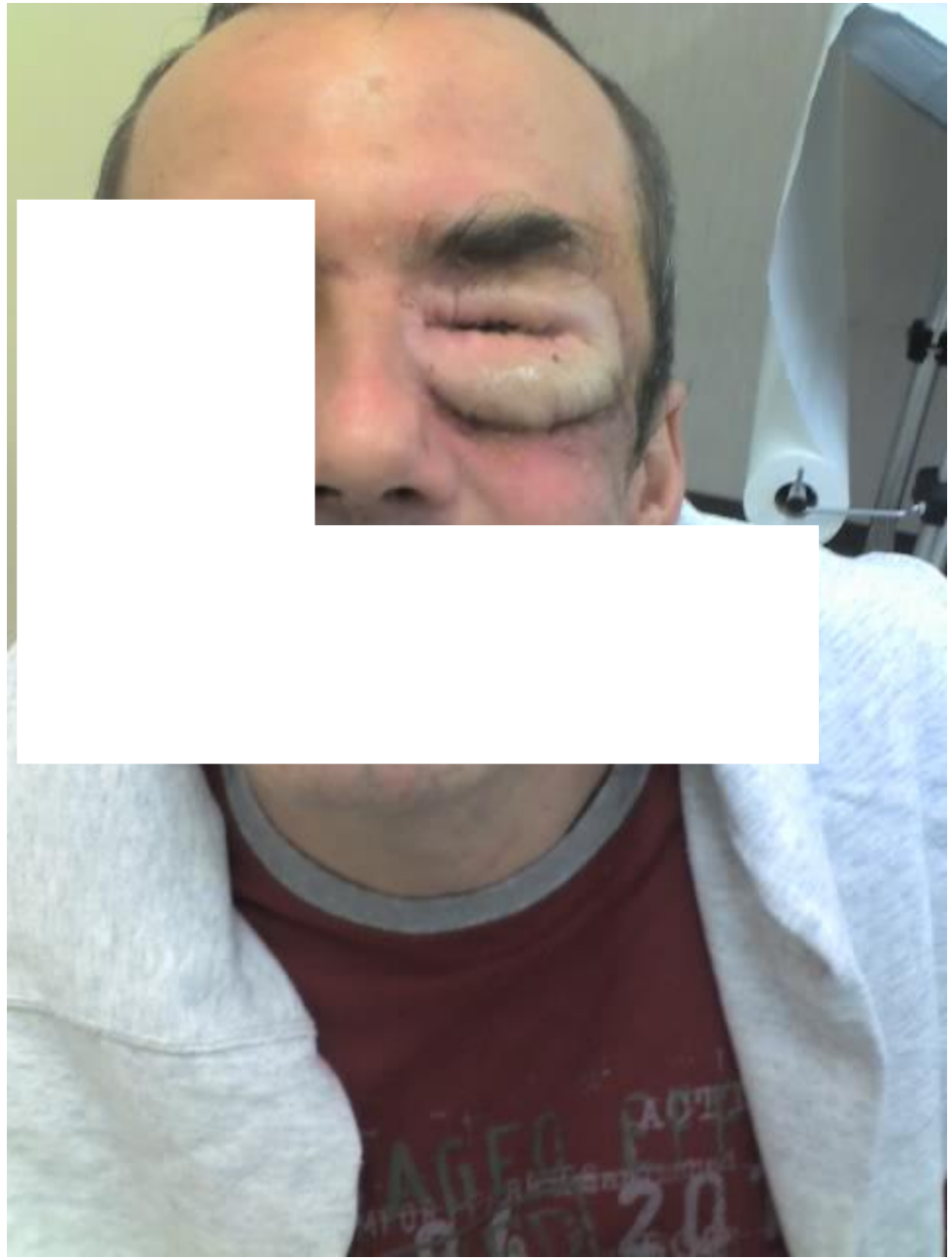
Ectima da *P. aeruginosa* in neutropenico



Fascite della palpebra sinistra da Pseudomonas in neutropenico







IDSA

Infezione	Durata terapia
Impetigine	7 gg
Ascesso	5-10 gg
Cellulite/erisipela	5 gg
Stafilococco superficiale	7 gg
Neutropenico	7-14 gg
Piomiosite	14-21 gg
MRSA out-patient	5-10 gg
MRSA in-patient	7-14 gg

