

Diagnostica delle infezioni del torrente circolatorio
ed infezioni dei device intravascolari: percorsi,
buone pratiche ed indicatori.

Aspetti Clinici

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Il sottoscritto Carlo Tascini

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009, dichiara che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- *Astra*
- *Advance*
- *Alfa Sigma*
- *Merck*
- *Pfizer*
- *Angelini*
- *Gilead*
- *Thermofischer*
- *Biotest*
- *Nordic*
- *Menarini*
- *Shionogi*
- *Hikma*
- *Viatrix*
- *Mundifarma*

CIED

- Cardiovascular Implantable Electronic device
- PM
- Defibrillatori (percentuale infezioni più alto)
- Risincronizzatori



Microbiology of cardiac implantable electronic device infections

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Table 2 Isolates from electrodes of cardiac implantable electronic devices (Pisa, 2000–2011)

	N	%
Total infected leads	1204	
Total isolates	1068	100.0
Gram positive	988	92.5
CoNS	737	69.0
<i>Staphylococcus aureus</i>	147	13.8
<i>Corynebacterium</i> spp.	53	5.0
<i>Propionibacterium</i> spp.	27	2.5
Gram negative	65	6.1
<i>Enterobacteriaceae</i> ³	32	3.0
<i>Pseudomonas</i> spp.	16	1.5
Candida spp.	11	1.0
<i>Candida albicans</i>	4	0.4
Molds	4	0.4

European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections—endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)

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Table 2 Pathogens isolated in patients undergoing interventions for device infection from three large patient cohorts in North America, Europe, and Asia

Pathogen	Percentage of isolates		
	North America ¹⁶	Europe ¹⁷	Asia ¹⁸
Coagulase-negative staphylococci		69	45.2
Methicillin-resistant	18.8		
Methicillin-sensitive	18.8		
<i>S. aureus</i>		13.8	4.1
Methicillin-sensitive	15.8		
Methicillin-resistant	15.0		
<i>Streptococcus</i> spp.	2.5		
<i>Enterococcus</i> spp.			
Vancomycin-sensitive	2.8		
Vancomycin-resistant	1.4		
<i>Cutibacterium</i> spp. (previously <i>Propionibacterium</i> spp.)		2.5	
<i>Corynebacterium</i>		5	
Gram-negative bacteria	8.9	6.1	9.1
<i>Enterobacteriaceae</i>		3	3.2
Non-fermentative bacilli, incl. <i>Pseudomonas</i> spp.		1.5	5.9
Anaerobes	1.6		
Fungi	0.9	1	0.9
Mycobacteria	0.2		

Coltura da elettrocatetere di pacemaker e defibrillatore Malattie Infettive di Pisa, 2000-2011		
	N	%
Stafilococchi coagulasi negativi	737	
<i>Staphylococcus epidermidis</i>	494	67,0%
<i>Staphylococcus capitis</i>	43	5,8%
<i>Staphylococcus schleiferi</i>	39	5,3%
<i>Staphylococcus hominis</i>	24	3,3%
<i>Staphylococcus lugdunensis</i>	17	2,3%
<i>Staphylococcus haemolyticus</i>	16	2,2%
<i>Staphylococcus cohnii</i>	8	1,1%
<i>Staphylococcus xylosus</i>	8	1,1%
<i>Staphylococcus sciuri</i>	7	0,9%
<i>Staphylococcus warneri</i>	5	0,7%
<i>Staphylococcus saprophyticus</i>	4	0,5%
<i>Staphylococcus simulans</i>	2	0,3%
Altri CoNS	70	9,5%

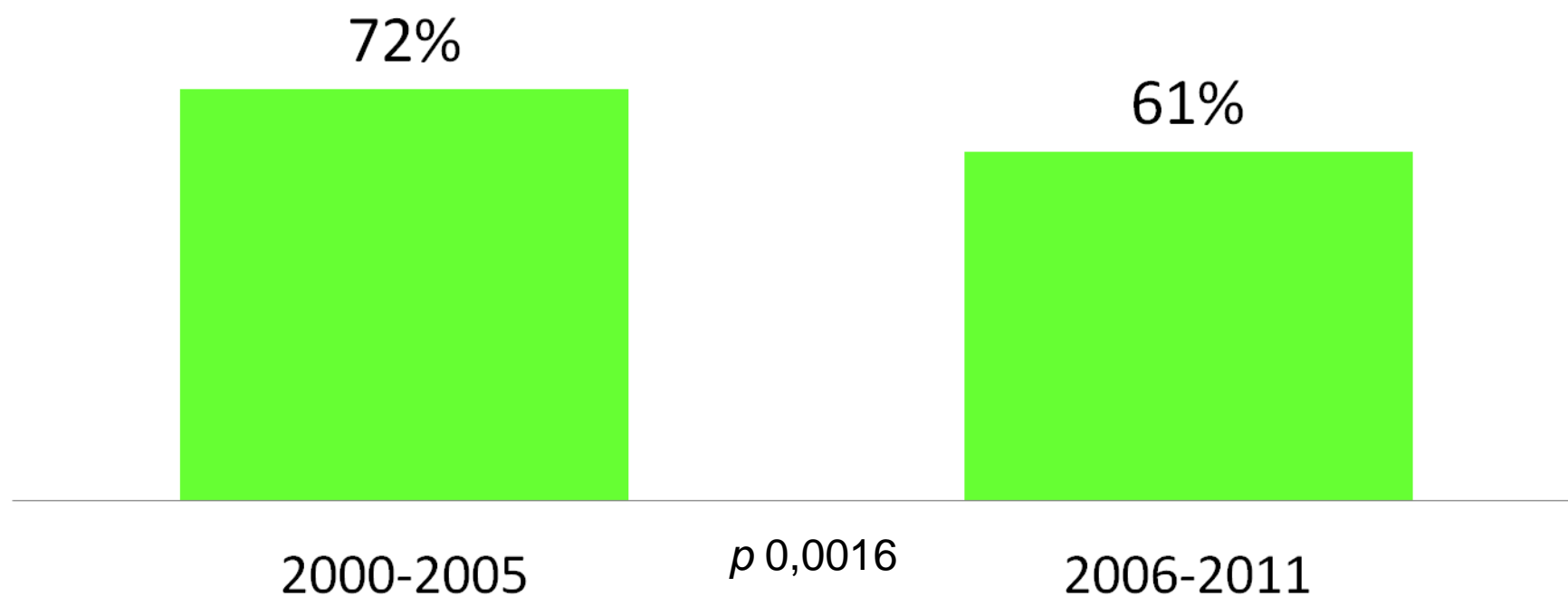
Role of the Preaxillary Flora in Pacemaker Infections

A Prospective Study

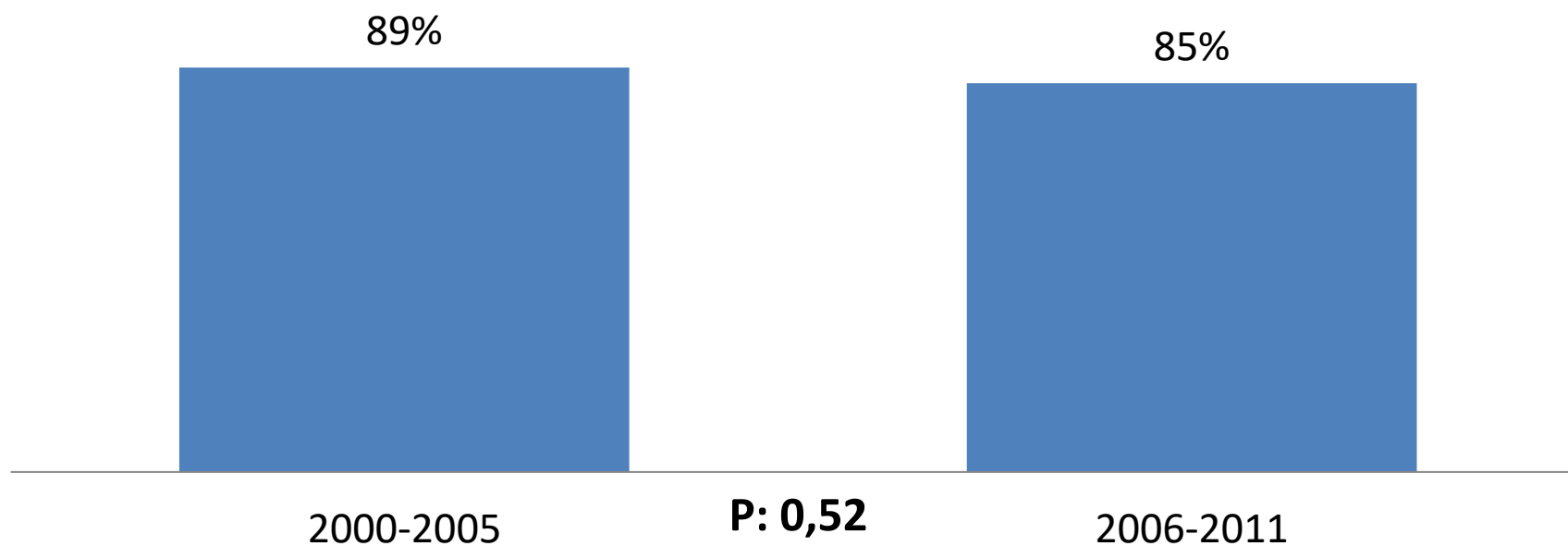
Antoine Da Costa, MD; Hervé Lelièvre, PhD; Gilbert Kirkorian, MD; Marie Célard, MD;
Philippe Chevalier, MD, PhD; François Vandenesch, MD, PhD;
Jerome Etienne, MD, PhD; Paul Touboul, MD

Conclusions—This study strongly supports the hypothesis that pacemaker-related infections are mainly due to local contamination during implantation. *S schleiferi* appears to play an underestimated role in infectious colonization of implanted biomaterials and should be regarded as an important opportunistic pathogen. (*Circulation*. 1998;97:1791-1795.)

