SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

università di ferrara
DA SEICENTO ANNI GUARDIAMO AVANTI

CORSO ECM di Aggiornamento in Infettivologia

Casi Clinici Difficili in Patologia Infettiva

28 novembre 2014

Aula Magna

Azienda Ospedaliero-Universitaria di Ferrara

Nuovo "Arcispedale S'Anna" Polo Ospedaliero Cona

Via Aldo Moro, 8—Cona Ferrara

Caso clinico II:

Infezione di tasca di Pace – maker da MRSA con MIC >1 per vancomicina

Presenter:
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Discussant:

C. Cancellieri, R. Cultrera

Infezioni dei device cardiaci impiantabili…

definizioni
dimensioni
eziologia

Infections involving cardiac implantable electronic devices

Author: Adolf W Karchmer, MD

- Like any other foreign bodies, implanted cardiac devices (ie, pacemakers and implantable cardioverter-defibrillators [ICDs]) can become infected. The presentation, consequences, and treatment of device infections vary according to the location and extent of infection and the clinical characteristics of the patient [1Baddour LM, Clinical practice. Infections of cardiovascular implantable electronic devices. N Engl J Med 2012].
- Device infections are generally considered in two categories:
  - **Pocket infections** – The term pocket infection is used when the infection involves the subcutaneous pocket containing the device and the subcutaneous segment of the leads (ie, not the transvenous segment). In some cases, part of the device or lead erodes through the overlying skin. Such an erosion can occur without overt evidence of infection, but there is inescapable contamination of the site and these cases are managed as pocket infections.
  - **Deeper infection** – This term is used when the infection involves the transvenous portion of the lead, usually with associated bacteremia and/or endovascular infection. Deep infection can occur with or without involvement of the generator pocket and can include device-related endocarditis in which there may be vegetations on the intracardiac portion of the lead.
- Alternatively, device infections may be classified by the mode of infection:
  - **Primary infections**, in which the device and/or pocket itself is the source of infection, usually due to contamination at the time of implant.
  - **Secondary infection**, in which the leads (and then sometimes the device and the pocket) are seeded due to bacteremia from a different source.

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- **Incidence** — The true incidence of cardiac device infection is difficult to determine due to the lack of a comprehensive registry or mandatory reporting. A range of values has been reported in a number of observational series [2-6]. In a review of 21 studies of pacemaker and ICD recipients with variable follow-up, the rate of infections ranged from 0.8 to 5.7 % [7 Eggimann P, 2000]. The following observations illustrate the range of findings:
- In a series of 8303 pacemaker insertions for which antistaphylococcal periprocedure prophylaxis was routinely administered, pacemaker-associated infection occurred in 468 patients (5.6%) [2 Arber 1994]. The infection in 44 of these patients (0.5% of all insertions) was consistent with a precise definition of pacemaker endocarditis.
- In a population-based survey in France in 1999, the annual age- and sex-standardized incidence of pacemaker endocarditis was 550 cases per one million pacemaker recipients [3 Duval X]. Among 33 patients with definite pacemaker lead endocarditis, 16 also had valvular involvement (10 tricuspid and six aortic or mitral valves). 12 other patients had valvular endocarditis without evidence of pacemaker involvement.
- In a retrospective cohort study of residents of Olmsted County, Minnesota between 1975 and 2004, 1524 cardiac device patients were identified [4 Uslan DZ, 2007]. Over 7578 device-years of follow-up, the incidence of definite device infection was 1.9 per 1000 device-years. The incidence of infection was significantly higher for ICDs than for pacemakers (8.9 versus 1.0 per 1000 device-years).
- In a prospective study of 6319 consecutive recipients of pacemakers or ICDs in 44 medical centers in France during 2000, during 12 months of follow-up the rate of infection was 0.68 per 100 patients (95% CI, 047 to 0.89), and infection plus erosions were noted in 1.19 per 100 patients (95% CI, 0.92 to 1.46) [8].

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- **Risk factors** — A variety of factors and comorbid conditions have been associated with pacemaker and ICD infection [3,7-11 Sohail MR, Am J Cardiol. 2013]:
  - Recent manipulation of the device, particularly elective secondary manipulations such as generator exchange
  - Temporary pacing prior to permanent device placement
  - Diabetes mellitus
  - Underlying malignancy
  - Operator inexperience
  - Advanced patient age
  - Prior treatment with anticoagulants or glucocorticoids
  - Generator replacement
  - Heart failure
  - Renal dysfunction (glomerular filtration rate <60 mL/min)
  - Female gender
- Recent manipulation of the device (eg, newly implanted device, device revision, or generator change) is the most clearly identified and causal of these risk factors [7].

