

LE INFEZIONI NEL PAZIENTE CON DEVICES: UN PROBLEMA IRRISOLTO DA CONOSCERE, APPROFONDIRE E RISOLVERE

La profilassi antibiotica peri-procedurale
e la terapia antibiotica nelle infezioni CIED:
linee guida e vita reale



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DIAGNOSIS

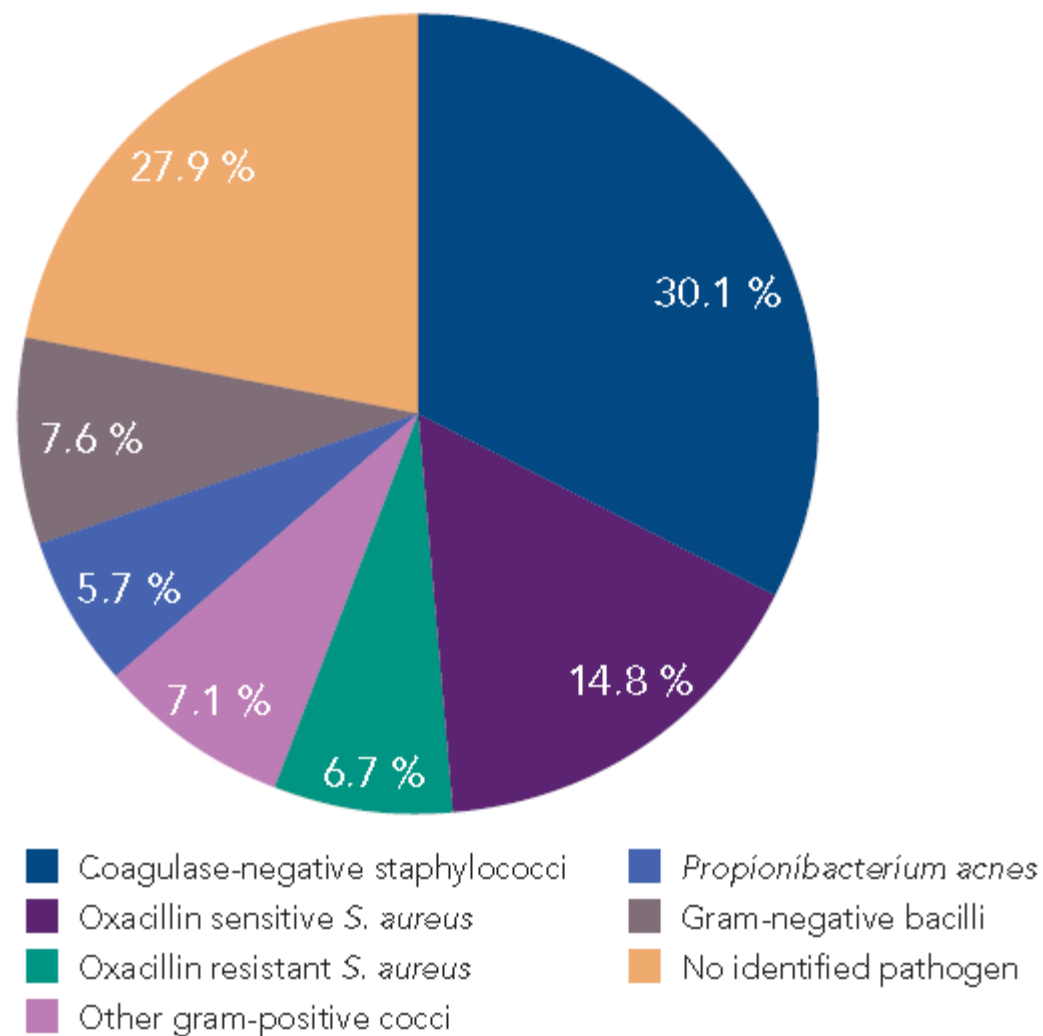
Microbial contamination of a device can occur:

- (i) during manufacture or packaging;
- (ii) prior to implantation;
- (iii) during implantation;
- (iv) secondary to surgical site infection;
- (v) via haematogenous seeding from a distant site; or
- (vi) via contamination after erosion through the skin.

† Asymptomatic colonization of ICEDs can occur with normal skin commensals and this may develop into symptomatic infection at a later stage

DIAGNOSIS

Figure 2: Pie Graph Showing Distribution of Infective Agents Identified at our Tertiary Centre in 197 Patients with Infected Cardiac Implantable Electronic Device



VARIABILE		PAZIENTI SOTTOPOSTI A IMPIANTO DI CIED	
		N°	%
Sesso	Uomini	516	65,40%
	Donne	273	34,60%
Età	Età media	75,41	
	Intervallo di età	19-99	
	≥65 anni	671	14,96%
	<65 anni	118	85,04%
Fattori di rischio	BMI (media, %normopeso)	26,00	31,05%
	Ipertensione	619	78,65%
	Diabete	185	23,54%
	Dislipidemia	257	32,66%
	Creatinina sierica		
	Fumo	241	30,62%
	TAO	154	19,77%
Tipo di dispositivo	PM	614	77,92%
	ICD	174	22,08%
Elettrocateri	Mono-camerale	181	25,82%
	Bi-camerale	427	60,91%
	Bi-ventricolari	93	13,27%

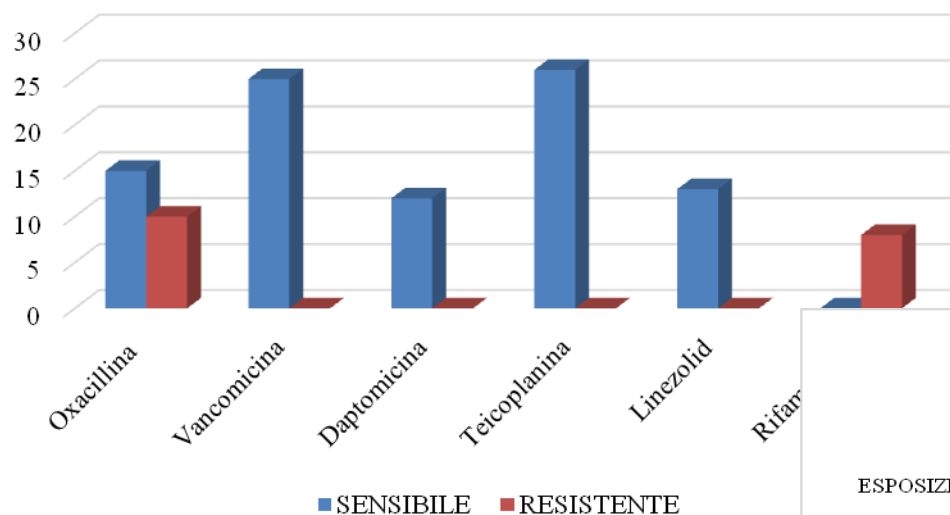


MICRORGANISMO ISOLATO	Studio attuale	Sohail et al.; 2007	Bongiorni et al.; 2012
CoNS	67,86%	42%	69%
S.aureus	25,00%	29%	13,80%
Gram positivi	3,57%	4%	7,50%
Gram negativi	3,57%	9%	6,10%
Altri	0%	16%	3,40%

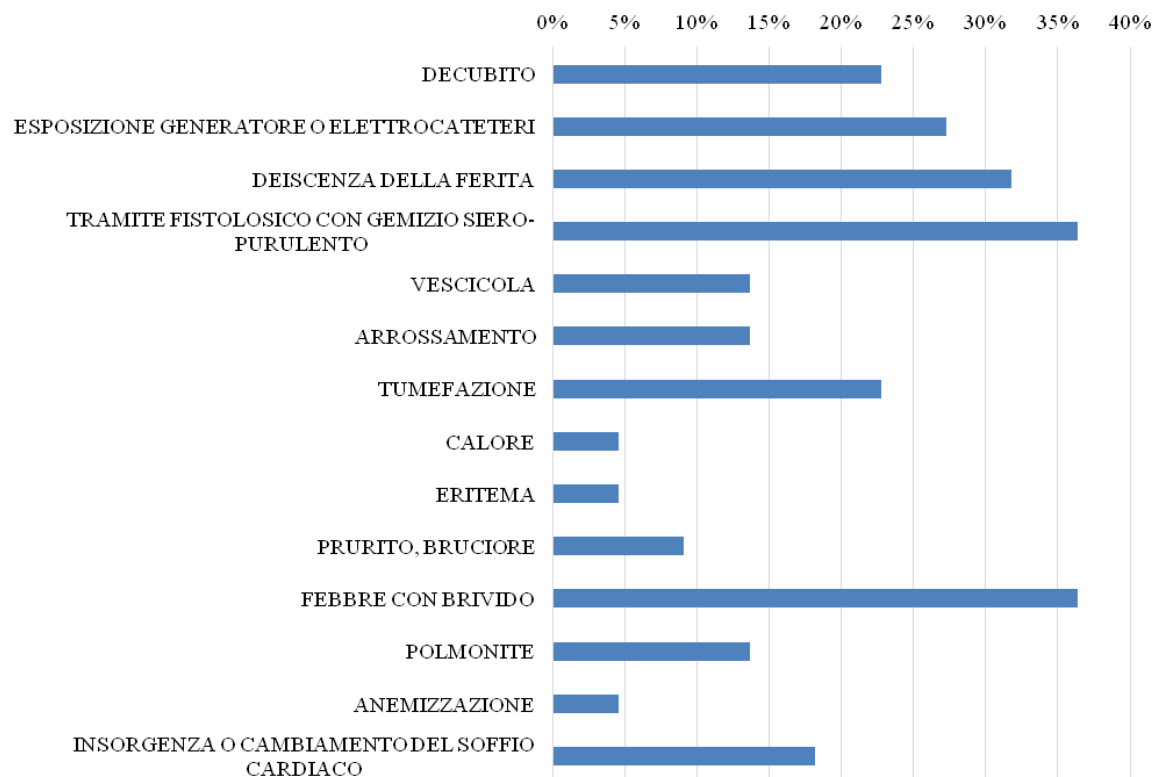
MICRORGANISMO ISOLATO	TAMPONE	EMOCOLTURE	TOT. n. (%)
S.aureus	5	2	7 (25,00%)
S.schleiferi	1	0	1 (3,57%)
S.epidermidis	5	3	8 (28,57%)
S.haemoliticus	1	1	2 (7,14%)
S.hominis	2	2	4 (14,29%)
S.lugdunensis	1	0	1 (3,57%)
S.warnerii	0	1	1 (3,57%)
S.capitis	0	2	2 (7,14%)
E.fecalis	1	0	1 (3,57%)
E.cloacae	1	0	1 (3,57%)