Immunoglobuline

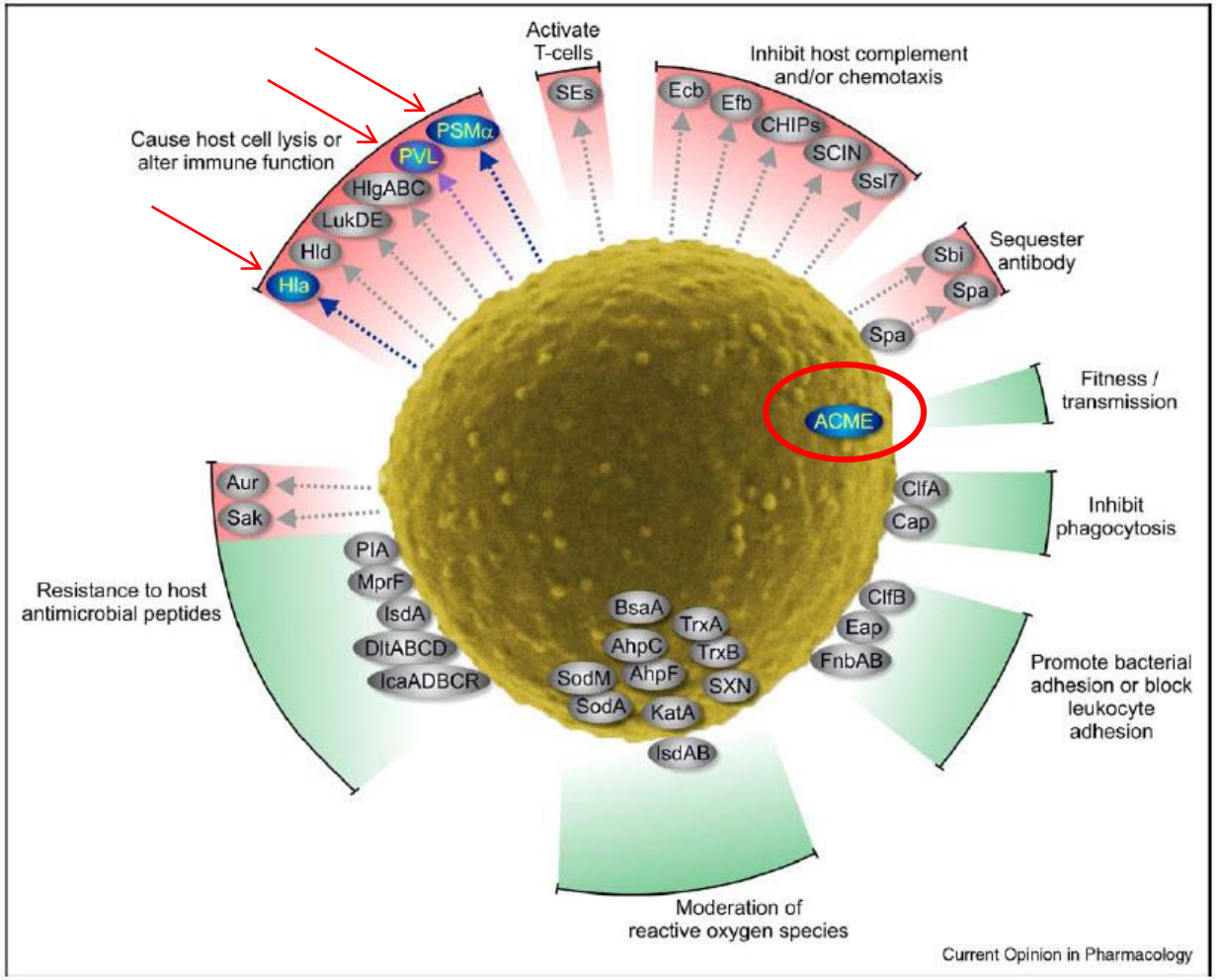
- Discusse da alcune linee guida ma rimane controversa
- WSES raccomanda Ig nelle forme necrotizzanti in shock settico (raccomandazione debole)
- IDSA non fornisce raccomandazioni
- SIS nella toxin shock syndrome

Camera iperbarica

- Non ci sono studi prospettici randomizzati
- La camera iperbarica non deve mai ritardare la chirurgia
- IDSA non la raccomanda
- Le linee guida giapponesi le considerano solo per le forme da anaerobi (clostridi)

Increased virulence in CA-MRSA USA 300 appears to be *linked* to virulence factors *or a*lterations in gene regulation

- Phenol soluble modulins
- **Panton-Valentine leukocidin**
- α-hemolysins
- Arginine catabolic mobile element (ACME)
- agr (accessory gene regulator)



Kobayashi SD, DeLeo FR. An update on community-associated MRSA virulence. *Curr Opin Pharmacol.* 2009;9(5):545-551.