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- In registry of 6319 consecutive patients undergoing implantation of a pacemaker or ICD, device-related infections occurred over the ensuing 12 months in 0.56% of initial implantations and 0.99% of non-denovo implantations [8 Klug D, Circulation. 2007].

  The other risk factors for device infection noted were:
  - Fever within 24 hours of implantation (adjusted OR 5.8)
  - Use of temporary pacing prior to implantation (adjusted OR 2.5)
  - Early reintervention (adjusted OR 15.0)

- Risk factors for permanent pacemaker infection were further analyzed in a case-control study in which 29 such patients were matched with 58 uninfected controls with a permanent pacemaker [12 Sohail MR, Clin Infect Dis. 2007]. On multivariable analysis, only two independent risk factors for infection were identified:
  - long-term glucocorticoid therapy (odds ratio 13.9);
  - the presence of more than two pacing leads compared with two pacing leads (odds ratio 5.4).

  On the other hand, antibiotic prophylaxis prior to pacemaker implantation had a protective effect (odds ratio 0.09).

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- **MICROBIOLOGY** — *S. aureus* and coagulase-negative staphylococci, often *S. epidermidis*, cause 65 to 75 % of generator pocket infections and up to 89 % of device-related endocarditis [5,12,19,20].

  Episodes arising within 2 weeks of implantation are more likely to be due to *S. aureus* [21,22]. Seeding of the device from systemic bacteremia primarily occurs with *S. aureus* infections. Among staphylococci causing device infection, methicillin resistance should be assumed until tests demonstrate methicillin susceptibility.
- Streptococci, *Corynebacterium* spp, *Propionibacterium acnes*, gram-negative bacilli, and *Candida* spp have caused occasional pulse generator pocket infections and device-related endocarditis.
- Among 162 episodes of precisely defined pacemaker endocarditis, coagulase-negative staphylococci caused 61% and *S. aureus* caused 30% [2,3,14,15]. Methicillin resistance was common among all of these staphylococci. Polymicrobial infection occurred in 18 patients, and cultures were negative in seven (table 1).
- In a series of 44 episodes of device endocarditis between 1991 and 2003, the number of infections due to coagulase-negative staphylococci, S. aureus, fungi, gram-negative bacilli, and P. acnes was 18, 18, 3, 2 and 1, respectively. One case was polymicrobial. Among the 3 fungal infections, there were 2 cases of *A. fumigatus* and one case of *C. albicans* [23]. Blood cultures were positive in 34 episodes (77%) and in 10 patients with negative blood cultures, 6 had received prior antibiotics [23].

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Microbiology of pacemaker endocarditis

Organism	Number of patients (%)*
Coagulase-negative staphylococci	99 (61)
Staphylococcus aureus	49 (30)
Enterobacteriaceae	8 (5)
Streptococci	7 (4)
Pseudomonas	6 (4)
Candida	3 (2)
Enterococci	3 (2)
Corynebacterium	2 (1)
Propionibacterium acnes	1 (<1)
Listeria	1 (<1)
Micrococci	1 (<1)

* 18 patients had polymicrobial infection.

Data compiled from: Arber, N, Pras, E, Copperman, Y, et al. Medicine (Baltimore) 1994; 73:299;
Duval, X, Selton-Suty, C, Alla, F, et al. Clin Infect Dis 2004; 39:68;
Klug, D, Lacroix, D, Savoye, C, et al. Circulation 1997; 95:2098;
Cacoub, P, Leprince, P, Nataf, P, et al. Am J Cardiol 1998;

Vi è un ruolo del tampone nasale in questa tipologia di pazienti? (decolonizzare se S. aureus MRSA +?)