**Oxacillin-susceptibility among CoNS isolated from CIED infections.
Pisa 2000-2011**



Coltura da elettrocatetere di pacemaker e defibrillatore
Malattie Infettive di Pisa, 2000-2011
Sensibilità all'oxacillina, *Staphylococcus aureus*



7.2 When should blood cultures be taken?

Summary:

- **Recommendation 7.2.1: Blood cultures should be taken prior to starting antimicrobial therapy. [B]**

Recommendation 7.2.2: On clinical suspicion of ICED infection in patients with a chronic or subacute presentation, three sets of aseptically collected, optimally filled blood cultures should be taken from peripheral sites with ≥ 6 h between them. [C]


Recommendation 7.2.3: To avoid undue delay in patients with suspected ICED and severe sepsis or septic shock at the time of presentation, two sets of optimally filled blood cultures should ideally be taken at different times within 1 h and prior to commencement of empirical antimicrobial therapy. [C]

- **Recommendation 7.2.4: Blood cultures should be taken 48–72 h after removal of an infected ICED. [C]**
- **Recommendation 7.2.5: Apply meticulous aseptic technique when taking blood cultures to reduce the risk of contamination with skin commensals. [B]**


crobials (either for treatment or prophylaxis). Whilst there is no good evidence to guide the timing or usefulness of blood cultures following ICED removal, a positive blood culture in this setting may indicate a persistent uncontrolled infection—re-implantation of a new ICED would be unwise in this situation. It should be noted that blood cultures lack sensitivity, particularly in patients already on antimicrobial therapy, and reliance on a negative blood culture alone in this situation would be equally unwise. Results of blood

Aprire le porte alla sostituzione in un tempo

to recover the most likely pathogens (Table 1). Suitable culture media and incubation conditions are as follows: chocolate agar (35–37°C in 5% CO₂ for 48 h), cysteine lactose electrolyte deficient (CLED) or MacConkey agar (35–37°C in air for 24 h), blood agar (35–37°C in an anaerobic cabinet for 48 h) and Sabouraud agar (30°C in air for 5 days). An enrichment broth (e.g. Robertson's cooked meat broth) should also be inoculated and incubated at 37°C for at least 48 h before subculture onto the same media. These media should recover the vast majority of bacteria and fungi that have been implicated in ICED infection.^{48,101}











Lead tips should also be cultured using the media listed above, though it is important to note that lead tips may become contaminated during the process of extraction if the generator pocket is infected, giving rise to false-positive results. ICED infection may occasionally be caused by fastidious or slow-growing bacteria such as *Mycobacterium* spp.,^{102,103} *Nocardia* spp.⁴⁸ and auxotrophic staphylococci.¹⁰⁴ If culture of pocket-site tissue is negative despite convincing evidence of infection, microbiologists may wish to consider prolonged incubation of media or, preferably, referral of tissue for amplification and sequencing of bacterial 16S ribosomal RNA genes to detect atypical causes not detected by routine culture. The use of sonication for the recovery of bacteria from ICEDs may have a useful role to play in patients with clinical signs of infection and this merits further study.⁶⁴



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Table 6 Recommendations for diagnosis of CIED infections by clinical findings and microbiology

Consensus statement	Statement class	Scientific evidence coding	References
At least three sets of blood cultures should be acquired in case of clinically suspected CIED endocarditis		E, O	19,65
Samples from the pocket should be cultured but only if acquired during removal and not passing through the sinus		E, O	19,65
Suspect CIED infections in case of vertebral osteomyelitis and/or embolic pneumonia (clinical signs and symptoms of CIED systemic infections may be difficult to recognize as only fever may be present)		E, O	61,65
Cultures of extracted CIED should be performed		E, O	66
PCT may be useful in case of infective endocarditis and embolism and/or in case of <i>S. aureus</i> CIED-related infective endocarditis		E, O	64
Increased incubation time (10–14 days) for slowly-growing microorganism may be considered in case of CIED-related infective endocarditis and persistent negative blood cultures		E	67
The usefulness of sonication of CIED to enhance microbial detection during removal/extraction is still under evaluation but may be used with caution when interpreting results		E, O	68–70
Cultures from the sinus of the CIED pocket or from parts of the device exposed		E	19

CIED, cardiac implantable electronic device; E, expert opinion; M, meta-analysis; O, observational studies; PCT, procalcitonin; R, randomized trials.

Systemic infections

Without vegetation on leads or valves ± pocket infection

Empirical treatment: (directed at methicillin-resistant staphylococci and Gram-negative bacteria):

Vancomycin (Daptomycin is an alternative)

Vancomycin: 30–60 mg/kg/d i.v. in 2–3 doses (Daptomycin 8–10 mg/kg od)

+

+ 3rd generation Cephalosporin (or a broader betalactam antibiotic) or Gentamicin

Cephalosporin: standard dose i.v. or Gentamicin 5–7 mg/kg i.v. od^b

To be adjusted after culture result

If sensitive staphylococcus: Flucloxacillin i.v. (1st generation cephalosporin i.v. as an alternative)

Flucloxacillin i.v. dosages as above.
(1st generation cephalosporin standard dose i.v.)

Duration post-extraction: 4 weeks (2 weeks if negative blood culture, see text)

CIED endocarditis with vegetation on leads and/or valves ± embolism

Empirical treatment:

Vancomycin (Daptomycin is an alternative)

Vancomycin; 30–60 mg/kg/d i.v. in 2–3 doses (Daptomycin 8–10 mg/kg od)

+

+ 3rd generation Cephalosporin (or a broader betalactam antibiotic) or Gentamicin

Cephalosporin; standard dose or Gentamicin 5–7 mg/kg i.v. od^b

Adjust to culture result according to ESC endocarditis guidelines 2015

If prosthetic valve and staphylococcal infection: Rifampicin to be added after 5–7 days

Rifampicin: 900–1200 mg/day orally (or i.v.) in 2 doses



O, R

19,59,65,81



O, R

59

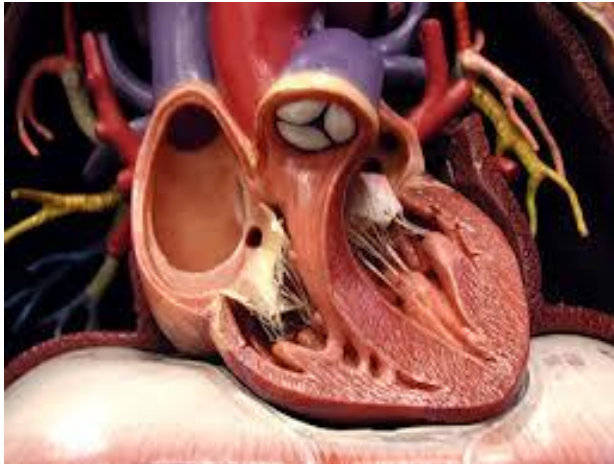
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Daptomycin Concentrations in Valve Tissue and Vegetation in Patients with Bacterial Endocarditis

Carlo Tascini,^a Antonello Di Paolo,^b Roberta Poletti,^c Sarah Flammini,^a Michele Emdin,^c Ilaria Ciullo,^a Enrico Tagliaferri,^a Annette Moter,^d Francesco Menichetti^a

Antimicrobial Agents and Chemotherapy, 2013; 57(1): 601



S. oralis (MIC_{daptomicina}, 0,094 → 0,25 mg/L)

Daptomicina 10 mg/kg

C_{max}: 81,8 mg/L
C_{min}: 14,8 mg/L

Aortic valve: 8,6 µg/g
Mitral valve: 30,8 µg/g
Mitral vegetation: 26,0 µg/g

Daptomycin Concentrations in Valve Tissue and Vegetation in Patients with Bacterial Endocarditis

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In a patient with mitral-aortic native-valve *Streptococcus oralis* endocarditis, daptomycin concentrations in aortic and mitral valves were 8.6 and 30.8 µg/g, respectively, and 26 µg/g in the mitral vegetation. In the case of porcine-aortic-valve *Staphylococcus epidermidis* endocarditis, the daptomycin concentrations were 53.1 µg/g in the valve and 18.1 µg/g in perivalvular tissues. Daptomycin achieved apparently adequate tissue concentrations. *S. epidermidis* was eradicated, whereas *Streptococcus oralis* persisted, and its daptomycin MIC displayed a 4-fold increase.

TABLE 1 Main clinical, microbiological, and PK/PD data from two cases of endocarditis treated with daptomycin^a

Patient	Endocarditis	Organism in blood culture	Daptomycin MIC (mg/liter), basal	Body wt (kg)	Daptomycin				Concn (µg/g) in:		Tissue culture	Daptomycin MIC (mg/liter)
					Dose (mg/day)	C _{max} (mg/liter)	C _{min} (mg/liter)	C _{max} /MIC	Valve tissue	Vegetation		
61-year-old male	Mitro-aortic native valve	<i>Streptococcus oralis</i>	0.094	72	500 (6.9 mg/kg)	36.6 (day 5)	8.5 (day 5)	389				
					700 (9.7 mg/kg)	81.8 (day 15)	14.8 (day 15)	870	Mitral, 30.8 Aortic, 8.6	Mitral, 26	<i>S. oralis</i> (day 18)	0.38 (4-fold increase)
69-year-old male	Aortic, porcine prosthetic valve (Carpentier-Edwards)	<i>Staphylococcus epidermidis</i>	0.38	70	500 (7.1 mg/kg)	45.3 (day 5)	9.9 (day 5)	119	Valve, 53.1 Perivalvular, 18.1		Negative (day 37)	

^a Target values for C_{max}, C_{min}, and C_{max}/MIC were >60 mg/liter, <24 mg/liter, and >100, respectively.



Review

Daptomycin: The role of high-dose and combination therapy for Gram-positive infections

Ian M. Gould^{a,*}, José M. Miró^b, Michael J. Rybak^c

in a C_{\max} and C_{\min} at Day 15 of 81.8 mg/L and 14.8 mg/L, respectively (corresponding to 8.2 mg/L and 1.5 mg/L of free drug). The patient underwent surgical replacement and the daptomycin concentrations in the aortic and mitral valves were 8.6 $\mu\text{g/g}$ and 30.8 $\mu\text{g/g}$ of tissue (equivalent to 0.9 $\mu\text{g/g}$ and 3.1 $\mu\text{g/g}$ of free drug), respectively, and 26.0 $\mu\text{g/g}$ in the mitral vegetation (corresponding to 2.6 $\mu\text{g/g}$ of free drug). The second patient had a porcine aortic valve *Staphylococcus epidermidis* IE. Daptomycin was given at 7 mg/kg/day and the concentrations in valve and perivalvular tissue were 53.1 $\mu\text{g/g}$ and 18.1 $\mu\text{g/g}$ of tissue (corresponding to 5.3 $\mu\text{g/g}$ and 1.8 $\mu\text{g/g}$ of free drug). These outcomes demonstrate that, despite the use of high-dose daptomycin, the free-drug antibiotic concentration that was reached in the vegetations and valve tissues is in the region of the MIC breakpoints for Gram-positive pathogens frequently associated with IE and, therefore, there is a risk of resistance developing. This is further evidence that supports the use of combination therapy in IE.