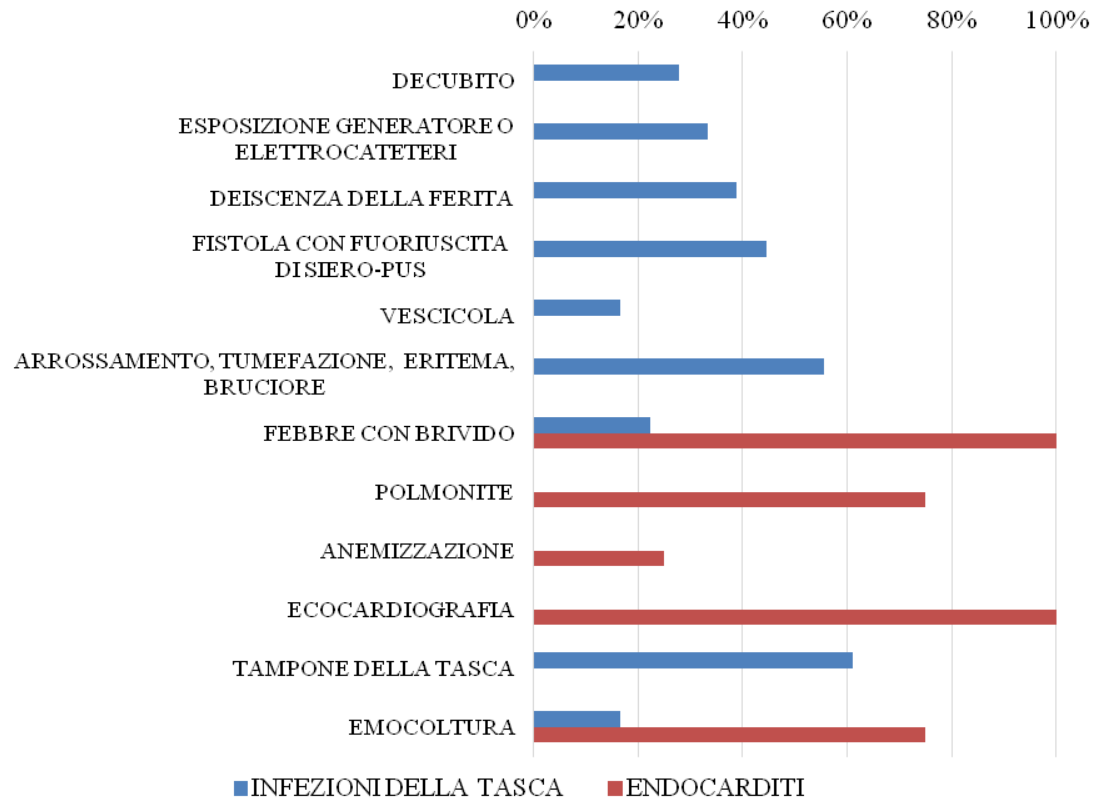
SENSIBILITA' E RESISTENZE DEI MICRORGANISMI ISOLATI



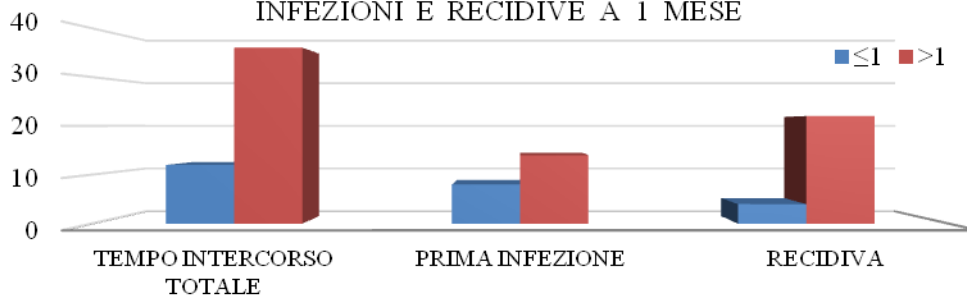
SEGNI E SINTOMI DELL'INFEZIONE DI CIED



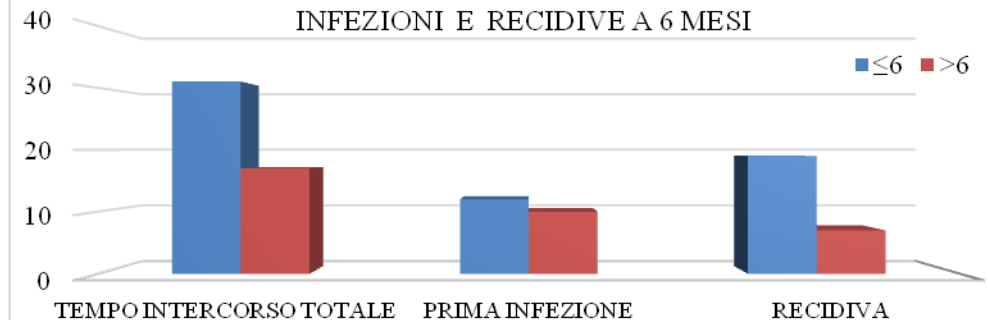
DIAGNOSI DELLE INFEZIONI DI CIED



INFEZIONI E RECIDIVE A 1 MESE



INFEZIONI E RECIDIVE A 6 MESI



DIAGNOSIS

J Orthop Sci (2006) 11:46–50

Antimicrobial susceptibility of *Staphylococcus aureus* and *Staphylococcus epidermidis* biofilms isolated from infected total hip arthroplasty cases

SEISUKE NISHIMURA, TOSHIYUKI TSURUMOTO, AKIHIKO YONEKURA, KOICHI ADACHI, and HIROYUKI SHINDO

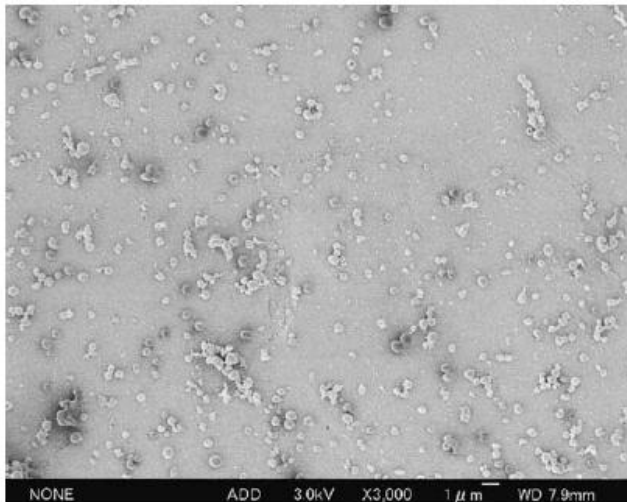


Fig. 1. Immediately after biofilm formation of ACTT 25923. Most of the bacteria were individually present, rarely bound to each other. $\times 3000$

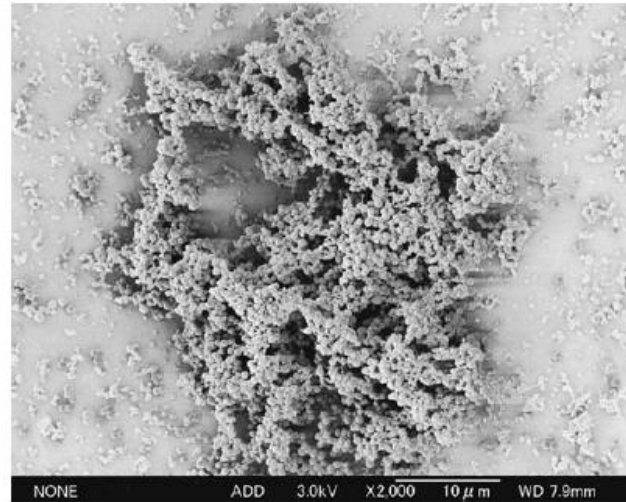


Fig. 2. At 24 h after biofilm formation, bacteria were bound to each other and formed microcolonies and small biofilms. $\times 2000$

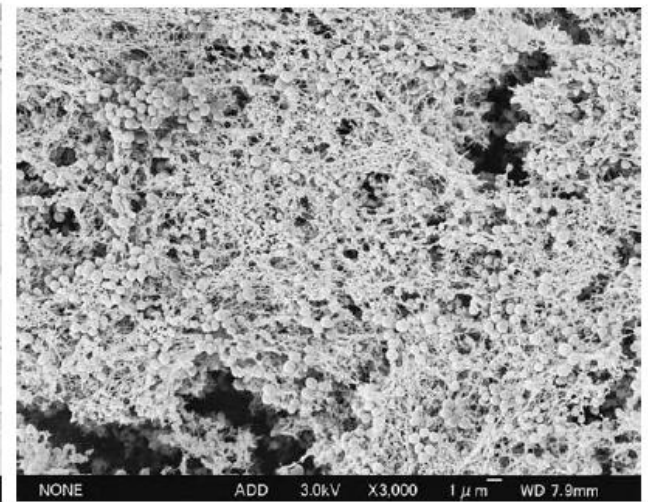


Fig. 3. Biofilms after 5 days. Whole surfaces of the materials were covered with proliferating bacteria, and abundant biofilm formation was noted in some protruding regions. $\times 3000$



Biofilm on Artificial Pacemaker: Fiction or Reality?