Ca-MRSA vs Ha-MRSA

Antibiotic	Ca-MRSA	HaMRSA
Oxacillin	R	R
Macrolide	S (usually)	R
Aminoglycoside	S (usually)	R
Quinolones (except delafloxacin)	S (usually)	R

Table 3. Risk factors for H-or CA-MRSA.

Source of MRSA	HA-MRSA [15,44]	CA-MRSA [40]
Risk factor	• Elderly age • Prolonged hospitalization • Invasive procedures • Prior colonization or infection • Recent antimicrobial exposure • Comorbidities such as ◦ Cancer ◦ Cardiovascular disease ◦ Chronic kidney disease	• Children < 2 y • Athletes • Injection drug users • Homosexual males • Military personnel • Inmates of correctional facilities • Residential homes, or shelters • Vets, pet owners, and pig farmer • Patients with post-flu-like illness and/or severe pneumonia • Patients with concurrent SSTI, history of colonization or recent infection with CA-MRSA • Individuals with a history of antibiotic consumption in the previous year, particularly quinolones, or macrolide

CA = community-acquired; HA, hospital-acquired; MRSA = methicillin-resistant *S. aureus*; SSTI = skin and soft tissue infection.

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Relationship between Adherence to Oral Antibiotics and Postdischarge Clinical Outcomes among Patients Hospitalized with *Staphylococcus aureus* Skin Infections

Samantha J. Eells,[a,b,c] Megan Nguyen,[a,d] Jina Jung,[d] Raul Macias-Gil,[a] Larissa May,[e] Loren G. Miller[a,b]

Division of Infectious Diseases, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California, USA[a]; David Geffen School of Medicine at UCLA and Harbor-UCLA Medical Center, Los Angeles, California, USA[b]; Science 37, Inc., and Department of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, California, USA[c]; College of Pharmacy, Western University of Health Sciences, Pomona, California, USA[d]; Department of Emergency Medicine, University of California—Davis. Sacramento. California. USA[e]

TABLE 3 Multivariate analysis of risk factors associated with poor clinical response after 30 days

Variable	Odds ratio (95% confidence interval)	*P* value
Overall electronically measured adherence	0.16 (0.02–0.99)	0.049
Diabetes	0.40 (0.15–1.0)	0.05
Illicit drug use	0.36 (0.13–0.99)	0.048