Reduced glycopeptide and lipopeptide susceptibility in *Staphylococcus aureus* and the “seesaw effect”: Taking advantage of the back door left open?

Jessica K. Ortwine^{a,**}, Brian J. Werth^{b,1}, George Sakoulas^{d,e}, Michael J. Rybak^{b,c,*}

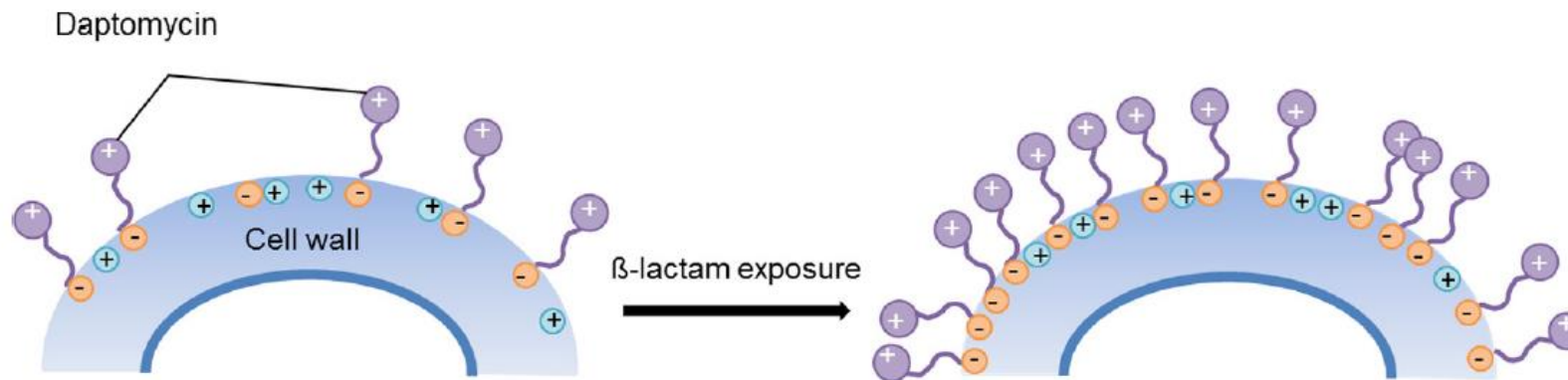


Figure 2. Proposed mechanisms for daptomycin and beta-lactam synergy. Daptomycin acts like a cationic peptide antibiotic and is attracted to the negative charge of the bacterial cell membrane. Once in contact with the cytoplasmic membrane (CM) daptomycin disrupts the CM causing a rapid release of electrolytes from the cytoplasm leading to depolarization and death of the cell. Exposure to beta-lactams increases the negative charge of the cell surface leading to an increase in daptomycin binding and improved bactericidal activity.



Ceftobiprole for the treatment of infective endocarditis: A case series

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Mariano Bernardo^f, Daniela Francisci^d, Chiara Oltolini^b, Giulia Palmiero^a,
Paolo Scarpellini^b

Objectives: Ceftobiprole is a relatively new cephalosporin with broad-spectrum activity and good tolerability. Despite its promising characteristics, to our knowledge, only two case reports, previously published also by some of us, is available concerning its administration for the treatment of infective endocarditis. Hereby we report our experience in this field.

Methods: All the patients with infective endocarditis treated with ceftobiprole were enrolled.

Results: 12 cases of endocarditis were treated with ceftobiprole, 11/12 in combination with daptomycin and 1/12 as monotherapy. Gram-positive bacteria were isolated in 12/12 patients; 3 cases were polymicrobial.

Cure rate was 83% (10/12 patients). In 9/12 (75%) cases, patients were switched to ceftobiprole following failure of previous antimicrobial regimen. In 3/3 patients in which ceftobiprole was administered because of persistently positive blood culture, bacteraemia clearance was rapidly achieved.

Conclusions: Ceftobiprole, especially in combination, could be a promising alternative treatment for infective endocarditis.

Ceftobiprole is a relatively novel fifth-generation cephalosporin with demonstrated *in vitro* activity against both Gram-positive and Gram-negative clinically relevant micro-organisms including methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae*, expanded spectrum beta-lactamases (ESBL) non-producing *Enterobacteriaceae* [1,2]; moreover, in a recent study by Pfaller et al. [1], 72.7% of the *Pseudomonas aeruginosa* isolates resulted susceptible to ceftobiprole. While enterococci are intrinsically resistant to cephalosporins, ceftobiprole is also active against ampicillin-susceptible *Enterococcus faecalis* [1,2]. It also demonstrated good tolerability; discontinuation rate for ceftobiprole-related adverse events was just 5.8% in one of its registration trials [3].

In Europe, ceftobiprole was licensed for the treatment of community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) excluding ventilator-associated pneumonia (VAP) in the adult. However, there are some available studies on the use of ceftobiprole for the treatment of other infections such as skin and skin structures infections [4] as well as reports on animal models for the treatment of mediastinitis [5], osteomyelitis [6], urinary tract infections [7] and meningitis [8]. Endocarditis was also investigated, using animal models [9], although, to our knowledge, just a case report is currently available on the use of ceftobiprole for the treatment of endocarditis in human beings [10]. We hereby report our experience in this setting.

Table 1
Patients' characteristics and treatment history.

Patient (gender-age)	Year	Underlying conditions	Valve	Aetiology	Prior therapy	Indication for switch	Days on CBP	Concomitant antibiotics	Surgery	Time to apyrexia	Time to negative blood culture	Time to negative C-RP	Outcome
Pt 1 (F-39)	2016	IDU	T	MSSA	VAN + GEN + LFX	Persistent fever	35	DAPTO	Yes	30	na	na	Cured
Pt 2 (M-82)	2015	CIC, HTN, RI	A (BP) + M	Polymicrobial ^a	None	None	10	DAPTO	Yes	na	na	na	Cured
Pt 3 (M-76)	2018	PIE, CIC, AF, HTN	A (MP)	MSSA	CRO + LFX, DAPTO + CZA	Persistent fever and positive blood culture	9	DAPTO	No	Never but improving	2	Never but improving	exitus (fatal arrhythmia)
Pt 4 (M-77)	2018	CIC, AF, HTN	A (BP)	MRSE	None	None	8	DAPTO	No	5	2	Never but improving	Exitus (fatal arrhythmia)
Pt 5 (M-81)	2018	CIC, HTN, ictus cerebri	A (MP)	MR Staph. haemolyticus	DAPTO + MEM	Persistent fever	18	DAPTO	No	5	Negative before CBP	11	Cured
Pt 6 (M-46)	2018	IDU	T	MSSA	TCP + MEM	Persistent fever and positive blood culture	47	DAPTO	Yes	22	1	Never but improving	Cured
Pt 7 (M-92)	2018	CIC, AF, HTN	PMK	MSSA	DAPTO + CZA	Persistent fever, lung embolism	21	DAPTO	Yes	4	Negative before CBP	11	Cured
Pt 8 (F-20)	2016	SLE, HTN, APS, ictus cerebri, RI	M (MP)	Polymicrobial ^b	DAPTO + MEM	Concomitant pneumonia, persistent fever	18	None	No	1	Negative before CBP	Negative before CBP	Cured
Pt 9 (F-62)	2017	HTN, PMK	A (BP)	MRSE + MSSE	DAPTO + OXA	None	59	DAPTO + RIF	No	1	4	Never but improving	Cured
Pt 10 (F-69)	2016	RI, KT, vasculitis, ictus cerebri, AF	M	MRSA	PTZ	Concomitant pneumonia, RI	30	DAPTO	No	1	9	Never but improving	Cured
Pt 11 (M-66)	2015	RI, COPD, PIE	A (BP)	MRSA	DAPTO + PTZ	Persistent positive blood cultures	84	DAPTO	Yes	Afebrile before CBP	12	Never but improving	Cured
Pt 12 (F-76)	2015	DM, HTN, PMK, PIE	M (MP), PMK	MRSA	TMP/SMX + DAPTO + GEN	Increased vegetation size	28	TMP/SMX (later switched for FOF) + DAPTO	No	Afebrile before CBP	Negative before CBP	30	Cured

Abbreviations: Pt, patient; F, female; M, male; C-RP, C-reactive protein; IDU, intravenous drug user; CIC, chronic ischaemic cardiopathy; HTN, hypertension; RI, renal insufficiency; PIE, previous infective endocarditis; AF, atrial fibrillation; SLE, systemic lupus eritematosus; APS, anti-phospholipid syndrome; KT, kidney transplantation; DM, diabetes mellitus; T, tricuspid valve; A, aortic valve; M, mitral valve; BP, biologic prosthesis; MP, mechanic prosthesis; PMK, pace-maker; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; VAN, vancomycin; GEN, gentamicin; LFX, levofloxacin; CRO, ceftriaxone; CZA, cefazolin; DAPTO, daptomycin; MEM, meropenem; CBP, ceftobiprole; TCP, teicoplanin; OXA, oxacillin; RIF, rifampin; PTZ, piperacillin-tazobactam; TMP-SMX, trimethoprim-sulfamethoxazole; FOF, fosfomycin; na, not available.

^a MRSE, *Staphylococcus haemolyticus*, *Staphylococcus hominis*, *Streptococcus sanguinis*, *Streptococcus anginosus*.

^b Methicillin-resistant *S. aureus*, *E. cloacae*.