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- **PREVENTION** — Assiduous aseptic technique in a controlled environment should be used when implanting pacemakers or ICDs and when changing pulse generator units [30]. Since operator experience affects outcome, the procedure should generally be performed by an individual who has done many device implantations [43,44 Byrd CL, Pacing Clin Electrophysiol. 1999].
- **Prophylaxis at implantation** — Systemic antibiotic prophylaxis is generally advised for surgical implantation of foreign devices. Microbiologic and epidemiologic data suggest that contamination with skin flora is responsible for a significant proportion of device infections.
- Evidence of benefit comes from a meta-analysis of seven randomized trials (only one of which was double-blind and placebo-controlled) that evaluated antibiotic prophylaxis administered immediately before permanent pacemaker implantation in 2023 patients [45 Da Costa A, Circulation. 1998]. A consistent protective effect was noted for short-term pocket infection, skin erosion, or septicemia (odds ratio 0.26, 95% CI 0.10 to 0.66) [45]. The systemic antimicrobials used were antistaphylococcal penicillins and first generation cephalosporins, although the regimens varied considerably between trials.
- A low rate of infection with prophylaxis was also noted in a subsequent review of 852 patients who underwent placement of a new pacemaker or replacement of a pulse generator and received 2 g of cefazolin intravenously over 20 minutes before beginning the procedure [46 Bertaglia E, Pacing Clin Electrophysiol. 2006]. 9 patients (1%) had minor infectious complications within the first two months. 6 patients (0.7%) had major infectious complications between 12 and 55 months.

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- Antibiotic prophylaxis reduces risk for device infection [8,12,47]. A randomized trial demonstrated that patients randomized to receive cefazolin prior to device implantation had a lower infection rate than those who received placebo (0.6 versus 3.3 percent) [47de Oliveira JC, Circ Arrhythm Electrophysiol. 2009].
- Based upon these observations, the **American Heart Association** recommends prophylaxis with antistaphylococcal antimicrobial drugs at the time pacemakers are implanted or generator units exchanged. The dosing regimens are similar to those used for cardiac surgery (eg, cefazolin 1 to 2 g IV within 60 minutes of surgical incision or, if there is concern about cephalosporin allergy or colonization by methicillin-resistant staphylococci, vancomycin 1 g IV 90 to 120 minutes of incision) [30,48]. For patients who cannot tolerate beta-lactam antibiotics or vancomycin, daptomycin or linezolid are alternatives [30].
- **Endocarditis prophylaxis** — Transient bacteremia associated with mucosal trauma rarely results in pacemaker or ICD infection. As a result, prophylaxis at times of mucosal trauma or manipulation is not recommended for patients with pacemakers or ICDs unless they have another significant independent indication for endocarditis prophylaxis [30,49 Wilson W, Guidelines From the American Heart Association].

Antimicrobial prophylaxis for cardiac surgery in adults

Nature of operation	Common pathogens	Recommended antimicrobials	Usual adult dosage*	Redose interval•
Cardiac procedures: coronary artery bypass, cardiac device insertion procedures (eg, pacemaker implantation), placement of ventricular assist devices	Staphylococcus aureus, S. epidermidis	Cefazolin	<120 kg: 2 g IV ≥120 kg: 3 g IV	4 hours
		OR cefuroxime	1.5 g IV	4 hoursΔ
		OR vancomycin◊	15 mg/kg IV (max 2 g)	N/A
		OR clindamycin	900 mg IV	6 hours

IV: intravenous. * Parenteral prophylactic antimicrobials can be given as a single IV dose begun within 60 minutes before the procedure. If vancomycin is used, the infusion should be started within 60 to 120 minutes before the initial incision to have adequate tissue levels at the time of incision and to minimize the possibility of an infusion reaction close to the time of induction of anesthesia.
• For prolonged procedures (>3 hours) or those with major blood loss, or in patients with extensive burns, additional intraoperative doses should be given at intervals one to two times the half-life of the drug for the duration of the procedure in patients with normal renal function.
Δ Some experts recommend an additional dose when patients are removed from bypass during open-heart surgery.
◊ Use of vancomycin is appropriate in hospitals in which methicillin-resistant S. aureus (MRSA) and S. epidermidis are a frequent cause of postoperative wound infection, in patients previously colonized with MRSA or for those who are allergic to penicillins or cephalosporins. Rapid IV administration may cause hypotension, which could be especially dangerous during induction of anesthesia. Even when the drug is given over 60 minutes, hypotension may occur; treatment with diphenhydramine and further slowing of the infusion rate may be helpful. For procedures in which enteric gram-negative bacilli are common pathogens, many experts would add another drug such as an aminoglycoside (gentamicin 5 mg/kg IV), aztreonam (2 g IV), or a fluoroquinolone (ciprofloxacin 400 mg IV or levofloxacin 500 mg IV).
Adapted from: Treatment Guidelines from The Medical Letter, October 2012; Vol. 10 (122):73. www.medicalletter.org. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Surg Infect (Larchmt) 2013; 14:73.