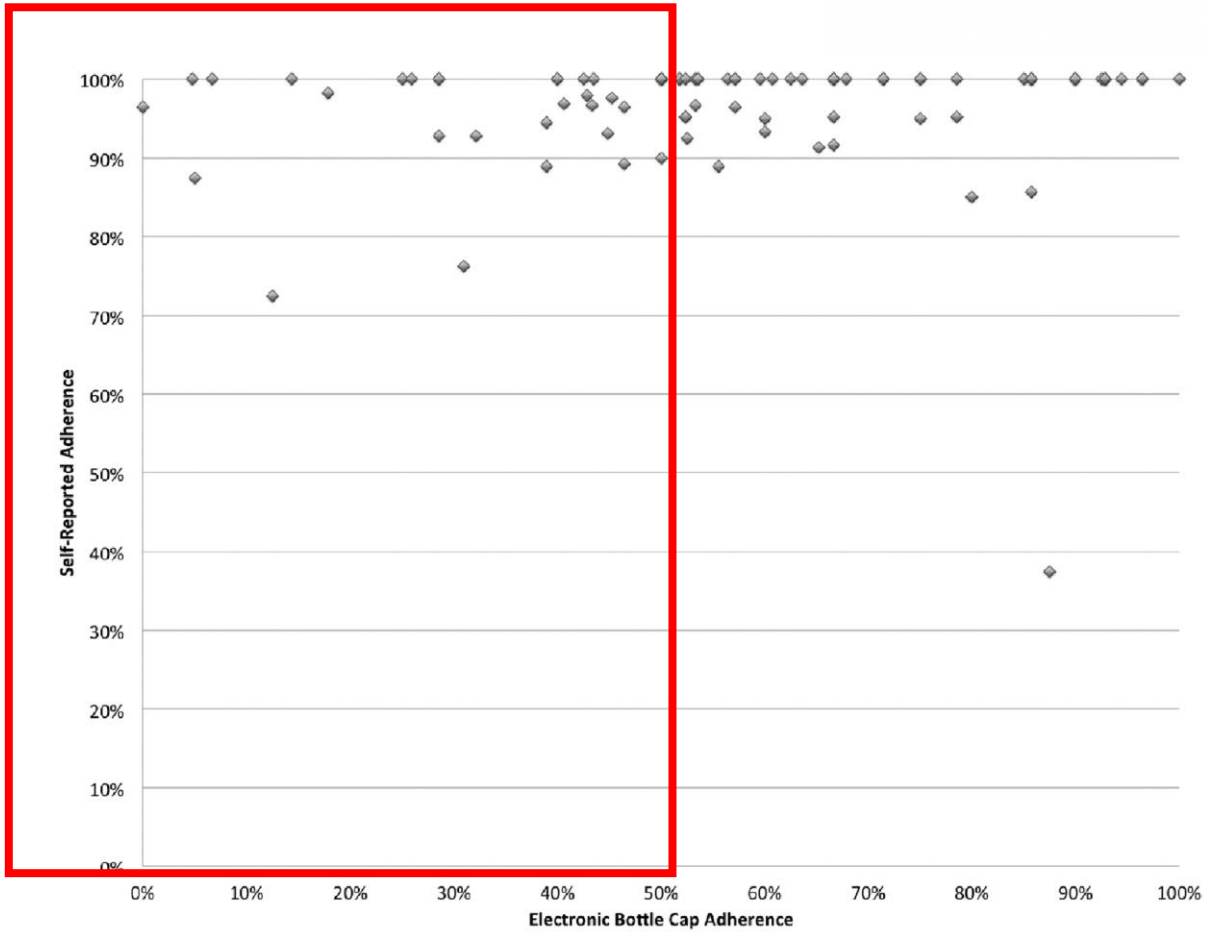

FIG 1 Self-reported adherence compared to electronic bottle cap adherence.

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Review

Antimicrobial stewardship in patients with acute bacterial skin and skin-structure infections: An international Delphi consensus

Alex Soriano[a], Stefania Stefani[b], Mathias W. Pletz[c], Francesco Menichetti[d,*], on behalf of the Italian Group for Antimicrobial Stewardship (GISA)

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[b] Department of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy
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Domain	Statement	Consensus (%)	
		Negative	Positive
	[illegible]	[illegible]	[illegible]
4.3. I consider that long-acting drugs can be useful for ASPs in ABSSSI because they:			
	Guarantee patient adherence	0	100
	Avoid the need for a central venous catheter	2	98
	Reduce the length of hospitalisation	0	100
	Avoid long-term admission from the ED to a hospital ward, where possible	4	96
	Reduce intestinal selective pressure (including *Clostridioides difficile* overgrowth)	14	86
	Reduce the cost of ABSSSI management	7	93
	Have less side effects compared with other antibiotics, in my experience	12	88
4.4. I consider the following to be potential barriers to including long-acting drugs in ASPs for ABSSSI:			
	Restrictive hospital formulary (limiting access to new antibiotics)	11	89
	Direct acquisition cost	9	91
	The long-acting pharmacokinetic profile (safety point of view)	44	56
	Drug availability in the ED	21	79
	Lack of data in special populations	28	72
	The empirical approach used in the vast majority of patients	18	82
	Lack of personal clinical experience	30	70

Tissue and cell penetration of Oritavancin

- Oritavancin can penetrate cells and particularly the macrophages
- Bone penetration: penetrates both cancellous and cortical bone

Antibiotic	Cancellous bone (mg/l)	Cortical bone (mg/l)	Joint conc. (mg/l)
Linezolid	6.4[a]		> 4
Daptomycin	21.4[a]		21.6
Vancomycin	3.8	4.5	NA
Dalbavancin	13.4[b]	4.2	NA
Oritavancin	27[b,c]	65.6	NA

J Antimicrob Chemother 2021; 76 Suppl 4: iv9–iv22
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Journal of Antimicrobial Chemotherapy

Current and future options for treating complicated skin and soft tissue infections: focus on fluoroquinolones and long-acting lipoglycopeptide antibiotics

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[1]Department of General, Visceral and Thoracic Surgery, Klinikum Hannoversch-Muenden, Goettingen University, Germany; [2]Cellular and Molecular Pharmacology, Louvain Drug Research Institute, Université catholique de Louvain (UCLouvain), Brussels, Belgium