Santos APA *et al.* Arq Bras Cardiol 2011;97(5):e113-e120

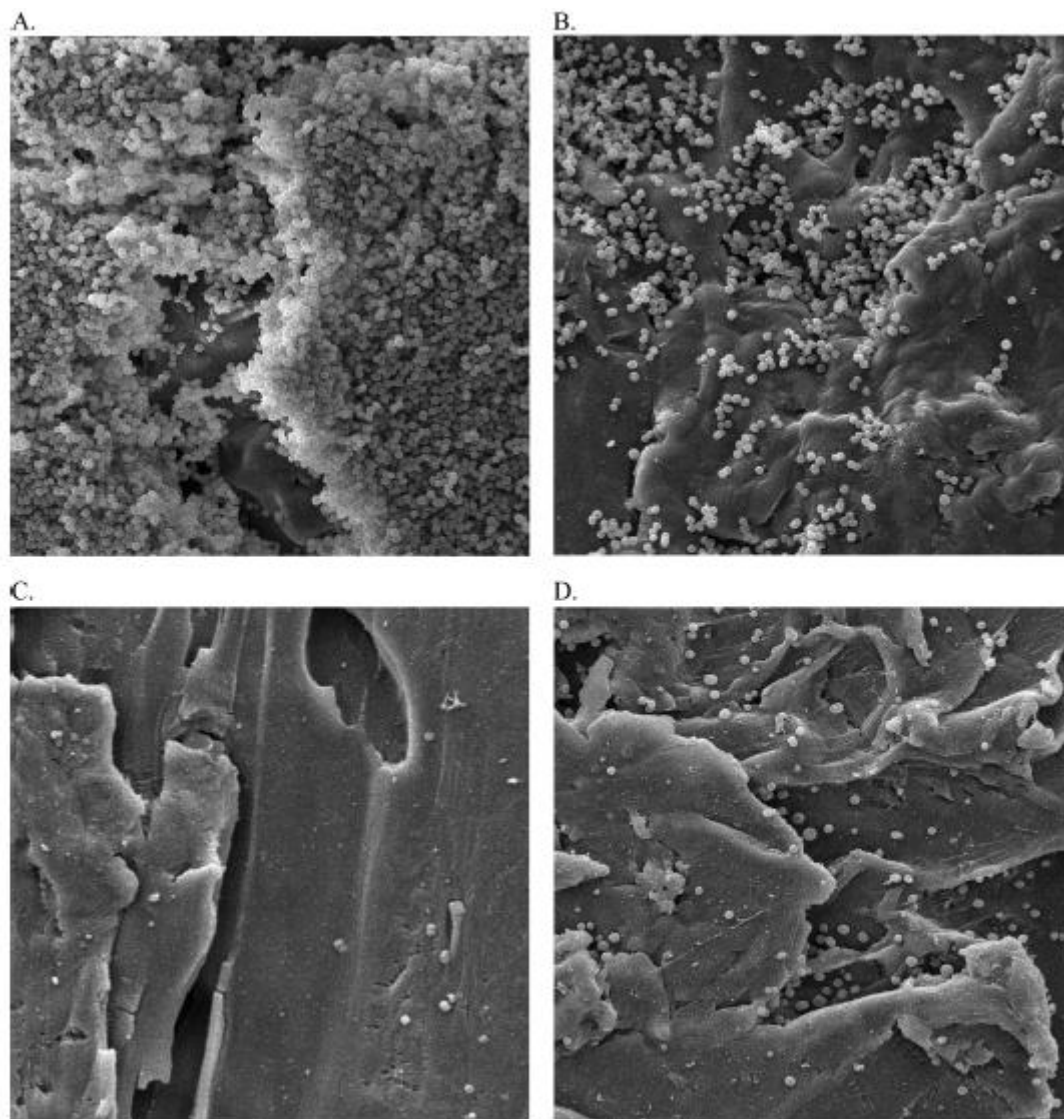
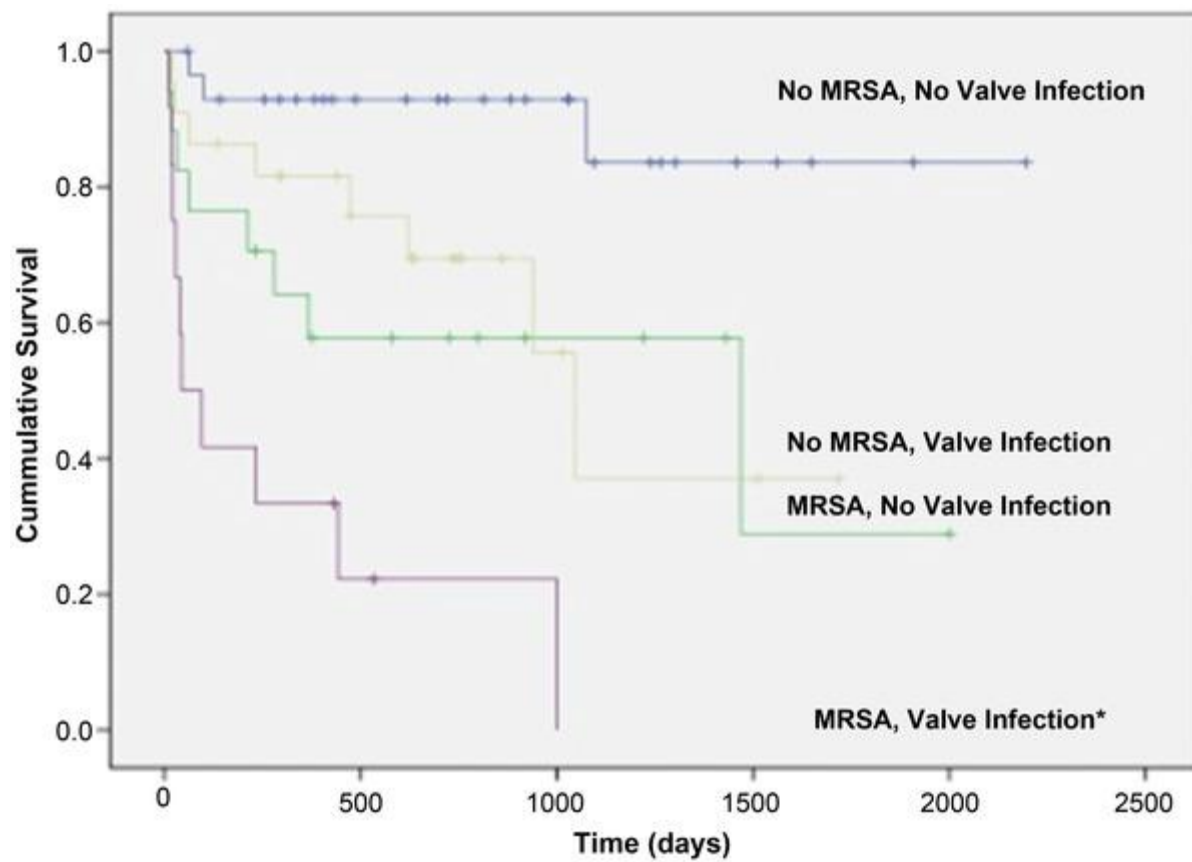


FIG. 2. SEM images of coupon surfaces to assess the presence and structure of the matrix of a SH1000 biofilm. Images were collected at 2,000X magnification. (A) Before any drug exposure; (B) after 72 h of daptomycin exposure; (C) after 72 h of daptomycin plus clarithromycin exposure; (D) after 72 h of moxifloxacin plus clarithromycin exposure.





Guidelines for the diagnosis, prevention and management of implantable cardiac electronic device infection. Report of a joint Working Party project on behalf of the British Society for Antimicrobial Chemotherapy (BSAC, host organization), British Heart Rhythm Society (BHRS), British Cardiovascular Society (BCS), British Heart Valve Society (BHVS) and British Society for Echocardiography (BSE)

Sandoe JAT, *et al.* J Antimicrob Chemother, 2014: 1-35

Pathogen (number of studies reporting this pathogen)	Range in studies using patients as the denominator	Range in studies using isolates as the denominator
CoNS (17)	10% ^a –68%	42%–77%
<i>Staphylococcus aureus</i> (16)	24%–59%	10%–30%
Gram-negative bacilli (11)	1%–17%	6%–11%
<i>Enterococcus</i> spp. (6)	5%–6% ^b	0.4%–10% ^b
<i>Streptococcus</i> spp. (5)	4%–6% ^b	3%–10% ^b
<i>Propionibacterium</i> spp. (3)	—	0.8%–8%
Fungi (5)	0.5%–2%	0.4%–1.4%

^aThis study only used blood cultures and had high culture negativity (49%).

^bThis study reported *Streptococcus* and *Enterococcus* spp. together.