2023 ESC Guidelines for the management of endocarditis

Developed by the task force on the management of endocarditis of the European Society of Cardiology (ESC)

Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Nuclear Medicine (EANM)

When indicated, definite reimplantation should be postponed if possible, to allow a few days or weeks of antibiotic therapy.	Ila	C	If CIED reimplantation is indicated after extraction for CIED-related IE, it is recommended to be performed at a site distant from the previous generator, as late as possible, once signs and symptoms of infection have abated and until blood cultures are negative for at least 72 h in the absence of vegetations, and negative for at least 2 weeks if vegetations were visualized.	I	C
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12.4.8. Device reimplantation

The indication for reimplantation should always be carefully evaluated and no part of the removed CIED system should be reimplanted. Quality of evidence regarding timing of reimplantation is poor.⁷⁰⁹ Reimplantation should be performed at a site distant from that of the previous generator, and delayed until signs and symptoms of local and systemic infection have resolved and blood cultures are negative for at least 72 h after extraction in the absence of vegetations or ‘ghosts’ (fibrous remnants after lead extraction, which have been associated with death and reinfection),⁷¹⁰ or after 2 weeks of negative blood cultures if vegetations were visualized.^{701,711}

One Stage Side-to-Side Replacement of Infected Pulse Generators and Leads

RAMAVATHI NANDYALA and VICTOR PARSONNET

From the Pacemaker and Defibrillator Evaluation Center at Newark Beth Israel Medical Center, an affiliate of the Saint Barnabas Health Care System; Newark, New Jersey

Infected and contaminated cardiac pulse generators and leads must be removed entirely in order to effect a cure. We have shown through our experience with 68 consecutive cases that explantation of the offending system and replacement of a new device on the opposite side can be safely accomplished in one sitting—a side-to-side replacement—as long as there is appropriate case selection. There were no early or late infections of the new operative site. (PACE 2006; 29:393–396)

pacemaker, reoperation, infection

Clinical Presentation

Erosion of the device hardware, either the pulse generator or the leads, was present in 28 (41%) patients, cellulitis or abscess formation in 23 (35%), and persistent bacteremia and echo-identified endocarditis in 17 (24%) (Table II). The vegetations, often multiple, were identified by transesophageal echocardiogram. They ranged in size from 0.3 to 1.2 cm. They were treated by complete extraction of the infected old and new leads and at the same time replacement of a new dual-chamber system on the contralateral noninfected side.

CIED Re-implantation

Systematic review and meta-analysis

- Results: 280 screened studies, 8 included
- 96 participants per study (range 15–220 participants). The pooled incidence rate of device reinfection was 0.45% (95% CI, 0.02% to 1.23%) per person year.
- **A longer time to device reimplantation >72 hours was associated with a trend towards higher rates of reinfection** (unadjusted incident rate ratio 4.8; 95% CI 0.9 to 24.3, $p=0.06$); however, the meta-regression analysis was unable to adjust for important clinical covariates.
- There did not appear to be a difference in reinfection rates when time to reimplantation was stratified at 1 week. Heterogeneity was moderate ($I^2=61\%$).

BMJ Open Timing of device reimplantation and reinfection rates following cardiac implantable electronic device infection: a systematic review and meta-analysis

Derek Chew,^{1,2} Ranjani Somayaji,^{3,4,5,6} John Conly,^{3,4,5,6,7,8} Derek Exner,^{1,2,6}
Elissa Rennert-May^{3,4,6}





Table 1 Characteristics of included studies

Study	N	Age, yr, mean (SD)	Female, %	Device type	Pathogen	Local infection only, %	Time to reimplantation	Device reinfection, %	Death, %	Follow-up, months
Amraoui <i>et al</i> ²⁷	80	71 (13)	20	PM, ICD	NR	61	4–14 days	0	5.0	12
Boyle <i>et al</i> ¹³	220	68 (14)	19	NR	NR	58	10 days IQR 6–19	1.8	11.4	6
Chua <i>et al</i> ²⁸	123	66 (16)	29	PM, ICD	CoNS: 46 <i>S. aureus</i> : 9.0	74	5 days (range 0–68 days)	3	8.1	14
Deharo <i>et al</i> ²⁹	59	71 (14)	26	PM, ICD, CRT	CoNS: 42 <i>S. aureus</i> : 30 GNB: 11	41	24 days (10–1192 days)	1.7	3.3	25
Molina ³⁰	26	50 (NR)	NR	PM, ICD	NR	NR	2–6 weeks	0.09	0	312
Mountantonakis <i>et al</i> ³¹	15	77 (12)	27	PM, ICD	CoNS: 40 <i>S. aureus</i> : 27 GNB: 20	100	0 (same day)	0	NR	40
Saeed <i>et al</i> ³²	168	67 (7)	32	PM, ICD, CRT	NR	82	3 days IQR 1–10	5.4	NR	229
Tascini <i>et al</i> ³³	79	60 (30)	23	PM, ICD	CoNS: 70 <i>S. aureus</i> : 14 GNB: 12	72	2 days	0	NR	14

CoNS, coagulase negative staphylococci; CRT, cardiac resynchronisation therapy; GNB, gram negative bacilli; ICD, implantable cardioverter defibrillator; IQR, interquartile range; NR, not reported; PM, pacemaker; Yr, year.

Article

Safety and Efficacy of a Single Procedure of Extraction and Reimplantation of Infected Cardiovascular Implantable Electronic Device (CIED) in Comparison with Deferral Timing: An Observational Retrospective Multicentric Study

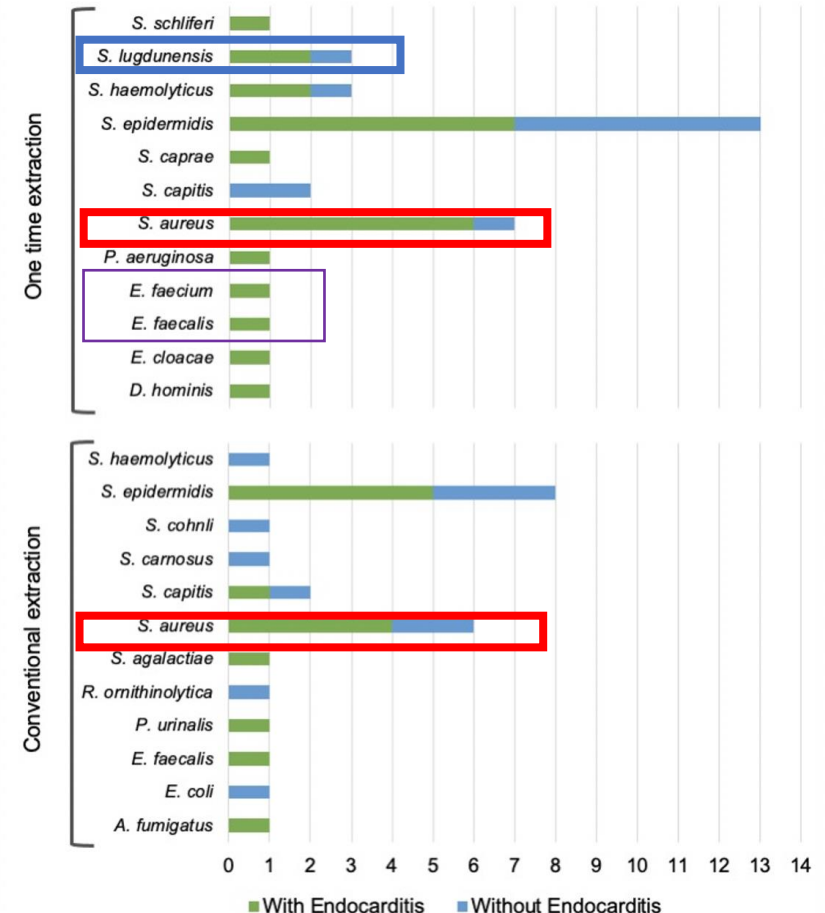
Carlo Tascini ^{1,2}, Simone Giuliano ², Vittorio Attanasio ³, Luca Segreti ⁴, Andrea Ripoli ⁵, Francesco Sbrana ⁶ , Sergio Severino ⁷, Chiara Sordelli ⁷, Sara Hana Weisz ⁷ , Agnese Zanus-Fortes ², Gabriele Maria Leanza ^{2,*} , Novella Carannante ³, Andrea Di Cori ⁴ , Maria Grazia Bongiorno ⁴, Giulio Zucchelli ⁴ and Stefano De Vivo ⁸

- Retrospective analysis comparing the outcome and safety of a single-procedure device extraction and contralateral implantation
- versus the standard-of-care (SoC) two-stage replacement for infected CIEDs.
- 66 patients with CIED infections who were treated at two Italian hospitals.
- 27 underwent a single procedure, whereas 39 received SoC treatment.
- All patients were followed up for 12 months after the procedure

One stage extraction of cardiovascular devices: an observational retrospective multicentric study.

Carlo Tascini¹, Simone Giuliano¹, Vittorio Attanasio², Luca Segreti³, Andrea Ripoli⁴, Francesco Sbrana⁵, Sergio Severino⁶, Chiara Sordelli⁶, Sara Hana Weisz⁶, Agnese Zanus-Fortes¹, Gabriele Maria Leanza¹, Novella Carannante², Maria Grazia Bongiorno³, Giulio Zucchelli³, Stefano De Vivo⁷

Patient characteristics	One-time extraction (n = 27)	Conventional extraction (n = 39)	P
Device extraction and implant			
Time from device implant (years)	2 [1 - 7]	9 [4 - 13]	0.002
Time from diagnosis to extraction (days)	27 [12 - 30]	60 [30 - 90]	<0.001
Length of procedure (minutes)	140 [102 - 180]	151 [120 - 224]	0.192
Final Diagnosis			
Endocarditis	18 (66.7%)	17 (43.56%)	0.082
Localized infection	17 (33.3%)	18 (56.4%)	0.144
Endocarditis+BSI	8 (29.6%)	6 (15.4%)	0.223
Vegetation			
Vegetation	14 (51.9%)	15 (38.5%)	0.409
Vegetation size (median, range-mm)	3.12 ± 0.91	4.07 ± 1.12	0.857
Positive blood culture	12 (44.44%)	13 (33.3%)	0.511
Concomitant sepsis	3 (11.1%)	2 (5.1%)	0.393
Anticoagulant therapy	15 (55.6%)	16 (41.0%)	0.318
Antibiotic Therapy (admission)			
Overall	9 (33.3%)	21 (53.6%)	0.163
Gram Negative coverage	7 (25.9%)	9 (23.0%)	1.000