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Table 3 Pharmacokinetics and dosing of new lipoglycopeptides

Parameter	Antibacterial		
	Oritavancin	Telavancin[a]	Dalbavancin[b]
Dosing			
Creatinine clearance >50 mL/min	1200 mg single dose; 3 h infusion [6]	10 mg/kg q24h [10]	1000 mg day 1 + 500 mg day 7 [14]
Creatinine clearance 30–50 mL/min	1200 mg single dose; 3 h infusion [6]	7.5 mg/kg q24h [10]	1000 mg day 1 + 500 mg day 7 [14]
Creatinine clearance 10–<30 mL/min	1200 mg single dose; 3 h infusion [6]	10 mg/kg q48h [10]	750 mg day 1 + 375 mg day 7 [14]
C_{max} (mg/L)	138 [6]	94/108 [10]	287 [14]
AUC_{24} (mg·h/L)	1110 [6]	666/780 [10]	3185 [14]
AUC_{∞} (mg·h/L)	2800 [6]	747/NA [10]	23,443 [14]
Protein binding (%)	85 [6]	90 [10]	93 [14]
$t_{½\alpha}$ (h)	2.29 [6]	8/8.1 [10]	NA
$t_{½\beta}$ (h)	13.4 [6]		NA
$t_{½\gamma}$ (h)	245 [6]		346 [14]
Clearance (L/h)	0.445 [6]	0.97/0.90 [10]	0.015 [14]
V_{ss} (L)	87.6 [6]	10.15/9.31 [10]	7.93 [176]
Macrophages/plasma	142.7[c] [177]	6.67 (24 h) [178]	NA
ELF/serum	4.6[c] [177]	0.7 [179]	NA

AUC_{∞} area under the concentration–time curve from time zero to infinity, *AUC_{24}* area under the concentration–time curve from time zero to 24 h, *C_{max}* maximum concentration, *ELF* epithelial lining fluid, *NA* not available, *qxh* every *x* h, *$t_{½\alpha}$* initial or disposition half-life, *$t_{½\beta}$* terminal elimination half-life in a 2-compartment model, *$t_{½\gamma}$* terminal elimination half-life in a 3-compartment model, *V_{ss}* apparent volume of distribution at steady state

[a] Pharmacokinetic data given for single dose/multiple dose of 10 mg/kg

[b] Pharmacokinetic data for a single dose of 1000 mg

[c] For an 800 mg dose

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Current and future options for treating complicated skin and soft tissue infections: focus on fluoroquinolones and long-acting lipoglycopeptide antibiotics

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Oritavancin

Binds D-Ala D-Ala
+ D-Ala D-Lac

Hydrophobic moiety

This positive charge in this position is important for chloride activity, only present in oritavancin