Clinical practice guidelines for antimicrobial prophylaxis in surgery

DALE W. BRATZLER, E. PATCHEN DELLINGER, KEITH M. OLSEN, TRISH M. PERL, PAUL G. AUWAERTER, MAUREEN K. BOLON, DOUGLAS N. FISH, LENA M. NAPOLITANO, ROBERT G. SAWYER, DOUGLAS SLAIN, JAMES P. STEINBERG, AND ROBERT A. WEINSTEIN

Am J Health-Syst Pharm. 2013; 70:195-283

- Although vancomycin is commonly used when the risk for MRSA is high, data suggest that vancomycin is less effective than cefazolin for preventing SSIs caused by methicillin-susceptible *S. aureus* (MSSA).73,74 For this reason, vancomycin is used in combination with cefazolin at some institutions with both MSSA and MRSA SSIs.

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- Colonization and resistance.
- A national survey determined that *S. aureus* nasal colonization in the general population decreased from 32.4% in 2001–02 to 28.6% in 2003– 04 ($p < 0.01$), whereas the prevalence of colonization with MRSA increased from 0.8% to 1.5% ($p < 0.05$) during the same time periods.
- Colonization with MRSA was independently associated with health care exposure among men, having been born in the United States, age of >60 years, diabetes, and poverty among women.
- The question of what antimicrobial surgical prophylaxis to use for patients known to be colonized or recently infected with multidrugresistant pathogens cannot be answered easily or in a manner that can be applied uniformly to all patient scenarios. Whether prophylaxis should be expanded to provide coverage for these pathogens depends on many factors, including the pathogen, its antimicrobial susceptibility profile, the host, the procedure to be performed, and the proximity of the likely reservoir of the pathogen to the incision and operative sites.
- While there is no evidence on the management of surgical antimicrobial prophylaxis in a patient with past infection or colonization with a resistant gram-negative pathogen, it is logical to provide prophylaxis with an agent active against MRSA for any patient known to be colonized with this gram-positive pathogen who will have a skin incision;

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- Preoperative screening and decolonization
- *S. aureus* is the most common pathogen causing SSIs, accounting for 30% of SSIs in the United States. Colonization with *S. aureus*, primarily in the nares, occurs in roughly one in four persons and increases the risk of SSI by 2- to 14-fold.146-152 A national survey assessing nasal colonization with *S. aureus* in the general population conducted from 2001 through 2004 found that while the rate of colonization with *S. aureus* decreased from 32.4% in 2001–02 to 28.6% in 2003–04 ($p < 0.01$), the rate of colonization with MRSA increased from 0.8% to 1.5% ($p < 0.05$).
- FDA has approved intranasal mupirocin to eradicate MRSA nasal colonization in adult patients and health care workers. It is noted in the prescribing information that there are insufficient data to support use in prevention of autoinfection of high-risk patients from their own nasal colonization with *S. aureus*.
- However, additional data have demonstrated that the use of intranasal mupirocin in nasal carriers of *S. aureus* decreases the rate of *S. aureus* infections. One meta-analysis of seven studies focused on surgical patients only; the other meta-analysis of nine studies included high-quality studies in dialysis patients.
- Recent studies have confirmed that *S. aureus* decolonization of the anterior nares decreases SSI rates in many surgical patients. The data are most compelling in cardiac and orthopedic surgery patients.

Clinical practice guidelines for antimicrobial prophylaxis in surgery

Dale W. Bratzler, E. Patchen Dellinger, Keith M. Olsen, Trish M. Perl, Paul G. Auwaerter, Maureen K. Bolon, Douglas N. Fish, Lena M. Napolitano, Robert G. Sawyer, Douglas Slain, James P. Steinberg, and Robert A. Weinstein

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- Most studies conclude that the use of preoperative intranasal mupirocin in colonized patients is safe and potentially beneficial as an adjuvant to i.v. antimicrobial prophylaxis to decrease the occurrence of SSIs. However, the optimal timing and duration of administration are not standardized. In most studies, mupirocin was used for five days before the operation.