Patient characteristics	Single procedure (n=27)	SoC (n=39)	P
Pacemaker	40.7%	100%	< 0.001
ICD	22.2%	0	0.008
Biventricular defibrillator implant	37.0%	0	< 0.001
Time from implant (years)	2 (1-7)	9 (4-13)	0.002
Time to extraction (days)	27 (12-30)	60 (30-90)	< 0.001
Anti-biofilm active therapy	81.5%	38.5%	0.001
1-month survival	88.9%	100%	0.126
12-month survival	81.5%	84.6%	0.737

May 2nd 2019

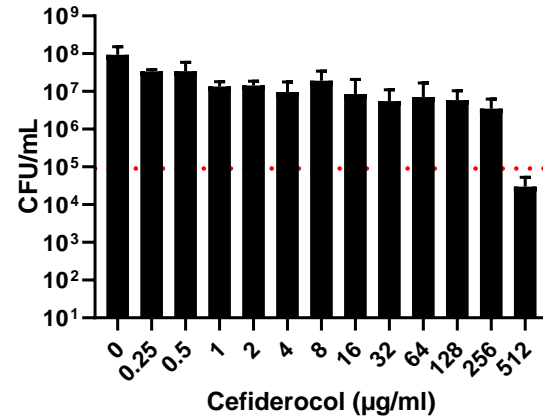
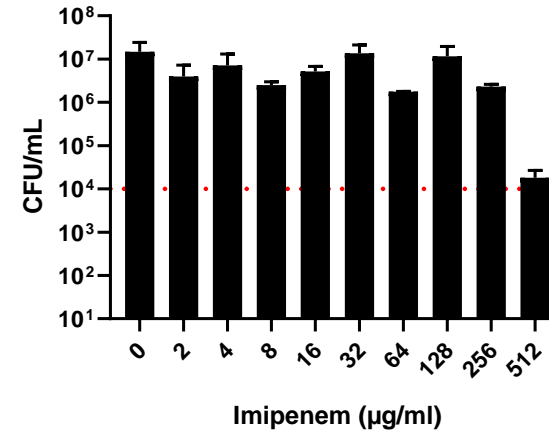
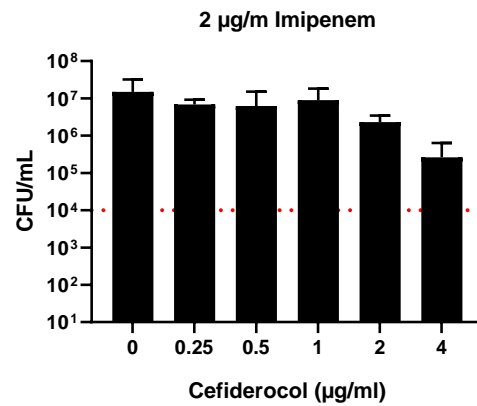
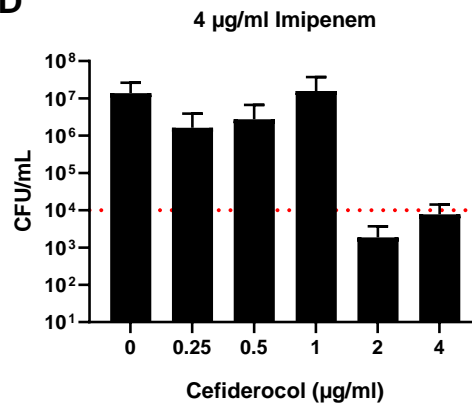
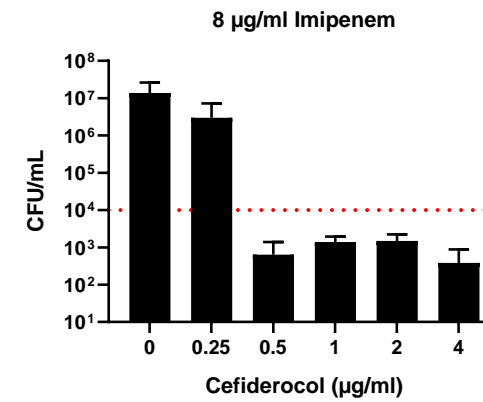
Ceftazidime/avibactam (MIC >16mg/L)
Caftolozane/tazobactam (MIC =32mg/L)
ceftazidime (MIC >16mg/L)
Imipenem (MIC <0.5mg/L),
Meropenem (MIC =8mg/L)



April 25th 2019

May 19th 2019

One-stage re-implantation of CIED endocarditis relapsed with ceftolozane/tazobactam and ceftazidime/avibactam and treated with imipenem and cefiderocol , in vitro activity of cefiderocol alone or in combination with imipenem(Prof Di Luca)

A**B****C****D****E**

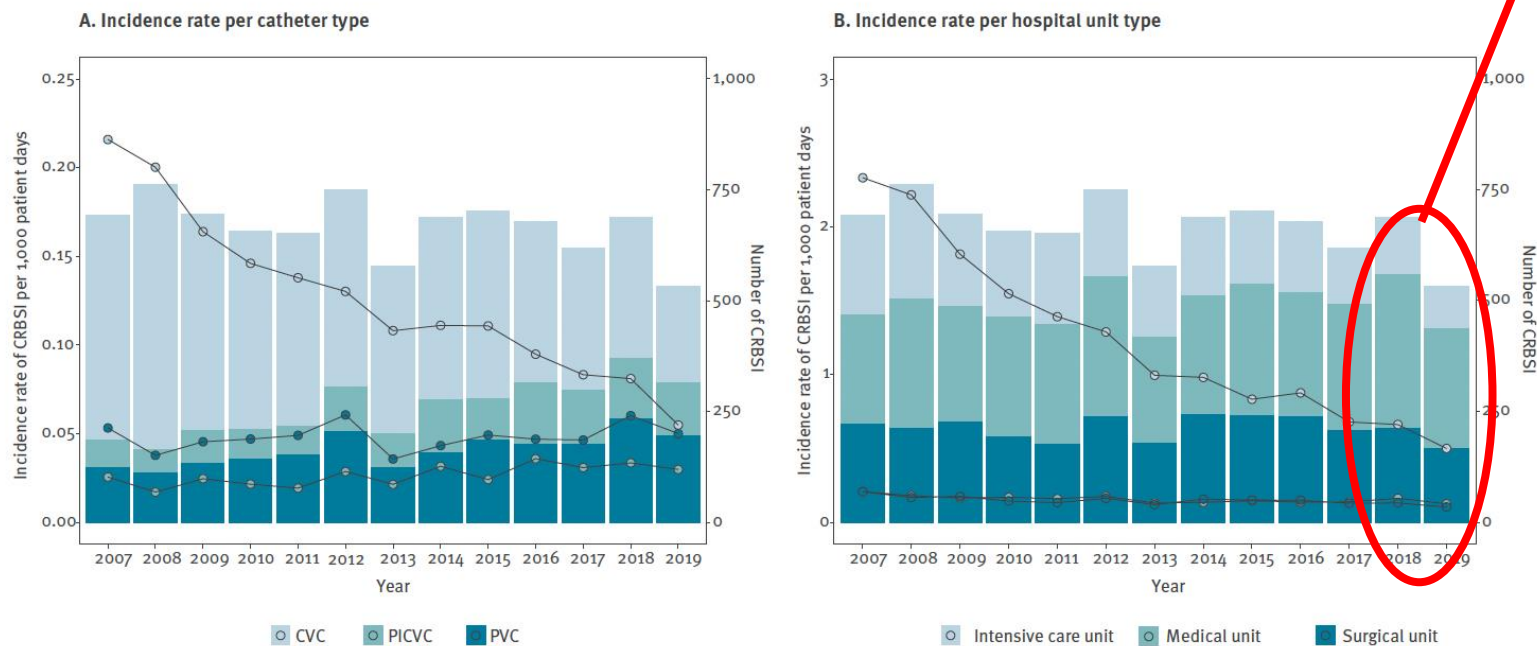
Cefiderocol (A) and Imipenem (B) tested against biofilm-embedded cells of *P. aeruginosa* CTN-1. Different concentrations of cefiderocol were also tested in combination with 2 μg/ml (C), 4 μg/ml (D) e 8 μg/ml (E) imipenem. Dashed red line indicated a reduction of 3 log₁₀ CFU/ml number in comparison to the untreated control (0μg/ml).

Trends in the epidemiology of catheter-related bloodstream infections; towards a paradigm shift, Spain, 2007 to 2019

Laia Badia-Cebada^{1,2}, Judit Peñafiel³, Patrick Saliba⁴, Marta Andrés⁵, Jordi Càmaras^{6,7,8}, Dolors Domenech⁹, Emili Jiménez-Martínez¹⁰, Anna Marrón¹¹, Encarna Moreno¹², Virginia Pomar¹³, Montserrat Vaqué¹⁴, Enric Limón⁴, Úrsula Masats¹⁵, Miquel Pujol^{16,17}, Oriol Gasch^{2,11,18}, on behalf of the VINCat programme (Infection Control Catalan Programme)¹⁹

FIGURE 1

Annual incidence rate of catheter-related bloodstream infection adjusted per 1,000 patient days stratified by (A) catheter type and (B) hospital unit type, Catalonia, Spain, 2007–2019 (n = 9,290)



CRBSI: catheter-related bloodstream infection; CVC: central venous catheter; PIVC: peripherally-inserted central venous catheters; PVC: peripheral venous catheters.

Solo 1/5 delle CR-BSI
in ICU

REVIEW

A state of the art review on optimal practices to prevent, recognize, and manage complications associated with intravascular devices in the critically ill



Jean-François Timsit^{1,2*}, Mark Rupp^{3,4}, Emilio Bouza^{5,6,7}, Vineet Chopra⁸, Tarja Kärpänen⁹, Kevin Laupland¹⁰, Thiago Lisboa^{11,12}, Leonard Mermel^{13,14}, Olivier Mimoz^{15,16,17}, Jean-Jacques Parienti^{18,19}, Garyphalia Poulakou²⁰, Bertrand Souweine^{21,22} and Walter Zingg²³

2/3 pazienti hanno CVC

CVCs are frequently used in critical care with up to two-thirds of patients admitted to French ICUs being exposed to at least one such device [1].