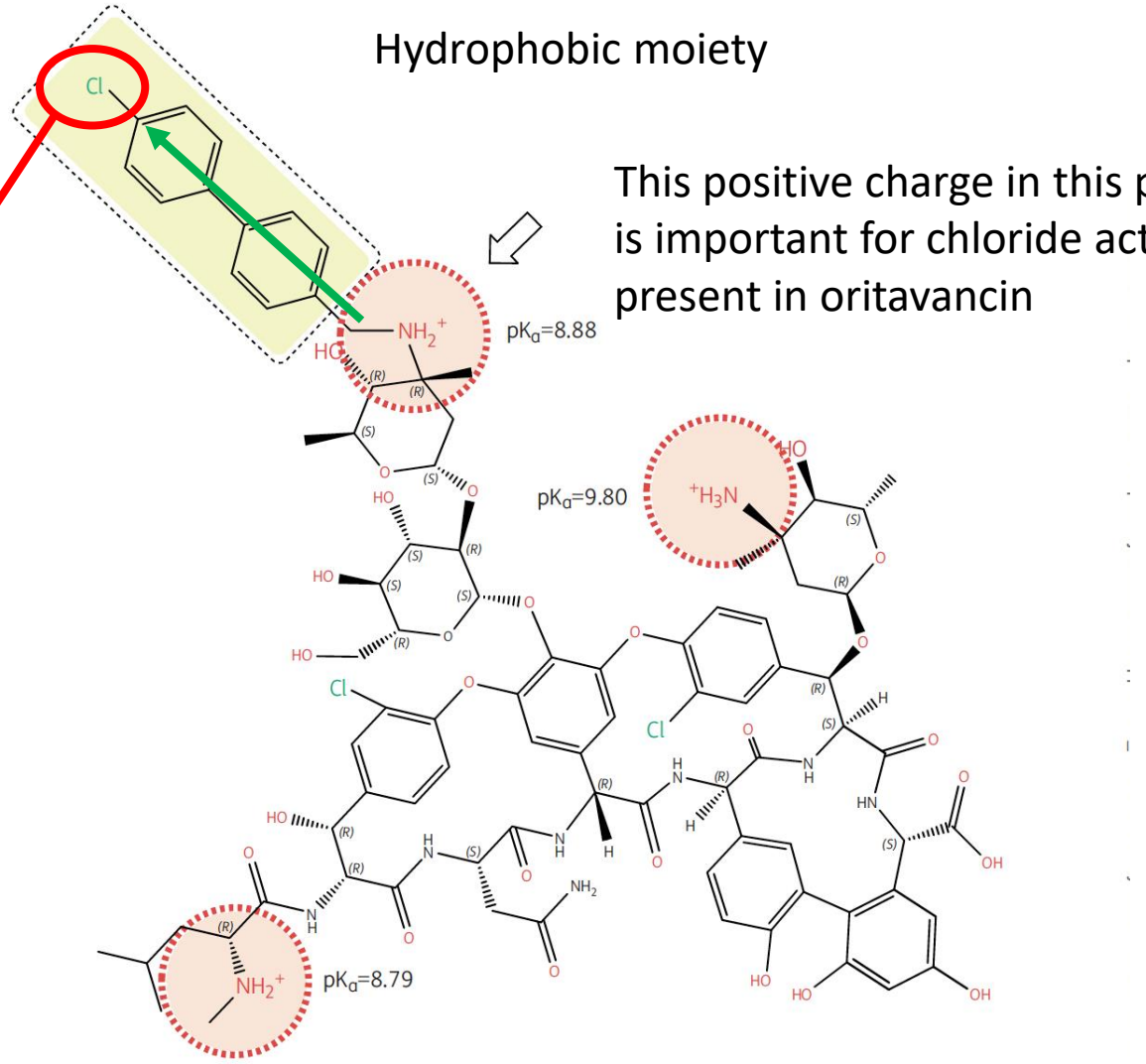

Figure 4. Structure of oritavancin with emphasis on its ionizable functions and hydrophobic side chain. Oritavancin is a large molecule compared to most other antibiotics (projection area: 183–281 Å^2; van der Waals volume: 1254 Å^3), which explains its lack of penetration through the outer membrane of Gram-negative organisms, hence its lack of activity against these pathogens, as well as its complete lack of oral bioavailability and necessity for parenteral administration. While the un-ionized form of oritavancin is highly lipophilic (logP = 9.32) due to the presence of the 4′-chlorobiphenyl methyl moiety (highlighted in yellow), the molecule is made polycationic at both pH 7.4 and 5.5 due to the presence of 3 amino functions with pK_as >8.5, and further gains in polarity due to the large number of ketones and hydroxyl functions with electronic de-localizations (several of which are involved in the binding of the D-Ala-D-Ala termini of the peptidoglycan precursors), showing a globally strong negative logD at both neutral and acidic pHs (−16.67 and −7.33 at pH 7.4 and 5.5, respectively). Oritavancin has, therefore, a marked amphiphilic character favouring its interaction with negatively charged membrane phospholipids (abundant in Gram-positive bacteria). This causes membrane rigidification and permeabilization,[88,89] which may contribute to, and enhance the bactericidal activity of oritavancin, including against intracellular,[90] and biofilm-encased *S. aureus*.[91,92] The 4′ chlorobiphenyl methyl increases the binding of oritavancin to the D-Ala-D-Ala terminus of the cell wall precursor so that modification of the terminal D-Ala to D-Lac in vancomycin-resistant organisms using the VanA mechanism is insufficient to markedly affect oritavancin activity.[93] The correct positioning of the 4′ chlorobiphenyl methyl moiety, however, requires the presence of a closely apposed positive charge (see arrow), which is specific to oritavancin. Structures and calculations were made with Marvin sketch 21.13 (Chemaxon, Budapest, Hungary).