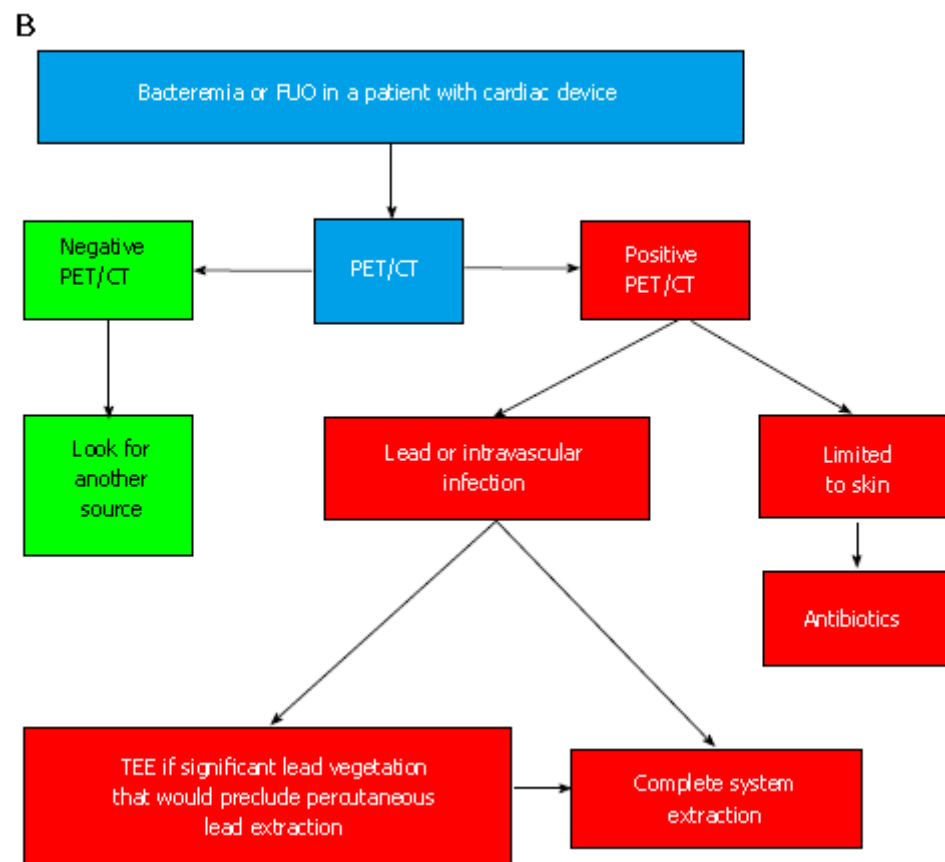
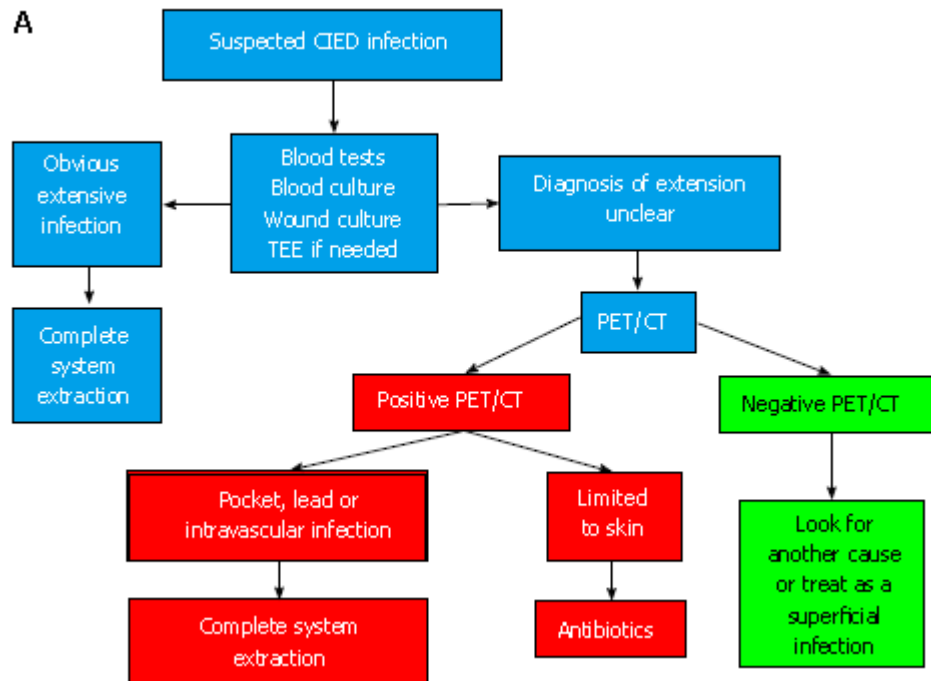
DIAGNOSIS

Role of radionuclide imaging for diagnosis of device and prosthetic valve infections

Sarrazin J-F *et al. World J Cardiol* 2016; 8(9): 534-546

Advantages	Limitations
¹⁸F-FDG PET/CT Excellent spatial resolution Short acquisition time High sensitivity for the detection of hypermetabolic activity Detection of peripheral events Detection of other sources of fever or bacteremia in patients with CIED Detection of CIED infection and PVE in cases of a negative TEE	Moderate radiation exposure (8-30 mSv depending on the study performed) Not available in several centers Physiological uptake of ¹⁸ F-FDG in the myocardium might prevent adequate detection of cardiac infection Recent surgery may demonstrate residual inflammatory changes without evidence of infection Possible uptakes can be found in active thrombi, cardiac tumours or metastasis, and foreign body reactions Possible false-negative test in patients with small vegetations or prolonged antibiotic therapy Less useful for infectious brain embolisms because of high glucose metabolism in the brain
WBC SPECT/CT High specificity for the presence of active infection	Time-consuming It involves blood products handling Cases of false-negative study seen with Candida and Enterococcus infection





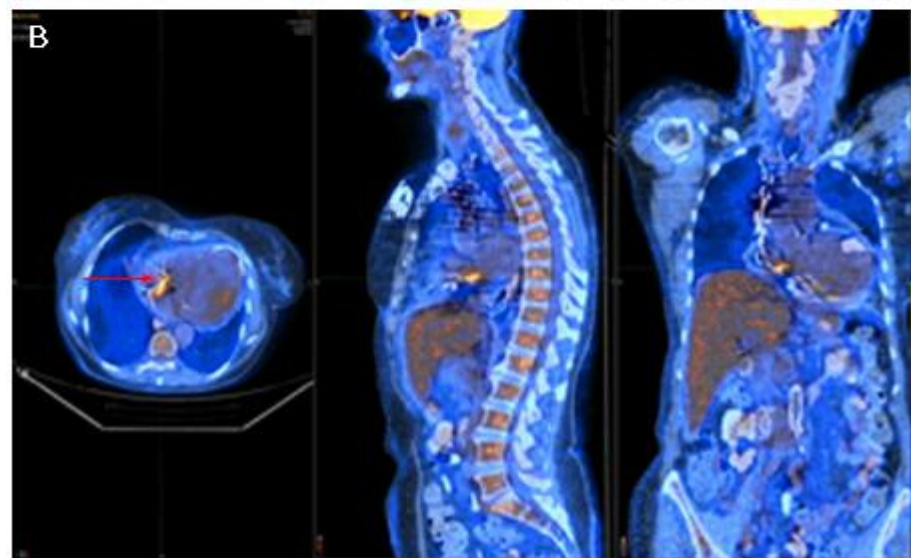
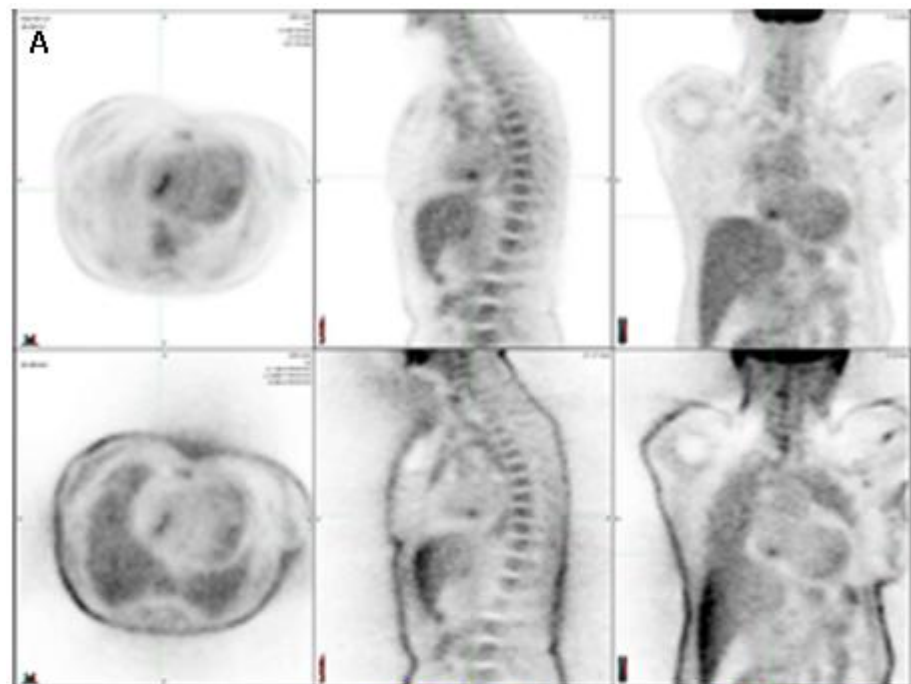
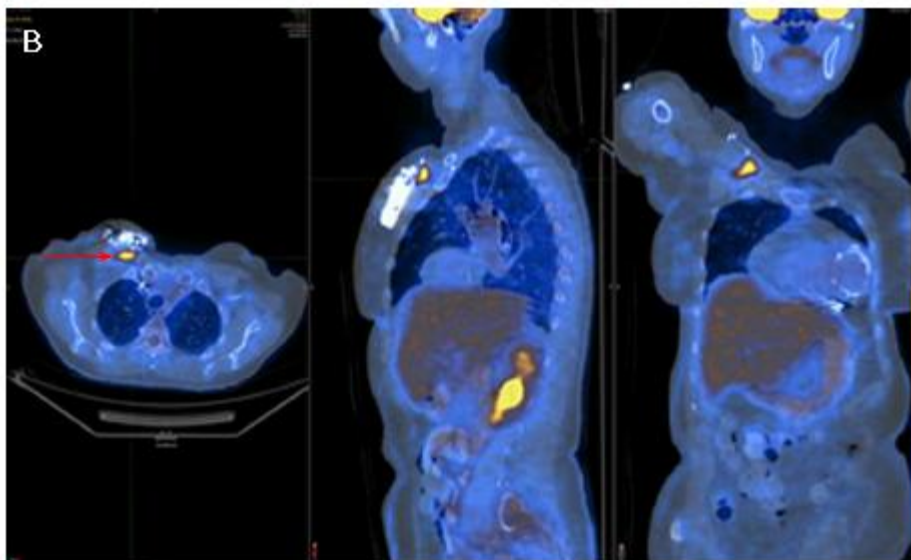
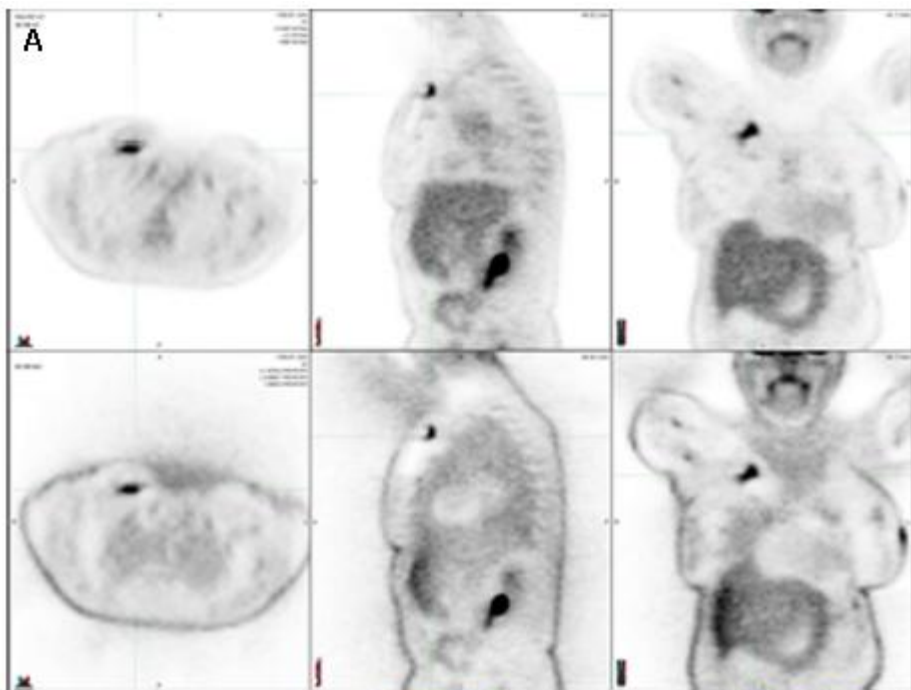