Spesso antibiotici


Introduction

Effective treatment of critically ill patients requires reliable vascular access in order to monitor patient status and deliver critically needed fluids, blood products, and medications. Unfortunately, mechanical, thrombotic, and infectious complications are not infrequent and result in substantial morbidity, mortality, and excess cost. This

REVIEW

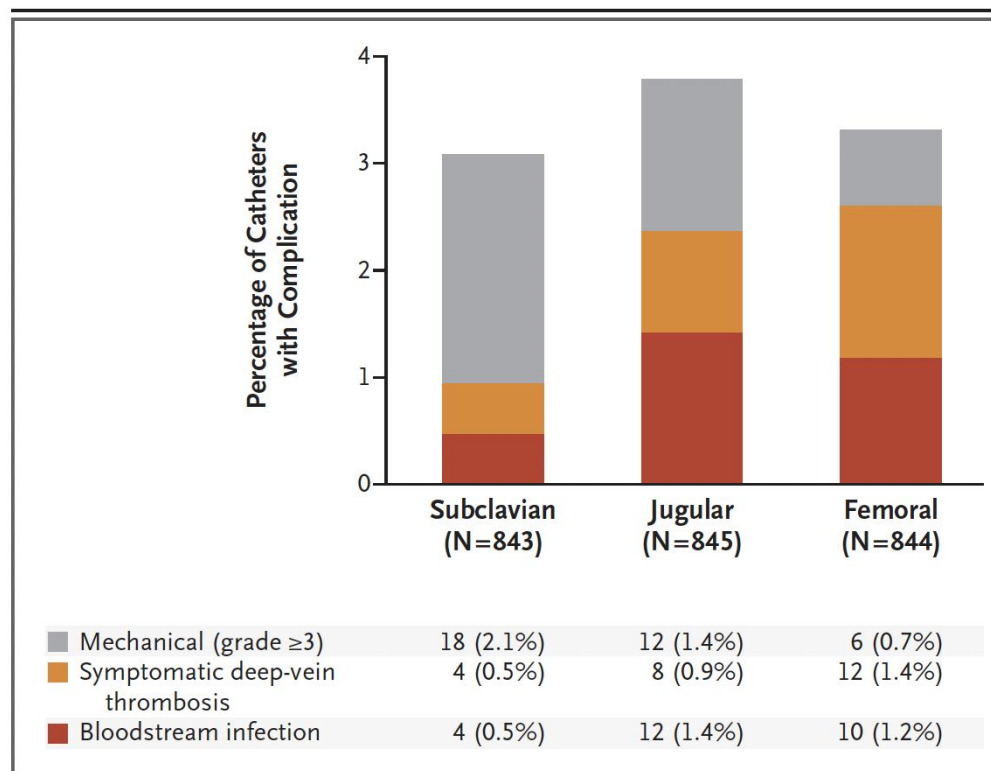


A state of the art review on optimal practices to prevent, recognize, and manage complications associated with intravascular devices in the critically ill

Jean-François Timsit^{1,2*} , Mark Rupp^{3,4}, Emilio Bouza^{5,6,7}, Vineet Chopra⁸, Tarja Kärpänen⁹, Kevin Laupland¹⁰, Thiago Lisboa^{11,12}, Leonard Mermel^{13,14}, Olivier Mimoz^{15,16,17}, Jean-Jacques Parienti^{18,19}, Garyphalia Poulakou²⁰, Bertrand Souweine^{21,22} and Walter Zingg²³

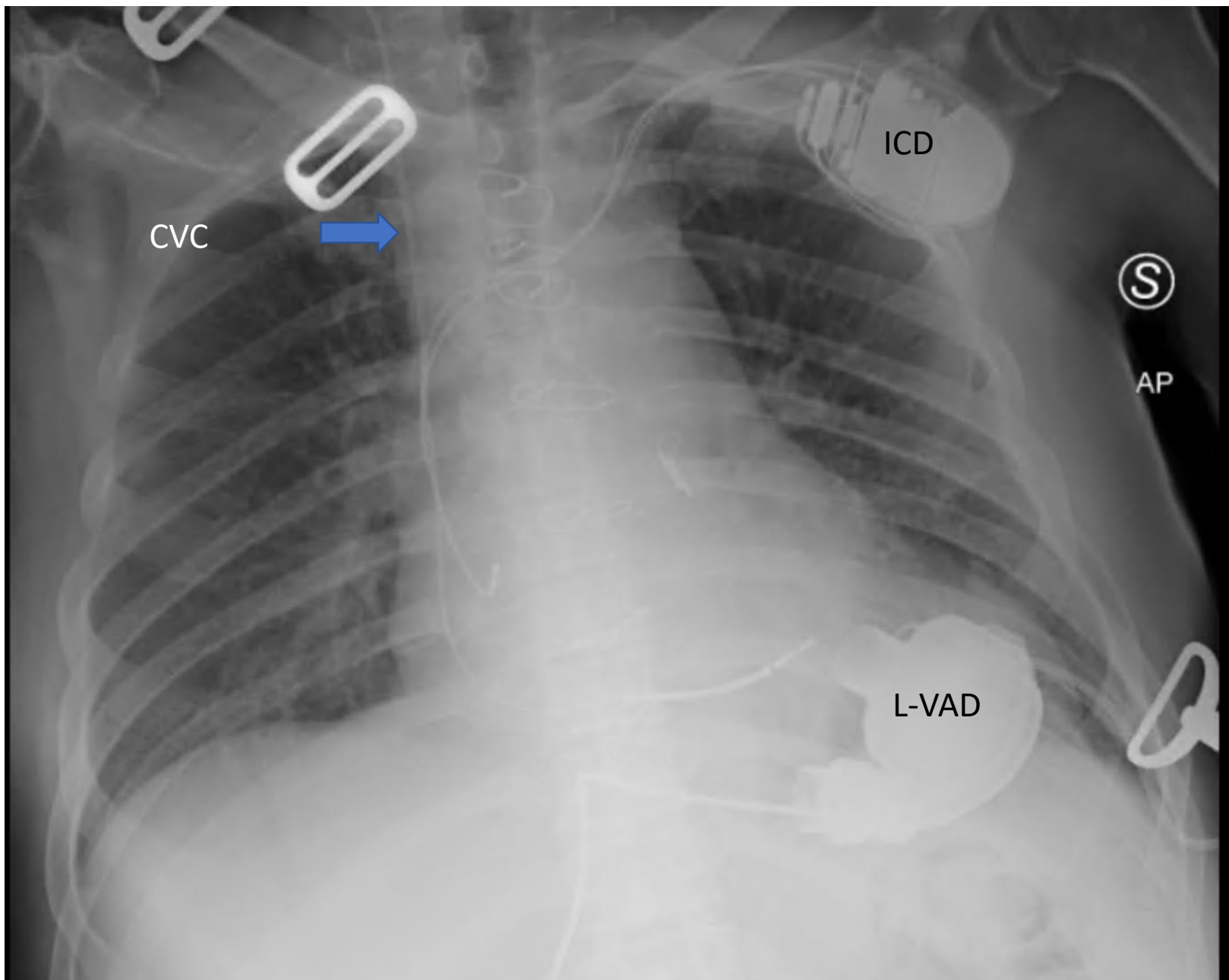
observed. As the cumulative risk of infection increases with the number of days the CVC is in place, prompt removal of unnecessary CVCs is mandatory [7]. In fact, in the before–after quasi-experimental Michigan Keystone Project, prompt CVC removal, together with hand hygiene, use of full-barrier CVC insertion precautions, skin disinfection with chlorhexidine, and avoidance of the femoral site decreased the incidence of central line-associated bloodstream infection (CLABSI) from 7.7 at baseline to 1.4 per 1000 catheter-days [8].

Intravascular Complications of Central Venous Catheterization by Insertion Site



Succlavia: più pneumotoraci
Giugulare: più infezioni (capelli?)
Femorale: infezioni e trombosi

Malato in reparto,
Stabile.
Abbiamo perso
il buon senso?



Paziente anziano

- switch da terapia ev a sottocute
- 18 g pip/tazo ic
- 4,5 g ogni 6 ore con ago flessibile sottocute addome

Pre

Data Nascita: 22/07/1962 Et : 60 Anni
 Richiesta: 55693011 del: 13/02/2023
 (UD)-1  piano, Pad. 8

Esame	Esito	U.M.	Intervalli di
Peso del paziente	60	kg	
Altezza	182	cm	
Data-ora del prelievo pre-dose	13.02.23 12.00		
PIPERACILLINA: Concentrazione pre-dose	69.59	mg/L	
Dose consigliata	18 gr ev ic	mg	
Intervallo di somministrazione	24	Ore	
Commento	Concentrazione in ambito di efficacia terapeutica		

Post

Richiesta: 55693053 del: 13/02/2023
 (UD)-1  piano, Pad. 8

Esame	Esito	U.M.	Intervalli di
Peso del paziente	60	kg	
Altezza	180	cm	
Data-ora del prelievo pre-dose	13.02.23 13.30		
PIPERACILLINA: Concentrazione pre-dose	85.22	mg/L	
Dose consigliata	4.5 gr SC II	mg	
Intervallo di somministrazione	6	Ore	
Data in cui ripetere il monitoraggio	mercoledì		
Commento	Concentrazione in ambito di efficacia terapeutica		



Pre



Post

Richiesta: 55694135 del: 14/02/2023
(UD)-1° piano, Pad. 8

Esame	Esito	U.M.	Intervalli di
Peso del paziente	60	kg	
Altezza	180	cm	
Data-ora del prelievo pre-dose	14.02.23 12.00		
PIPERACILLINA: Concentrazione pre-dose	84.50	mg/L	
Dose consigliata	4.5 gr SC II	mg	
Intervallo di somministrazione	6	Ore	
Commento	Concentrazione in ambito di efficacia terapeutica		

Data nascita: 22/07/1962 Età: 60 Anni
Richiesta: 55694190 del: 14/02/2023
(UD)-1° piano, Pad. 8

Esame	Esito	U.M.	Intervalli di
Peso del paziente	60	kg	
Altezza	180	cm	
Data-ora del prelievo pre-dose	14.02.23 13.30		
PIPERACILLINA: Concentrazione pre-dose	113.00	mg/L	
	Concentrazione post-dose, con data dell'ultima somminist. ore 12.00		
Dose consigliata	4.5 gr SC II	mg	
Intervallo di somministrazione	6	Ore	
Commento	Concentrazione in ambito di efficacia terapeutica		



Review

The Subcutaneous Administration of Beta-Lactams: A Case Report and Literary Review—To Do Small Things in a Great Way