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Christian Eckmann[1]* and Paul M. Tulkens[2]

[1]*Department of General, Visceral and Thoracic Surgery, Klinikum Hannoversch-Muenden, Goettingen University, Germany;* [2]*Cellular and Molecular Pharmacology, Louvain Drug Research Institute, Université catholique de Louvain (UCLouvain), Brussels, Belgium*

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These hydrophobic moieties determine their long half-lives but, most importantly, markedly improve their antimicrobial activity by increasing their membrane affinity and thus their concentration near the target.[96] This enhancement is particularly strong for oritavancin, which is avidly taken up by macrophage and other eukaryotic cells where it accumulates mainly in lysosomes.[96] This may partly explain its marked bactericidal effect against *S. aureus*, a phagolysosome-associated microorganism.

Mechanims of action of glyco-lipopeptides

Antibiotics	Bind to lipid II		Transpeptidation	Membrane permeabilization and depolarization
	Dimerization	Membrane anchorage		
Vancomycin	Yes	No	No	No
Teicoplanin	No	Yes	No	No
Dalbavancin	No	Yes	No	No
Oritavancin	Yes	Yes	Yes	Yes
Telavancin	Yes	Yes	Unknown	Yes

Drugs (2015) 75:2073–2095
DOI 10.1007/s40265-015-0505-8

REVIEW ARTICLE

Lipoglycopeptide Antibacterial Agents in Gram-Positive Infections: A Comparative Review

Françoise Van Bambeke[1]

Table 4 Main clinical trials involving new lipoglycopeptides for their current indications

Phase	Study name and/or ClinicalTrials.gov identifier	Study arm (number of patients; ITT)	Comparator (number of patients; ITT)	Indications	Outcomes	References
II	SIMPLIFI NCT00514527	ORI 1200 mg day 1 (99)	ORI 800 mg day 1 [+400 mg day 5] (100) ORI 200 mg/day for 3–7 days (103)	Acute bacterial skin and skin structure infections (wound infections, major abscess, and cellulitis)	Non-inferiority (15 % margin): • Clinical response at days 21–29	[3]
III	SOLO 1 NCT01252719	ORI 1200 mg day 1 (475)	VAN 1 g or 15 mg/kg bid 7–10 days (479)	Acute bacterial skin and skin structure infections (wound infections, major abscess, and cellulitis)	Non-inferiority (10 % margin): - No spreading or reduction of lesion size measured at 48–72 h, absence of fever, and no need for rescue antibacterials - Clinical cure within 7–14 days - ≥20 % reduction in lesion size at 48–72 h	[159]
III	SOLO 2 NCT01252732	ORI 1200 mg day 1 (503)	VAN 1 g or 15 mg/kg bid 7–10 days (502)	Acute bacterial skin and skin structure infections (wound infections, major abscess, and cellulitis)	Non-inferiority (10 % margin): - No spreading or reduction of lesion size measured at 48–72 h, absence of fever, and no need for rescue antibacterials - Clinical cure within 7–14 days - ≥20 % reduction in lesion size at 48–72 h	[158]

Clinical case: back to Udine

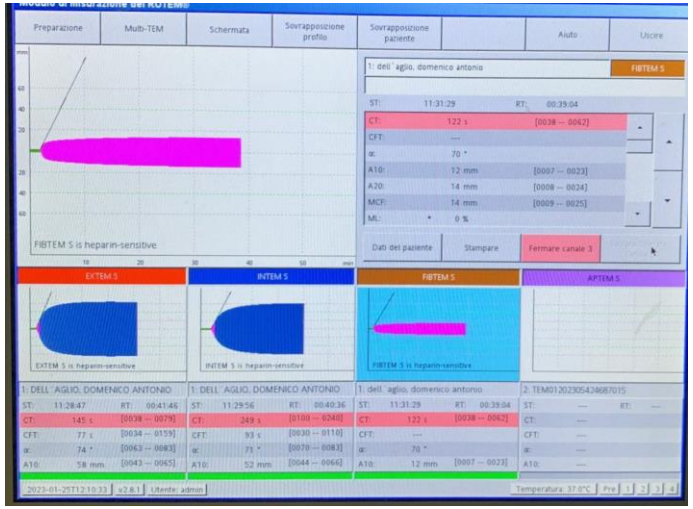
The INR was measured for the first two days due to interference of drug with in vitro testing (but not with the coagulation in vivo), since the patient was undergoing warfarin therapy and required INR monitoring (out of range result only observed on the first day).