Table 2 Sensibility and specificity of ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography and white blood cell single-photon emission computed tomography/computed tomography for both prosthetic valve endocarditis and cardiac device infection

	Test	Sensi- bility (%)	Speci- ficity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
Prosthetic valve endocarditis						
Saby <i>et al</i> ^[31]	PET/CT	73	80	89	68	78
Rouzet <i>et al</i> ^[32]	PET/CT	93	71	68	100	82
	WBC	64	100	100	100	82
Erba <i>et al</i> ^[34]	WBC	90	100	100	100	95
Cardiovascular implantable electronic device infection						
Bensimhon <i>et al</i> ^[24]	PET/CT	80	100	100	100	90
	Pocket	100	100	100	100	100
	Lead	60	100	100	100	80
Ploux <i>et al</i> ^[25]	PET/CT	100	93	N/A	N/A	96.7
Sarrazin <i>et al</i> ^[26]	PET/CT	88.6	85.7	N/A	N/A	87.2
Cautela <i>et al</i> ^[27]	PET/CT					
	Pocket	86.7	100	N/A	N/A	93.3
	Lead	30.8	62.5	N/A	N/A	46.7
Ahmed <i>et al</i> ^[28]	PET/CT					
	Pocket	97	98	N/A	N/A	97.5
Erba <i>et al</i> ^[29]	WBC	93.7	100	100	100	96.8

Table 3 Indications for the use of cardiac nuclear imaging in the context of cardiovascular implantable electronic device infection and prosthetic valve endocarditis

Accepted indication

Possible or rejected IE, but high suspicion of infection in patients with prosthetic valve

Potential indications

Unclear diagnosis of CIED infection

Evaluation of the extent of infection

Bacteremia or fever of unknown origin in patients with CIED

Cases with high clinical suspicion of IE but negative TEE and/or negative blood cultures

Search for embolic events

Monitoring the success of antibiotic therapy





Review

^{18}F FDG-positron emission tomography (PET) has a role to play in the diagnosis and therapy of infective endocarditis and cardiac device infection

B. Cherie Millar ^a, Bernard D. Prendergast ^b, Abass Alavi ^c, John E. Moore ^{a,*}

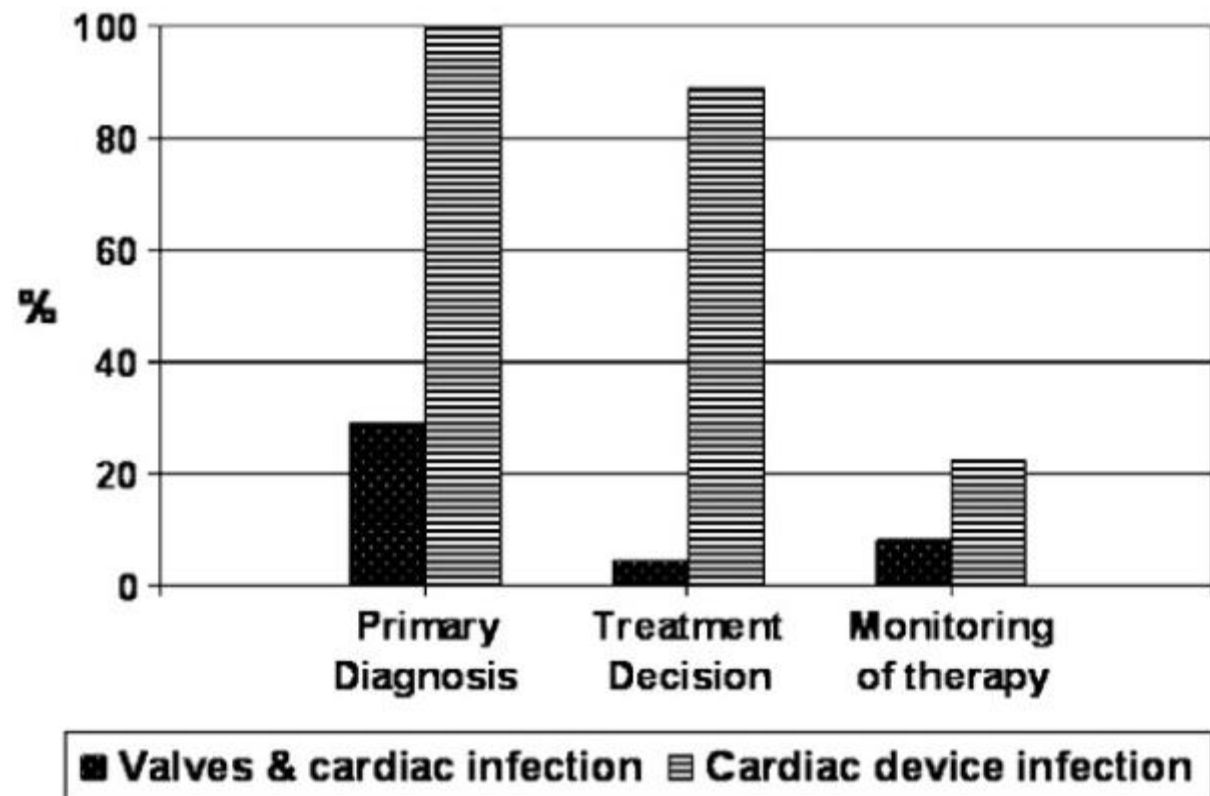


Table 6Advantages and limitations of ^{18}F FDG-PET/CT in the diagnosis of IE and CIED related infections.

Advantages of PET/CT	Limitations of PET/CT
Non-invasive ^{18}F FDG has a short half life (110 min) and is quickly removed. Images can be generated in a short turnaround time (approximately 2 h) Excellent spatial and contrast resolution allowing the precise detection and delineation of infected sites Allows the investigation of other sources of infection within the body should cardiac related infection not be evident in the presence of fever/bacteremia of unknown origin Has proven useful in detecting cardiac related infections particularly prosthetic valve and CIED infection in the absence of echocardiographical evidence Has proven useful in indicating the need for surgical removal or sole antimicrobial therapy in patients with suspected CIED infection	Patients exposed to radioactive tracer and in the case of PET/CT hybrid investigations most of the radiation is caused by the CT. Cost Lack of availability particularly within Europe. PET/CT scanners for cardiological purposes are generally limited to large centers. Recent surgical procedures such as aortic root replacement may cause artifacts due to post surgery inflammatory response and not infection. Reduced uptake of ^{18}F FDG tracer may be attributed to small vegetations below the detection threshold of PET (<4 mm), as well as any subsequent reduction in the inflammatory process i.e., resolution of the infection or the immunomodulatory effect of certain antibiotics e.g., azithromycin To date there has not been a large scale study on the clinical value of PET/CT in relation to the diagnosis and clinical management of patients with cardiac infection. Data from such a study would be required before there could be a general acceptance of the routine use of this technology in relation to cardiac infection. Implantable cardioverter defibrillator leads frequently result in artifacts of sufficient magnitude to impact on clinical interpretation. Software-based corrections in CT-based attenuation correction algorithms are necessary for accurate cardiac imaging.



Early diagnosis of cardiac implantable electronic device generator pocket infection using ^{18}F -FDG-PET/CT

^{18}F -FDG-PET/CT Fozia ZA *et al.* European Heart Journal - Cardiovascular Imaging (2015) 16, 521-530

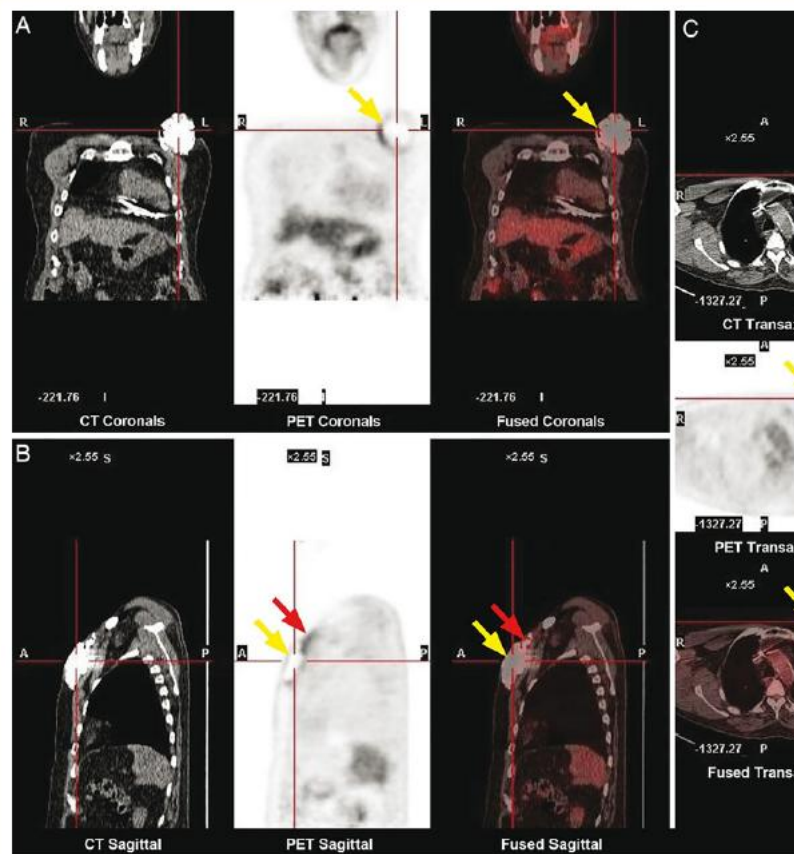


Figure 2 Example of a positive ^{18}F -FDG PET/CT scan in a Group 1 individual with pain at the generator is seen in the region of the left pre-pectoral pocket on the coronal views (yellow arrows). (B) In the sagittal seen on the muscular aspect of the pre-pectoral generator (yellow arrows) and along the proximal portion of the ^{18}F -FDG uptake visualized on the muscular aspect of the generator pocket (yellow arrows).