Gabriele Maria Leanza ¹ , Beatrice Liguoro ¹, Simone Giuliano ^{2,*} , Chiara Moreal ³ , Luca Montanari ³,
Jacopo Angelini ⁴, Tommaso Cai ^{5,6} , Rita Murri ^{1,7}  and Carlo Tascini ^{2,3} 



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**Médecine et
maladies infectieuses**

Médecine et maladies infectieuses 47 (2017) 92–141

Original article

Proposal for shorter antibiotic therapies

Propositions pour des antibiothérapies plus courtes

C. Wintenberger^a, B. Guery^b, E. Bonnet^c, B. Castan^d, R. Cohen^e, S. Diamantis^f, P. Lesprit^g,
L. Maulin^h, Y. Péanⁱ, E. Peju^j, L. Piroth^j, J.P. Stahl^k, C. Strady^l, E. Varon^m, F. Vuotto^b,
R. Gauzit^{n,*}, Recommendation Group of the SPILF

5. Central venous catheter-related bacteremia (CRB)

Suggested treatment durations:

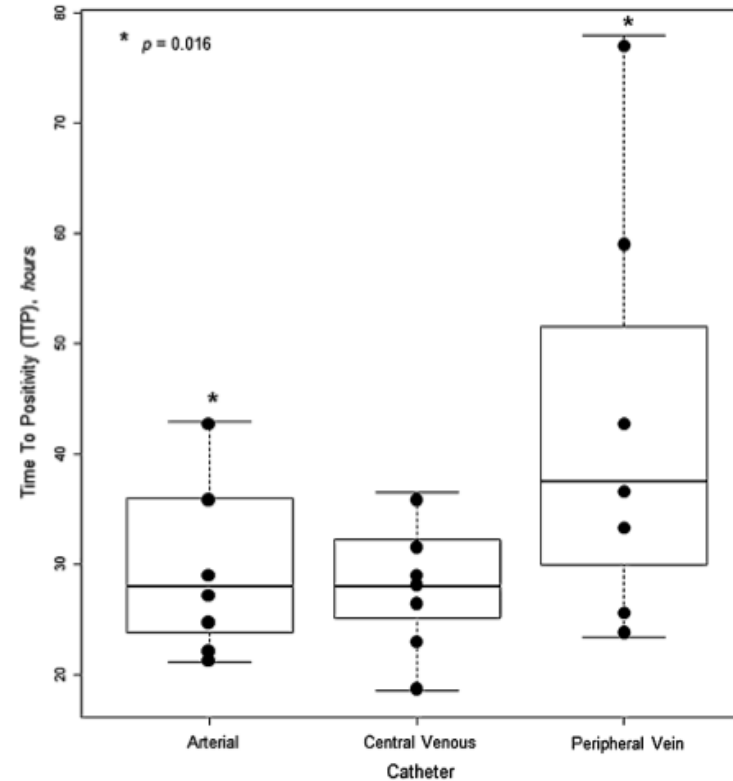
- 5 days: coagulase-negative staphylococci CRB, following catheter removal;
- 7 days: CRB caused by *Streptococcus*, *Enterococcus*, and Gram-negative bacilli, following catheter removal;

- 10 days: (+ antibiotic lock therapy): CRB without catheter removal, UNLESS *S. aureus* CRB;
- 14 days: *S. aureus* CRB, following catheter removal;
- 21 days: infected thrombosis.

NB – Treatment duration may be modified for secondary localization or infective endocarditis.

Arterial blood culture have reduced TTP with respect to venous blood cultures

- Reduced O_2 in venous blood may prolong the lag phase of candida
- Increased CO_2 may reduce the inoculum of candida in venous blood



Tascini C, Intensive Care Med 2014

Protocollo di studio

Versione n. 1.1 del 03/08/2016

Emocolture Venose versus Arteriose nella determinazione eziologica delle setticemie e delle endocarditi

Studio EVA (Emocolture Venose vs Arteriose)

Promotore e Sperimentatore

DOTT. CARLO TASCINI

DIRETTORE I.U.O.C. OSPEDALE COTUGNO

CENTRO DELLO STUDIO

Ospedale Cotugno, Azienda Ospedaliera dei Colli, Napoli

Personale coinvolto

Ospedale Cotugno, Azienda Ospedaliera dei Colli, Napoli

Dott. Carlo Tascini, UO Malattie Infettive ad Indirizzo Neurologico, Principal Investigator

Dott.ssa Novella Carannante UO Malattie ad Indirizzo Neurologico

Dott. Susanna Cuccurullo Microbiologia Cotugno- Monaldi

Dott. Mariano Bernardo Microbiologia Cotugno- Monaldi

C.P.S.I. Raffaele Bellopede Ps -Accettazione Osp Cotugno

1) Basi razionali e finalità della ricerca

La setticemia e l'endocardite sono motivo di accessi al Pronto Soccorso e ospedalizzazione frequenti. L'emocoltura rimane l'unica analisi microbiologica in grado di determinare l'eziologia di patologie infettive del torrente circolatorio, delle quali l'endocardite è la patologia più grave. Secondo le linee guida ESCMID 2015 sull'endocardite, l'identificazione microbiologica si raggiunge in circa l'85% dei casi. Il restante 15% si divide in endocarditi con emocolture negative per antibiotico-terapia fatta prima del prelievo e quelle negative per difficile isolamento del germe in causa (es. gruppo HACEK) o perché si tratta di germi intracellulari e quindi non isolabili con le comuni metodiche utilizzate (es. Coxiella e Bartonella) [1].

La presente ricerca introduce due aspetti innovativi nella diagnostica delle setticemie e delle endocarditi, sfruttando elementi noti da tempo.

La metodica che si va ad utilizzare, Isolator microTube, fu messa a punto nel 1976 da Dorn et al. [2] per migliorare la diagnosi proprio di quei casi in cui entravano in gioco germi più difficili da isolare, sfruttando il principio della lisi-centrifugazione. Questo metodo è stato ottimizzato anche per i pazienti pediatrici, data la possibilità di utilizzare piccoli volumi di sangue (0.5 – 1.5 mL). L'Isolator permette anche di ridurre al minimo i tempi diagnostici. Studi condotti sulla presente metodica in confronto con la metodica usualmente utilizzata (BACTEC) non hanno risolto la superiorità di un metodo rispetto all'altro [2, 3].

I vantaggi offerti dalla presente metodica sono principalmente quello di utilizzare una provetta in grado di lisare i leucociti e quindi di liberare in circolo anche i batteri intra-cellulari, aumentando la carica batterica totale in circolo e permettendo anche la diagnosi di quei germi altrimenti difficili da isolare; la possibilità di prelevare una piccola quantità di sangue e distribuirla direttamente su terreno agarizzato solido, che ne permette, in caso di crescita batterica o fungina, l'isolamento e quindi la possibilità di eseguire subito test di sensibilità, senza necessità di subcoltivare nuovamente il germe dal flacone delle emocolture e aspettare la crescita; l'esatta valutazione della carica batterica/mL (CFU/mL), attraverso la conta manuale delle CFU cresciute sul terreno.

Carey [2] nel 1983 ha inoltre dimostrato un anticipo di positivizzazione delle emocolture con Isolator di 4.1 ore rispetto allo standard of care.

Da sottolineare però, come questa metodica soffra di una percentuale maggiore di contaminazioni: 8.7% vs 3.1 fino a 5.9% vs 1% nello studio del 1996 di Enger et al. [2, 3].

Il secondo aspetto che si propone di verificare questo studio è la presenza di concordanza fra la carica batterica circolante nel torrente venoso e arterioso, attraverso il prelievo contemporaneo di un piccolo volume di sangue venoso ed arterioso. Gli studi che hanno comparato la carica batterica arteriosa e venosa sono molto datati e si riferiscono solo ad endocarditi sinistre da streptococco. Pertanto in tutte le altre condizioni di endocardite o setticemia senza endocardite non vi sono dati. Poiché spesso i pazienti giungono in ospedale già trattati con terapia antibiotica, il prelievo culturale da arteria potrebbe permettere, se l'ipotesi dello studio verrà verificata, un maggior numero di diagnosi microbiologiche.

Risultati Preliminari

19 Campioni analizzati :

11 negativi

8 positivi

Carica batterica dal prelievo arterioso è stata sempre maggiore mediamente del 40%



Table 2.
Suggested culture media and growth conditions.

No Medium	Incubation conditions	Discard
1 Blood Agar	Anaerobic 35-37°C	6 days
2 Chocolate Agar	5% CO ₂ , 35-37°C	4 days
1 Sab Dext Agar	Aerobic, 22-30°C	8 days

Plates should be pre-dried at least overnight at room temperature. This enhances absorption of the inoculum and reduces condensation on the plate lid.

Interpretation of Results

1 If a colony appears only within the area inoculated, it should be considered a significant positive culture regardless of genus or species. In adults, bacteraemia at a level of one colony forming unit or less per millilitre of blood is common. Therefore the recovery of a single colony on the streak with the ISOLATOR system can be significant.

2 If colonies appear on both the inoculated area and outside the inoculated area, consider the colony within the inoculated area as a positive culture and the one outside as a contaminant.