Guideline Title

Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant*Staphylococcus aureus* infections in adults and children.

Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, Kaplan SL, Karchmer AW, Levine DP, Murray BE, Rybak MJ, Talan DA, Chambers HF. Clin Infect Dis. 2011 Feb;52:1-38. [371 references]

What is the management of recurrent MRSA SSTIs?

14 Decolonization may be considered in selected cases if:

- A patient develops a recurrent SSTI despite optimizing wound care and hygiene measures (**C-III**).
- Ongoing transmission is occurring among household members or other close contacts despite optimizing wound care and hygiene measures (**C-III**).

15 Decolonization strategies should be offered in conjunction with ongoing reinforcement of hygiene measures and may include the following:

- Nasal decolonization with mupirocin twice daily for 5–10 days (**C-III**).
- Nasal decolonization with mupirocin twice daily for 5–10 days and topical body decolonization regimens with a skin antiseptic solution (e.g., chlorhexidine) for 5–14 days or dilute bleach baths. (For dilute bleach baths, 1 teaspoon per gallon of water [or ¼ cup per ¼ tub or 13 gallons of water] given for 15 min twice weekly for ~3 months can be considered.) (**C-III**).

16 Oral antimicrobial therapy is recommended for the treatment of active infection only and is not routinely recommended for decolonization (**A-III**). An oral agent in combination with rifampin, if the strain is susceptible, may be considered for decolonization if infections recur despite above measures (**C-III**).

17 The role of cultures in the management of patients with recurrent SSTI is limited:

- Screening cultures prior to decolonization are not routinely recommended if at least 1 of the prior infections was documented as due to MRSA (**B-III**).
- Surveillance cultures following a decolonization regimen are not routinely recommended in the absence of an active infection (**B-III**).

Ruolo della PET-TC nella diagnosi

Infections involving cardiac implantable electronic devices

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- **DIAGNOSIS — Imaging**
- Combined positron emission tomography (PET) with fluorodesoxyglucose marked by fluorine-18 (18F-FDG) and computed tomography (CT) can be useful in detection and localization of infection.
- PET technology may be useful for distinguishing soft tissue infection (which overlies the generator) from generator infection, and can define infection along the subcutaneous course of electronic leads and within the heart [33 Sarrazin JF, J Am Coll Cardiol. 2012 May;59(18):1616-25, 34 Imaging for infected cardiac implantable electronic devices: a new trick for your pet. Brinker J. J Am Coll Cardiol. 2012 May;59(18):1626-8].

- PET depends upon uptake of 18F-FDG by inflammatory cells at the site of infection. This raises questions about its utility in patients with leukopenia or after prolonged administration of antibiotics. Data are insufficient to allow precise estimates of sensitivity and specificity in assessing suspected electronic device infection. Although it is premature to suggest 18F-FDG PET be routinely applied in the evaluation of suspected infection of electronic devices, the technology may be useful in selected diagnostic dilemmas. Studies suggest that judicious use of this technology may alter management strategy. In one study, if 18F-FDG PET findings had been used in deciding management, device removal in 6 of 42 patients (15%) might have obviated [33].

Usefulness of fluorine-18 positron emission tomography/computed tomography for identification of cardiovascular implantable electronic device infections.

Sarrazin JF, J Am Coll Cardiol. 2012 May;59(18):1616-25.

OBJECTIVES: This study evaluated the usefulness of fluorodesoxyglucose marked by fluorine-18 ((18)F-FDG) positron emission tomography (PET) and computed tomography (CT) in patients with suspected cardiovascular implantable electronic device (CIED) infection.

BACKGROUND: CIED infection is sometimes challenging to diagnose. Because extraction is associated with significant morbidity/mortality, new imaging modalities to confirm the infection and its dissemination would be of clinical value.

METHODS: Three groups were compared. In Group A, 42 patients with suspected CIED infection underwent (18)F-FDG PET/CT. Positive PET/CT was defined as abnormal uptake along cardiac devices. Group B included 12 patients without infection who underwent PET/CT 4 to 8 weeks post-implant. Group C included 12 patients implanted for>6 months without infection who underwent PET/CT for another indication. Semi-quantitative ratio (SQR) was obtained from the ratio between maximal uptake and lung parenchyma uptake.