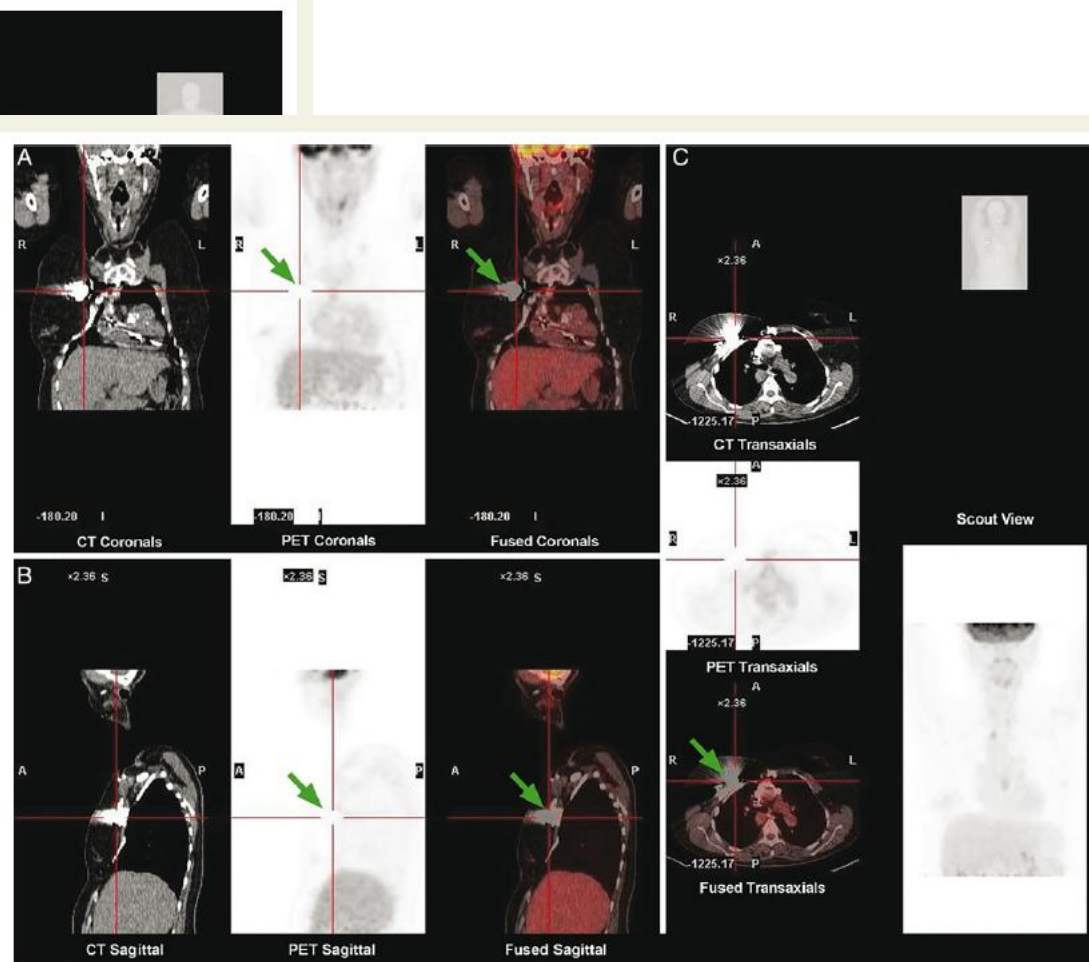


Figure 3 Example of a negative ^{18}F -FDG PET/CT scan in a Group 1 patient who presented with pain at the generator pocket site. This individual, with a history of grown up congenital heart disease and 20-year-old right-sided pacing leads (episode 16), presented with pain in the region of their right pre-pectoral pocket 4 years after generator box change. There is no evidence of increased ^{18}F -FDG uptake in the region of the right-sided generator pocket (green arrows) or along the proximal portion of the leads (A, B and C).

Radiolabeled WBC Scintigraphy in the diagnostic workup of patients with suspected device-related infections

Erba PA *et al.* JACC : Cardiovascular Imaging, 2013; 6: 1075-86

Table 3. Results and Diagnostic Performance of ^{99m}Tc -HMPAO-WBC Planar, SPECT, and SPECT/CT Acquisitions in Patients With CIED-Associated Infection (n = 32)

	Planar	SPECT	SPECT/CT
Result, n/N			
Positive for CIED	15/32	21/32	30/32
Doubtful for CIED infection	11/32	9/32	—
Negative for CIED infection	6/32	2/32	2/32
Correct extent for device infection	12/32	21/32	30/32
Correct exclusion device involvement	36/43*	42/43	43/43
Correct detection of embolism	12/18†	13/18†	15/18†
Correct detection of IE	3/6	4/6	6/6
Positive for other infections	9/15	13/15	15/15
Correct extent for other sites of infection	7/15	11/15	15/15
Diagnostic performance, 95% CI‡			
Sensitivity	53.1 (40.2–65.6)	71.9 (58.9–82.1)	93.7 (83.9–98)
Specificity	83.9 (72–91.5)	96.8 (87.9–99.4)	100 (92.8–100)
Accuracy	68.3 (55.2–79.1)	84.1 (72.3–91.7)	96.8 (88–99.4)
Positive predictive value	77.3 (64.7–86.5)	95.8 (86.6–99)	100 (92.8–100)
Negative predictive value	63.4 (50.3–74.9)	76.9 (64.3–86.2)	93.9 (84.1–98.1)

*Including 5 false positive cases due to sternal osteomyelitis and mediastinitis. †Including 3 false negative cases due to ophthalmitis and cerebral infection. ‡Planar versus SPECT: chi-square: 0.4, p = 0.5; planar versus SPECT/CT: chi-square: 3.5, p = 0.06; and SPECT versus SPECT/CT: chi-square = 4.5, p = 0.03 (McNemar test). ^{99m}Tc -HMPAO-WBC = Technitium-99m-hexamethyl propylene amine oxime-labeled autologous white blood cell; CI = confidence interval; CT = computed tomography; IE = infectious endocarditis; SPECT = single-photon emission CT.

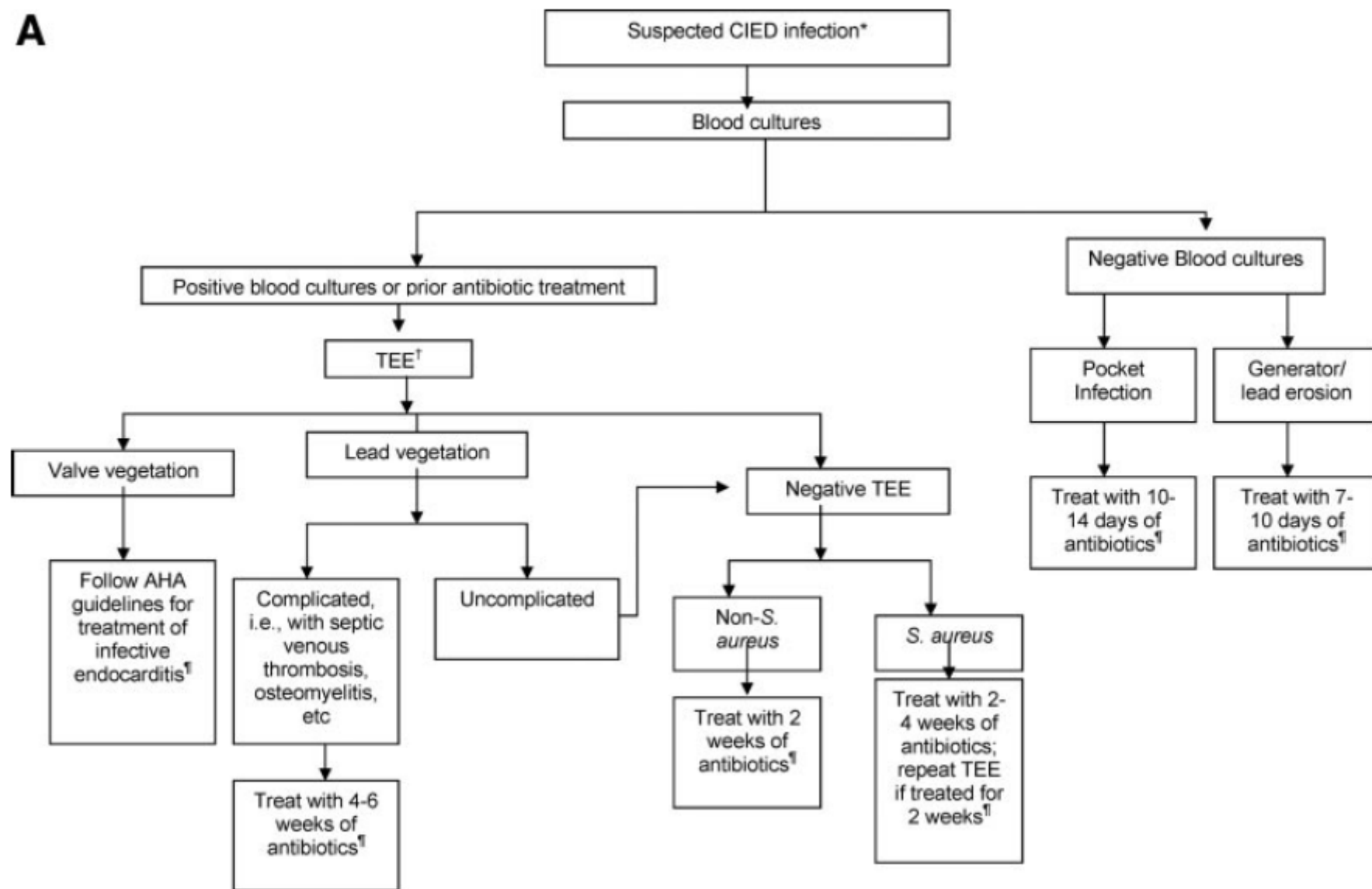
Radiolabeled WBC Scintigraphy in the diagnostic workup of patients with suspected device-related infections