27/12/22: INR 2.78

22/12/22: INR 2.65

20/12/22: INR 4.41 (1200 mg oritavancin)

16/12/2022: INR 2.5



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Effects of Oritavancin on Coagulation Tests in the Clinical Laboratory

Adam Belley,[a] Richard Robson,[b] John L. Francis,[c] Dorothy M. Adcock,[d] Stefan Tiefenbacher,[d] Christopher M. Rubino,[e] Greg Moeck,[a] David Sylvester,[a] Michael N. Dudley,[a] Jeffery Loutit[a]

The Medicines Company, Parsippany, New Jersey, USA[a]; Christchurch Clinical Studies Trust, Christchurch, New Zealand[b]; Florida Hospital Center for Thrombosis Research, Winter Park, Florida, USA[c]; Colorado Coagulation, Laboratory Corporation of America Holdings, Englewood, Colorado, USA[d]; Institute for Clinical Pharmacodynamics, Latham, New York, USA[e]

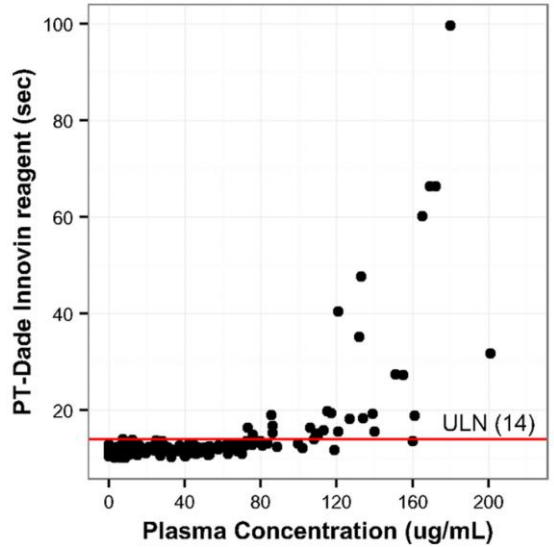

FIG 2 Relationship between oritavancin plasma concentrations and PT (using the Dade Innovin reagent) in participants ($n = 20$). The individual dots represent PT determinations observed at the corresponding oritavancin concentrations in subject plasma samples. The horizontal red line represents the upper limit of normal (ULN; 14 s) determined for the assay.

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TABLE 2 Time to resolution of elevations in PT/INR and aPTT test results in normal healthy volunteers ($n = 20$) in the phase 1 clinical study

Coagulation test	Reagent	Time to resolution[a] (h)	
		Mean (SD)	Median (min, max)
PT/INR	STA-Neoplastine CI Plus	0.00 (0.00)	0.00 (0.00, 0.00)
	HemosIL RecombiPlasTin 2G	1.50 (2.67)	0.00 (0.00, 6.00)
	Dade Innovin	8.42 (3.58)	6.18 (0.00, 12.00)
aPTT	STA-PTTa	89.75 (23.37)	96.00 (48.0, 144.2[b])
	HemosIL SynthASil	23.07 (13.82)	18.02 (6.1, 48.0)
	Dade Actin FSL	48.41 (28.86)	48.00 (6.4, 119.8)
	TriniCLOT aPTT HS	42.82 (23.73)	48.00 (6.4, 96.0)

TABLE 3 Maximum times to resolution of phospholipid-dependent and -independent coagulation test interference in participants administered a single 1,200-mg dose of oritavancin

Coagulation test	Maximum time to resolution (h)
Phospholipid dependent	
PT/INR	12
aPTT	120
ACT	24
SCT	18
DRVVT	72
APCR	Unaffected
Phospholipid independent	
Anti-factor Xa	Unaffected
TT	Unaffected
Anti-heparin-PF4	Unaffected
D dimer	72

Red man syndrome

ORIGINAL ARTICLE

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Drugs-associated with red man syndrome: An integrative approach using disproportionality analysis and Pharmip

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Results and discussion: Oritavancin exhibited a strong positive signal (PRR:1185.20 and ROR:1256), which suggests a higher risk for causing RMS. The literature search revealed the involvement of the MRGPRX2 gene in the development of RMS. PHARMIP study unearthed Carbonic anhydrase II (CA2) as the common off-label target among the drugs causing RMS. The results obtained from molecular docking studies reinforced the findings as mentioned earlier, wherein the highest docking score was disinterred for oritavancin (−9.4 for MRGPRX2 and − 8.7 for CA2).

Conclusioni

- Ci vuole un dottore
- Escludere le fasciti, sospiro di sollievo
- Evitare la terapia non necessaria
- Se necessario utilizzare farmaci potenti, ma con criterio
- Evitare le ospedalizzazioni