RESULTS: In Group A, **32** of 42 patients with suspected CIED infection had positive PET/CT. 24 patients with positive PET/CT underwent extraction with excellent correlation. In 7 patients with positive PET/CT, 6 were treated as superficial infection with clinical resolution. One patient with positive PET/CT but negative leukocyte scan was considered false positive due to Dacron pouch. 10 patients with negative-PET/CT were treated with antibiotics and none has relapsed at 12.9±1.9 months. In Group B, patients had mild uptake seen at the level of the connector. There was no abnormal uptake in Group C patients. Median SQR was significantly higher in Group A (A = 2.02 vs. B = 1.08 vs. C = 0.57; $p<0.001$).

CONCLUSIONS: PET/CT is useful in differentiating between CIED infection and recent post-implant changes. It may guide appropriate therapy.

Espianto del device?

44 Intravascular extraction of problematic or infected permanent pacemaker leads: 1994-1996. U.S. Extraction Database, MED Institute.

Byrd CL, Pacing Clin Electrophysiol. 1999;22(9):1348. University of Miami School of Medicine, Florida, USA

- Of the 400,000-500,000 permanent pacemaker leads implanted worldwide each year, around 10% may eventually fail or become infected, becoming potential candidates for removal. Intravascular techniques for removing problematic or infected leads evolved over a 5-year period (1989-1993). This article analyzes results from January 1994 through April 1996, a period during which techniques were fairly stable.
- Extraction of 3,540 leads from 2,338 patients was attempted at 226 centers. Indications were: **infection (27%),** nonfunctional or incompatible leads (25%), Accufix or Encore leads (46%), or other causes (2%). Patients were 64+/-17 years of age (range 5-96); 59% were men, 41% women. Leads were implanted 47+/-41 months (maximum 26 years), in the atrium (53%), ventricle (46%), or SVC (1%). Extraction was attempted via the implant vein using locking stylets and dilator sheaths, and/or transfemorally using snares, retrieval baskets, and sheaths.
- Complete removal was achieved for 93% of leads, partial for 5%, and 2% were not removed. Risk of incomplete or failed extraction increased with implant duration ($P<0.0001$), less experienced physicians ($P<0.0001$), ventricular leads ($P<0.005$), noninfected patients ($P<0.0005$), and younger patients ($P<0.0001$).
- Major complications were reported for 1.4% of patients (<1% at centers with>300 cases), minor for 1.7%. Risk of complications increased with number of leads removed ($P<0.005$) and with less experienced physicians ($P<0.005$); risk of major complications was higher for women ($P<0.01$). Given physician experience, appropriate precautions, and appropriate patient selection, contemporary lead removal techniques allow success with low complication rates.

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- **TREATMENT** — Successful treatment of an infected device, regardless of the involved component, generally requires removal of the entire system and administration of antimicrobials directed at the responsible organism(s) [20,21,23,27,30,32,35].
- There are three general components of therapy:
  - Antibiotics
  - Explantation of the device and usually the leads
  - Reimplantation of a new system
- The details of the therapeutic approach depend upon the extent of infection, the pathogen, and the patient's clinical profile.

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- **Antibiotic therapy** — Selection of an antibiotic regimen is based upon the extent of infection and which, if any, organism is identified.
- **Initial therapy** — Initial therapy is empiric, with intravenous antibiotics.

  - In cases where a cardiac pacemaker or ICD pocket infection is suspected, antibiotics including antistaphylococcal coverage should be initiated (after obtaining at least two independent blood cultures). Because of the high incidence of methicillin resistance with *S. aureus* and *S. epidermidis*, initial therapy with vancomycin is reasonable.
  - High dose daptomycin is a possible alternative to vancomycin for either initial empiric or definitive therapy of staphylococcal infection involving an implantable electronic cardiac device. Evidence supporting the alternative use of daptomycin include one study of 25 cases of device-related infection, in which high dose daptomycin (mean 8.3 mg/kg [range 6.4-10.7 mg/kg]) resulted in cure or improvement in 23 of 25 patients [36 Durante-Mangoni E, Clin Infect Dis. 2012]. Devices were explanted in 22 patients; 2 patients with retained devices remained bacteremic during therapy.
  - Caution is required when treating S. aureus infections with daptomycin in the setting of vancomycin failure; S. aureus non-susceptibility to daptomycin has been observed when the organism has persisted in spite of vancomycin therapy [37 van Hal SJ, Eur J Clin Microbiol Infect Dis. 2011]. Therefore, repeat testing of the S. aureus isolate associated with vancomycin failure should be performed to ensure susceptibility to daptomycin.