3 If a colony appears only outside the inoculated area, it may be considered a plate contaminant.

patogeno isolato	emo eva arteria (carica ufc/ml)	emo eva periferica (carica)	emocoltura tradiz
nessuno	neg	neg	neg
<i>Streptococcus mutans</i>	257	62	pos
<i>Staphylococcus epidermidis</i>	0	12	pos
nessuno	0	0	neg
nessuno	0	0	neg
nessuno	0	0	neg
<i>Staphylococcus epidermidis</i>	0	0	pos
<i>Staphylococcus aureus</i>	66	9	pos
<i>Streptococcus gallolyticus</i>	90	57	pos
<i>Staphylococcus aureus</i>	680	620	pos
<i>Klebsiella pneumoniae</i>	420	229	pos
nessuno	0	0	neg
<i>Streptococcus sanguinis</i>	51	37	pos
nessuno	0	0	neg
nessuno	0	0	neg
nessuno	0	0	neg
nessuno	0	0	neg
nessuno	0	0	neg
<i>Staphylococcus aureus</i>	8	0	pos
<i>Enterococco faecalis</i>	136	112	pos
<i>Staphylococcus aureus</i>	115	88	pos
<i>Staphylococcus aureus</i>	0	0	pos

NPT e Candida



mycoses

Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Original article

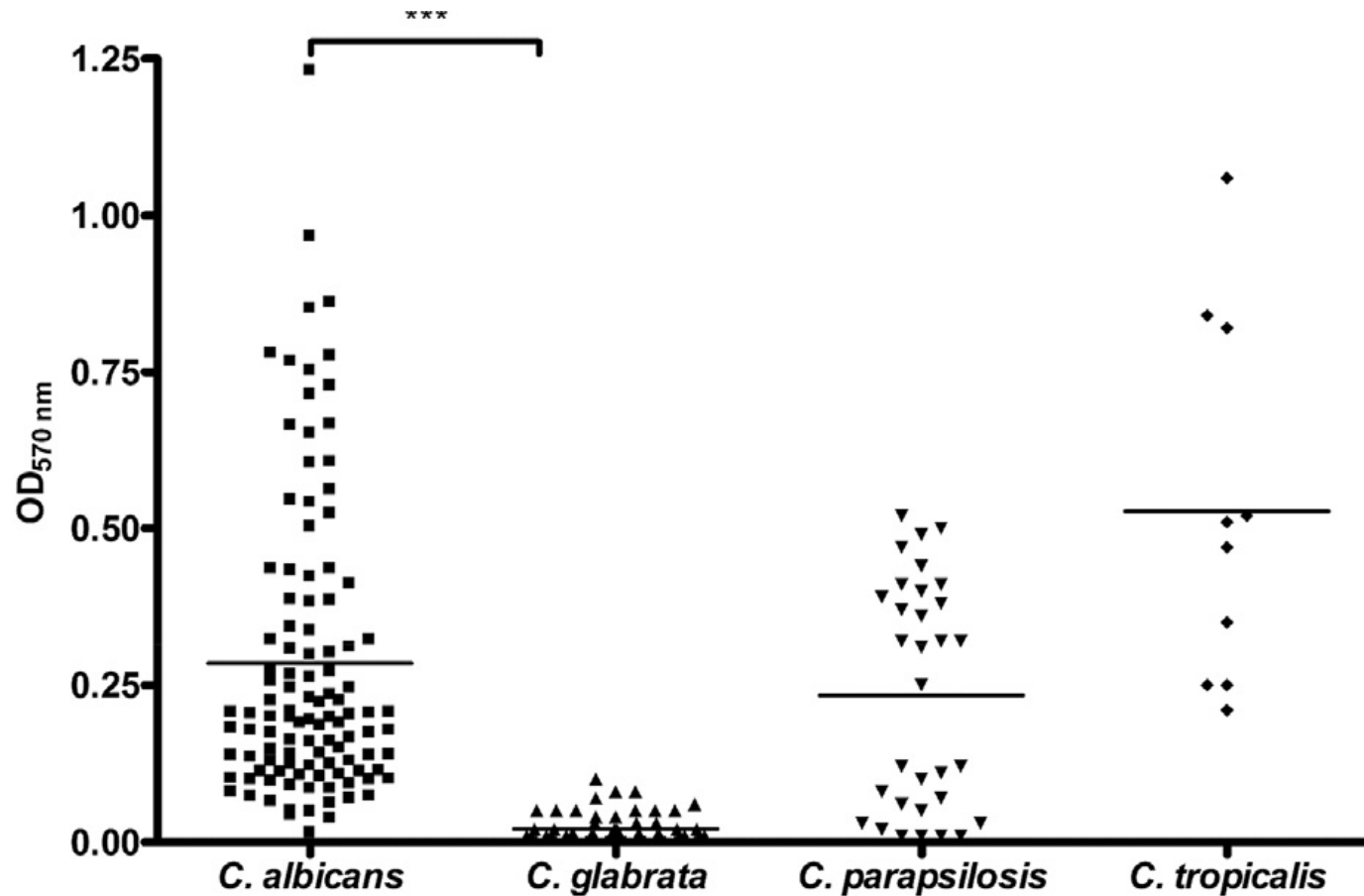
Peripheral and total parenteral nutrition as the strongest risk factors for nosocomial candidemia in elderly patients: a matched case–control study

Roberto Luzzati,¹ Silvia Cavinato,¹ Manuela Giangreco,² Gianluca Granà,¹ Sandro Centonze,³ Maria L. Deiana,⁴ Gianni Biolo⁵ and Fabio Barbone²

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Biofilm formation is a risk factor for mortality in patients with *Candida albicans* bloodstream infection—Scotland, 2012–2013

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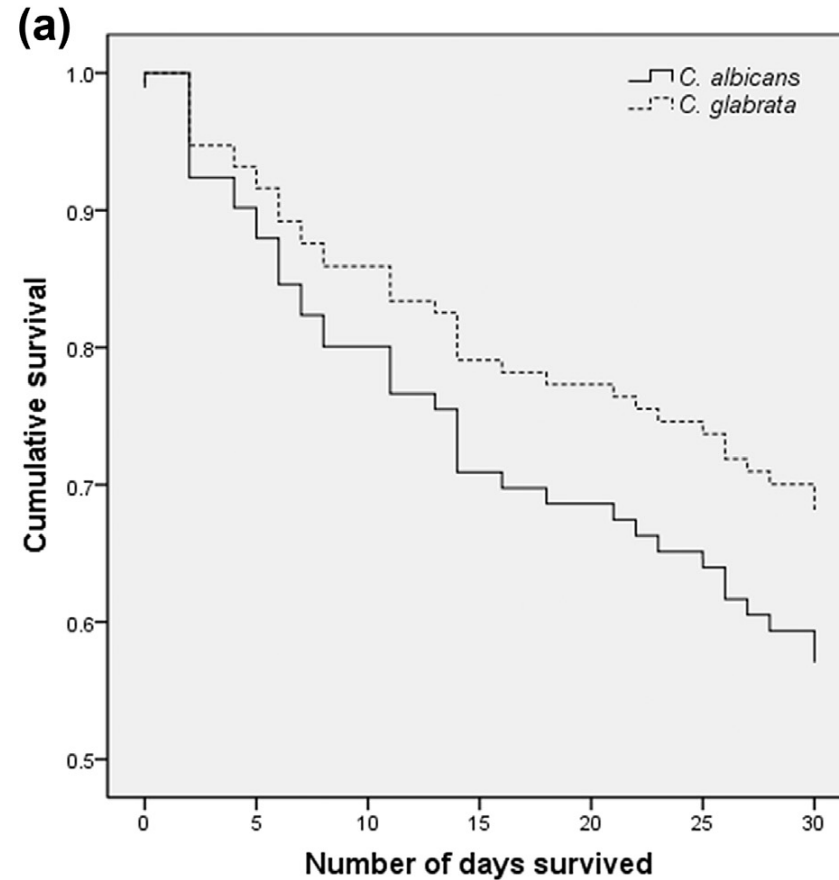


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Pazienti in
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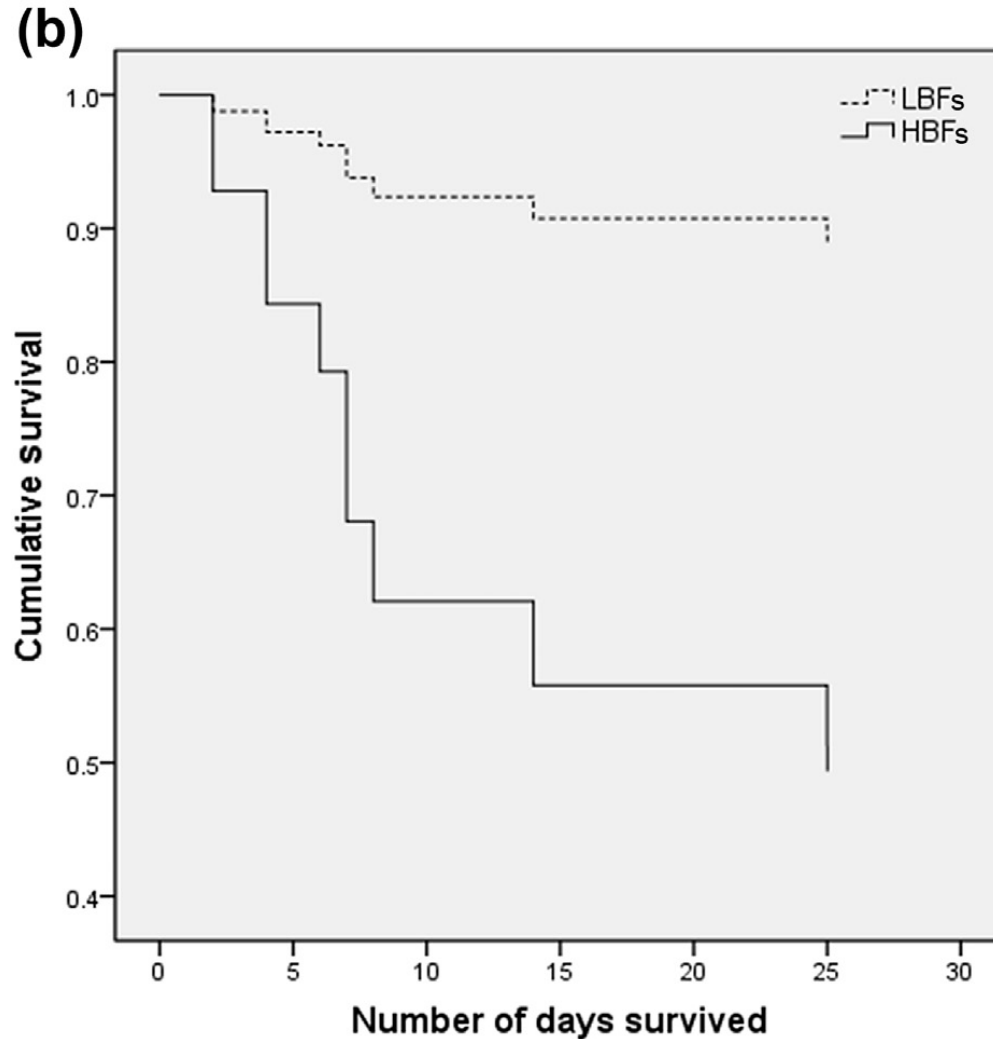


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Conclusioni

- CIED devono essere gestiti in centri specializzati
- Usare meno CVC
- Pensare ad alternative sempre
- Rivedere ogni volta l'indicazione
- Togliere appena possibile
- Biofilm?
- Terapia breve se source control