Erba PA *et al.* JACC : Cardiovascular Imaging, 2013; 6: 1075-86

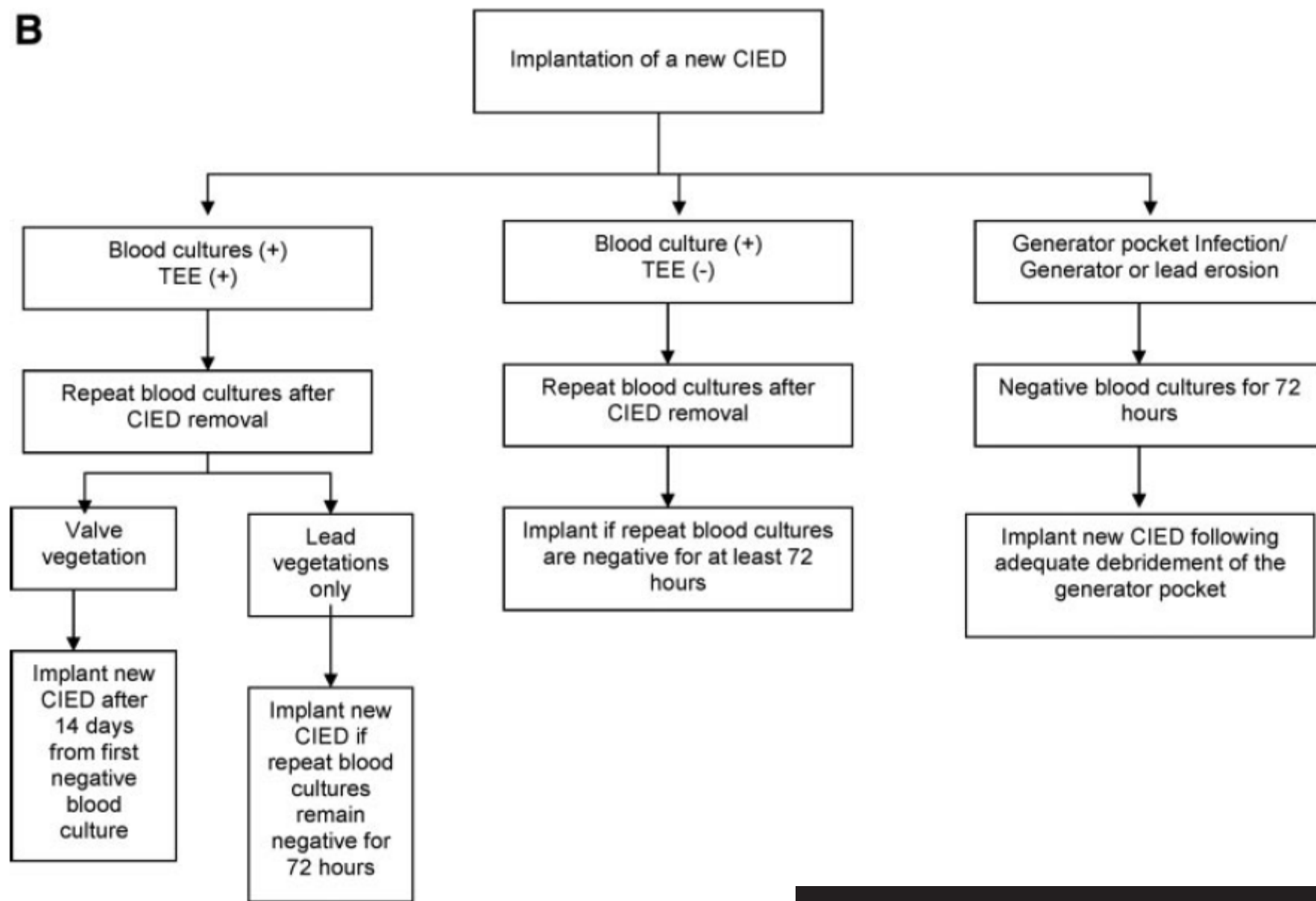
Table 4. Results of ^{99m}Tc -HMPAO-WBC Scintigraphy, Echocardiography, and Duke Criteria According to the Final Diagnosis of CIED Infection With All Examinations Performed at Baseline*

	^{99m}Tc -HMPAO-WBC	Echocardiography	Duke Criteria		
			Definite	Possible	Rejected
CIED infection (n = 32)			10/32	16/32	6/32
Positive	30/32	20/32			
Negative	2/32	12/32			
No CIED infection (n = 31)			0/31	8/31	23/31
Positive	0/31	4/31			
Negative	31/31	27/31			
Diagnostic performance, 95% CI					
Sensitivity	93.7 (83.9–98)	62.5 (49.4–74.1)	31.3† (20.5–44.3)	81.3 (69–89.6)	–
Specificity	100 (92.8–100)	87.1 (75.7–93.8)	100† (92.8–100)	74.2‡ (61.4–84)	–
Accuracy	96.8 (88–99.4)	74.6 (61.8–84.4)	65.1 (51.9–76.4)	52.4‡ (65.2–86.9)	–
Positive predictive value	100 (92.8–100)	83.3 (71.4–91.1)	100† (92.8–100)	76.5‡ (63.8–85.9)	–
Negative predictive value	93.9 (84.1–98.1)	69.2 (56.2–79.9)	58.5† (45.4–70.5)	79.3‡ (66.9–88.1)	–

* ^{99m}Tc -HMPAO-WBC versus echocardiography: chi-square: 2.6, $p = 0.1$; ^{99m}Tc -HMPAO-WBC versus Duke Criteria considering as positive for IE only the "definite" category: chi-square: 20, $p < 0.001$; ^{99m}Tc -HMPAO-WBC versus Duke Criteria considering as positive for IE both the *definite* and *possible* categories: chi-square: – 1.3, $p = 0.25$ (McNemar test). †Considering as positive for IE the only *definite* category. ‡Considering as positive for IE both the *definite* and *possible* categories. Abbreviations as in Table 3.

A

B



**Update on Cardiovascular Implantable Electronic Device
Infections and Their Management**

A Scientific Statement From the American Heart Association

Endorsed by the Heart Rhythm Society

Classe I

Almeno 2 emocolture prima dell'inizio della terapia antibiotica (C)

Alla rimozione del CIED microscopico diretto e colturale del tessuto della tasca e della punta elettrocatetere (C)

Sospetta infezione CIED (emocolture positive o negative dopo recente terapia antibiotica): TEE (C)

Tutti gli adulti con sospetta infezione di CIED dovrebbero essere sottoposti a TEE (B)

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Classe IIa

I pazienti dovrebbero essere valutati dal cardiologo o infettivologo se hanno febbre o sepsi (C)

Classe III

L'aspirazione percutanea della tasca del generatore non dovrebbe essere effettuata (C)

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Classe I

Ogni paziente dovrebbe essere valutato accuratamente per determinare se è necessario ancora l'impianto di un nuovo CIED (C)

La sostituzione del CIED non deve essere ipsilaterale al sito d'estrazione. Preferibile l'impianto controlaterale, in v. iliaca o epicardico (C)

Classe IIa

Emocolture positive prima dell'estrazione del CIED: il nuovo impianto può essere eseguito quando le emocolture risultano negative per almeno 72 ore dopo l'espianto del CIED infetto (C)

L'impianto transvenoso degli elettrocateri deve essere ritardato di almeno 14 giorni dopo l'estrazione del CIED, se vi è infezione valvolare (C)

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**Terapia antibiotica
infezione CIED**