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- **Antibiotic therapy** — Selection of an antibiotic regimen is based upon the extent of infection and which, if any, organism is identified.
- **Initial therapy** — Initial therapy is empiric, with intravenous antibiotics.

  - In cases with evidence of deeper infection (eg, device-related endocarditis, or pocket infection with bacteremia), we recommend the initiation of intravenous antibiotics as for bacterial endocarditis. At a minimum, therapy should include vancomycin or a comparable parenteral agent effective against methicillin-resistant staphylococci.
  - Once a causative organism is identified through blood and/or wound cultures, the antibiotic regimen can be tailored as appropriate.

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- **Duration** — The duration of therapy depends upon the nature of the infection.
  - For infections limited to the pocket and subcutaneous tissue (blood cultures are sterile and transesophageal echocardiography is negative), we recommend continuation of antibiotics for 10 to 14 days after explantation of the infected system [20 Sohail MR, J Am Coll Cardiol. 2007,30].
  - For device infection due to erosion of the generator in the absence of local inflammation, a 7 to 10 day course of antibiotics after explantation may be sufficient [30 Baddour 2010]
  - The timing of the transition to oral antibiotics depends on several factors, including the presence (or absence) of systemic signs of infection, the severity of the local infection, and the urgency of implanting a new system.
  - Patients with device-related endocarditis or with a generator pocket infection and bacteremia should receive a full course of parenteral antibiotics as would be given to treat endocarditis caused by the implicated organism [7,15 Cacoub P, Am J Cardiol. 1998;,38]. As noted above, approximately 50% of patients with pacemaker endocarditis have concurrent valvular infection [3,23].

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- **System removal 1—** When an infection is known to involve a pacemaker or ICD, removal of the device and leads is usually recommended [20,23,30].
- In some cases (eg, bacteremia from an unknown source), an initial strategy of aggressive intravenous antibiotic therapy with initial retention of the device and/or leads can be considered. It should be noted, however, that when device infection is highly likely, antibiotic therapy without device removal entails increased risk.
- Among 415 patients with infection of implanted electronic cardiac devices, of which 67% were caused by staphylococci, a multi-variate analysis adjusted for high-risk device removal indicated that patients who did not undergo device removal experienced a sevenfold (HR 6.97 [95% CI 1.36-35.6]) increase in 30 day mortality. Although device removal can be associated with complications and thus risk of death, immediate device removal (in contrast with removal after failure of antimicrobial therapy or no removal) was associated with a threefold (HR 0.35 [95% CI 0.16-0.75]) reduction in mortality at one year [39 Le KY, Heart Rhythm 2011].
- Another large study demonstrated that device removal during the index hospitalization was associated with decreased mortality at one year; failure to pursue device removal incurred increased mortality risk at one year [40 Athan E, ICE-PCS Investigators. JAMA. 2012].

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- **System removal 2 —** When an infection is known to involve a pacemaker or ICD, removal of the device and leads is usually recommended [20,23,30].
- Decisions regarding device and lead removal are based upon the following factors:
  - The location and extent of infection (eg, pocket infection, device-related endocarditis, or bacteremia of unknown source in a pacemaker or ICD patient)
  - The pathogen, with lead removal being particularly important in infections due to *S. aureus* [14,24,25,41].
  - The risk for bradyarrhythmias and/or tachyarrhythmias if the device is removed. Plans should be made for managing these issues until reimplantation of a new device is considered safe.
  - The age of the system, since leads that have been in place for more than 1 to 2 years are more difficult to extract. On the other hand, systems that have been in place for longer periods of time are less likely to be secondarily infected due to bacteremia.
  - The patient's overall condition and prognosis.
- Explantation of the pacemaker or ICD generator (ie, not the leads) is a relatively straightforward and safe procedure, and can be done as soon as the diagnosis is confirmed. Following explantation of the device, the infected subcutaneous pocket is usually packed open and treated with local wound care. In some cases, if the pocket is not purulent, primary closure can be performed after extensive debridement. In general, the system should be explanted as soon as is feasible after the diagnosis of infection is made.