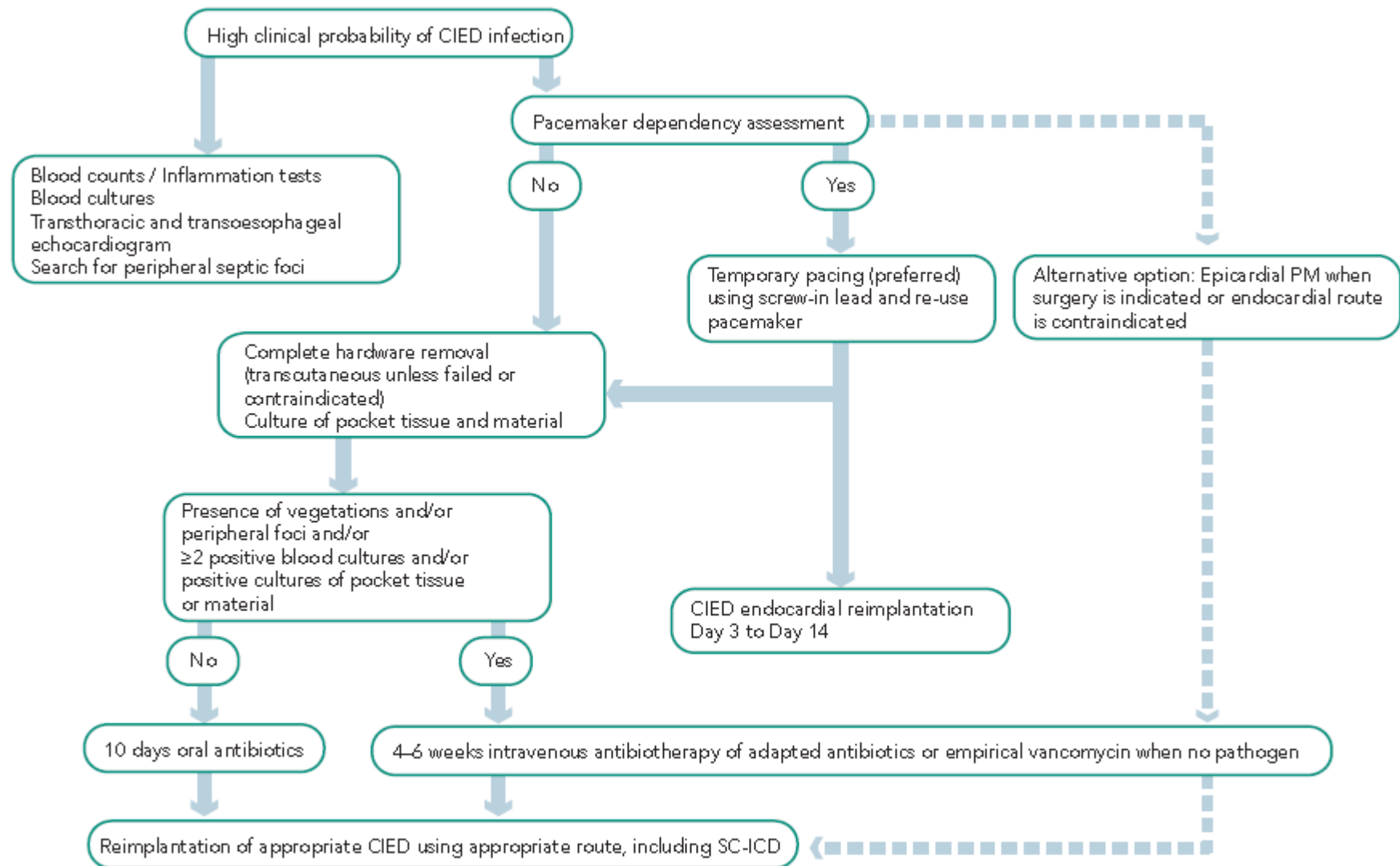
Classe I

La terapia antibiotica dovrebbe essere scelta sul pattern di sensibilità ottenuta (B)

La terapia antibiotica dovrebbe essere effettuata per almeno 10-14 giorni dopo la rimozione del CIED se infezione della tasca (C)

La terapia antibiotica dovrebbe essere effettuata per almeno 14 giorni dopo la rimozione del CIED se vi è batteriemia (C)

La terapia antibiotica dovrebbe essere effettuata da 4 a 6 settimane per infezioni complicate (C)



CIED = cardiac implantable electronic device; PM = pacemaker; SC-ICD = subcutaneous implantable cardioverter defibrillator



Risk score by Shariff *et al.*

1500 pz

1 point each:

- Diabetes Mellitus
- Congestive heart failure
- Renal impairment
- Oral anticoagulation use
- Corticosteroid use *
- Generator change/upgrade
- Prior CIED infection *
- More than 2 leads
- Epicardial lead*
- Temporary pacer placement*

Rischio a 6 mesi:

Score < 3: 1%

Score $\geq$ 3: 2,4%

J Cardiovasc Electrophysiol, 2015; 26: 783-789
Dato non presente nel nostro database



Gli score nei nostri pazienti

Osservazione retrospettiva nei 789 pazienti impiantati tra il 2010 e il 2013

Mittal <i>et al</i> score	Patients	%
Low risk (0-7)	420	58
Moderate risk (8-14)	299	42
High risk (15-25)	0	0

Non calcolabile per 70 pz per mancanza di una o più variabili

Shariff <i>et al</i> score	Patients	%
< 3	616	86
≥ 3	102	14

Non calcolabile per 71 pz per mancanza di una o più variabili



Risk factors - Systematic review & meta-analysis

Polyzos K et al, Europace 2015

Host related

- Diabetes
- CKD
- COPD
- Corticosteroid use
- Malignancy
- Heart failure
- Anticoagulant drug use

Procedure related

- Lack of ATB prophylaxis
- Replacement
- Revision
- Post-op complications (haematoma, lead dislodgement)
- Temporary pacing
- Procedure duration

Device

characterstics

- Abdominal pocket
- Dual-chamber
- ≥ 2 leads



Risk factors - Systematic review & meta-analysis

Polyzos K et al, Europace 2015

Host related

- Diabetes
- **CKD**
- COPD
- **Corticosteroid use**
- Malignancy
- Heart failure
- Anticoagulant drug use

Procedure related

- **Lack of ATB prophylaxis**
- Replacement
- Revision
- Post-op complications (**haematoma, lead dislodgement**)
- Temporary pacing
- **Procedure duration**

Device

characterstics

- **Abdominal pocket**
- Dual-chamber
- ≥ 2 leads

Large vegetation in a 60-year-old man with *Enterococcus faecalis* cardiac implantable electronic device infection

Sandrine Loron,¹ Arnaud Dulac,^{2,3} Olivier Jegaden,^{2,4} Tristan Ferry^{1,2,5}

BMJ Case Rep 2014. doi:10.1136/bcr-2014-206907



J Heart Valve Dis. 2014 Mar;23(2):219-21.

Ceftaroline for the treatment of prosthetic valve endocarditis due to methicillin-resistant *Staphylococcus aureus*.

Pagani L, Bonnin P, Janssen C, Desiovaux, Vitrat V, and Bru JP.

Abstract

The case is described of a frail patient who developed prosthetic valve endocarditis due to methicillin-resistant *Staphylococcus aureus* (MRSA). Conventional antimicrobial treatments either failed or were contraindicated, and the patient was judged unsuitable for a further valve replacement. A salvage therapy with high doses of a new cephalosporin, ceftaroline, given three times daily was undertaken; subsequently, the patient had not relapsed at two months after completing a six-week course of ceftaroline.

Ceftaroline deserves major attention as an alternative choice in difficult-to-treat MRSA endocarditis.



Lack of upward creep of glycopeptide MICs for methicillin-resistant *Staphylococcus aureus* (MRSA) isolated in the UK and Ireland 2001–07

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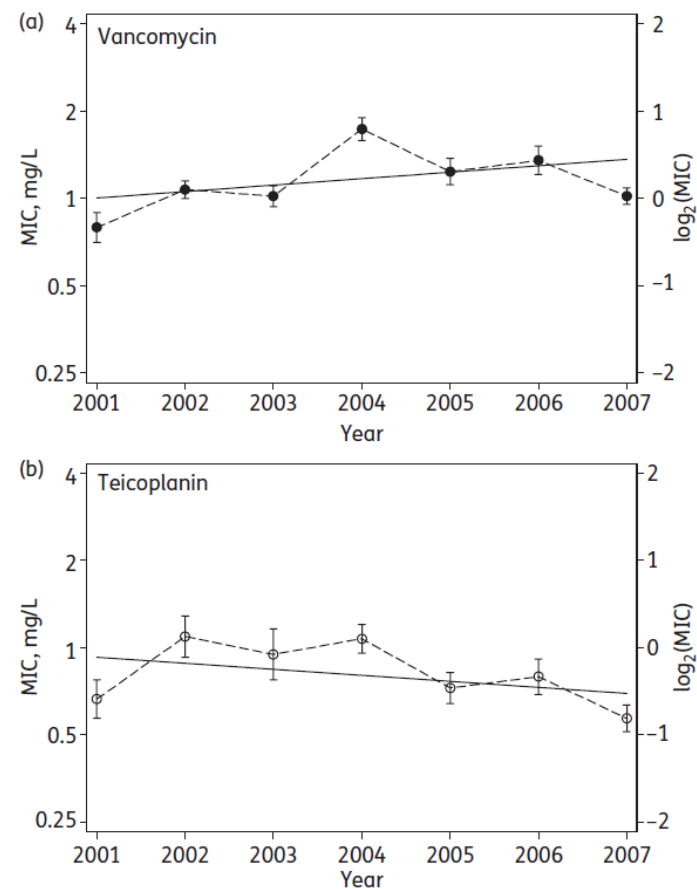


Figure 4. Appearance of MIC creep in original results. The points are conventional geometric means in each year based on the original MICs for the 271 MRSA, with bars showing 95% CI; the heavy black trend line is estimated by linear regression of log(MIC) on time for the individual isolates.

J Antimicrob Chemother 2013

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Evaluation of vancomycin and daptomycin MIC trends for methicillin-resistant *Staphylococcus aureus* blood isolates over an 11 year period

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AHA statement (endorsed by IDSA), 2010

“...there are no data to support the administration of postoperative antibiotic therapy, and it is not recommended because of the risk of drug adverse events, selection of drug-resistant organisms, and cost.”



Profilassi a Cona

A tutti i pazienti:

- ▶ Augmentin 2,2gr 1fl x 3 per 48h (dalla sera prima dell'impianto fino al giorno dopo l'impianto)
- ▶ A seguire, Augmentin 1gr 1cp x 3 per 7gg
- ▶ Se allergia alle penicilline: Clindamicina

	-1	CIED	1	2	3	4	5	6	7	8
h8		ev	ev	os	os	os	os	os	os	os
h16		ev	ev	os	os	os	os	os	os	os
h22	ev	ev	os	os	os	os	os	os	os	



Stima del rischio infettivo pre-impianto mediante score (Shariff?) e stratificazione del paziente.

Utilizzo di due schemi di profilassi antibiotica:

- Paziente a basso rischio: 2 sommin. ev il giorno dell'impianto
- Paziente a rischio non-basso: 48h ev + 7gg per os



CONCLUSIONI

- ▶ Tempo trascorso tra impianto e esordio della sintomatologia
- ▶ Durata dell'intervento
- ▶ Etiologia dell'infezione
- ▶ Biofilm
- ▶ Comorbidità
- ▶ Durata del trattamento
- ▶ Terapia antimicrobica pre-espianto
- ▶ Profilassi secondo definito score



CONCLUSIONI

Approccio terapeutico che tenga conto del paziente e della comunità

- Antimicrobial Stewardship
- risparmio di determinate molecole es. Fluorchinoloni, Carbapenemici ecc.
- Terapia mirata in tempi brevi

Conoscere la prevalenza dei microrganismi isolati

- isolamento microbiologico utile
- Conoscere i reparti di provenienza dei campioni biologici: Terapia intensiva, Rianimazione, Lungodegenze, ecc.
- Determinare l'antibiogramma di ciascun isolato: patogeni MDR

CONCLUSIONI

- ▶ Spettro antimicrobico idoneo
- ▶ Timing d'inizio della terapia adeguato
- ▶ Grado di esposizione all'antibiotico nella sede d'infezione ottimale
- ▶ Appropriatezza del dosaggio
- ▶ Idonea frequenza di somministrazione
- ▶ Monitoraggio delle concentrazioni plasmatiche
- ▶ Durata limitata alla risoluzione clinica