Infections involving cardiac implantable electronic devices

Author: Adolf W Karchmer, MD

- **Device removal indications** — The device should be removed whenever there is evidence that the device pocket or leads are infected [30]. This occurs in two settings:
  - Pocket infection with or without associated bacteremia
  - Lead infection, which is essentially synonymous with device-related endocarditis
- Device explantation is also recommended for patients with bacteremia even in the absence of evidence of device infection in the following settings:
  - *S. aureus* bacteremia without an alternative source.
  - Bacteremia due to any pathogen that persists or recurs without an alternative source despite appropriate antibiotic therapy.
  - When patients undergo valve replacement or repair for infective endocarditis (eliminates a source for potential relapse)

30 Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. Baddour LM, Circulation. 2010

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- Situations in which retention of the device may be attempted include:
  - Patients with bacteremia from a defined source other than the device (including valvular infection) if the following conditions are met:
    - there is no clinical or TEE evidence of lead infection;
    - there is no evidence of pocket infection;
    - and the device has not been recently manipulated.

    Such patients may be treated with antibiotics for the bacteremic disease and then observed for relapse. Subsequent unexplained relapse suggests device infection and a need to extract the system [3,25,30].
  - Patients with superficial cellulitis at the incision in whom the infection does not appear to extend into the generator pocket may be treated without device removal [30].

  However, this distinction is often difficult to make, and patients managed with device retention require close observation.
- In general, device retention is usually reserved for patients in whom device removal poses significant risks (eg, patients with major comorbidities, long standing devices, or who require continuous pacemaker support). Aggressive antibiotic therapy should be administered with this approach. If there is evidence of recurrent, persistent, or progressive infection despite appropriate intravenous antibiotic therapy, the system should be removed.

Infections involving cardiac implantable electronic devices

Author: Adolf W Karchmer, MD

- **Lead extraction indications** — Despite the challenges related to lead extraction, we favor lead removal in most cases that require device explantation, particularly the following settings [30].
  - Device-related endocarditis, since failure to remove an infected lead is associated with a high rate of relapsed infection and mortality even with a full course of appropriate antibiotic therapy [14-16,21,22,27,35,41].
  - Pocket infections requiring device explantation, even without evidence of deeper infection. In most cases, the risks of recurrent infection outweigh the risks of extraction. Leads that have been in place for more than 2 years can still be safely removed by experienced operators in most cases, although the risks are higher than with newer leads. The decision to attempt lead removal is individualized in these cases. ICD leads tend to have more extensive adhesions than pacemaker leads; thus, the type of leads can impact this decision.
  - Patients without overt evidence of pocket infection or endocarditis, but with *S. aureus* bacteremia that requires generator explantation.
  - Patients without overt evidence of pocket infection or endocarditis, but with *S. aureus* bacteremia or bacteremia with any pathogen that persists or recurs despite appropriate antibiotic therapy without an alternative source.
- In cases of pocket infection without bacteremia or endocarditis, lead retention may be considered for patients in whom severe comorbidities or extenuating circumstances exist (eg, extreme frailty) [42]. Some individuals with lead infection or endocarditis are managed without device and lead explantation; these are usually extremely frail patients with limited life expectancy or patients refusing device removal. In such cases, however, long-term oral suppressive antibiotics are usually the alternative to lead removal. These patients are at high risk of failure with relapse and increased mortality [23,30].

- Ed ora…

A voi la parola,

grazie

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CORSO ECM di Aggiornamento in Infettivologia

Casi Clinici Difficili in Patologia Infettiva

28 novembre 2014

Aula Magna

Azienda Ospedaliero-Universitaria di Ferrara

Nuovo "Arcispedale S'Anna" Polo Ospedaliero Cona

Via Aldo Moro, 8—Cona Ferrara

Guideline Title

Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant*Staphylococcus aureus* infections in adults and children.

Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, Kaplan SL, Karchmer AW, Levine DP, Murray BE, Rybak MJ, Talan DA, Chambers HF. Clin Infect Dis. 2011 Feb;52:1-38. [371 references]

- **What is the management of MRSA bacteremia and infective endocarditis?**
- **Bacteremia and Infective Endocarditis, Native Valve**
- For adults with uncomplicated bacteremia (defined as patients with positive blood culture results and the following: exclusion of endocarditis; no implanted prostheses; follow-up blood cultures performed on specimens obtained 2–4 days after the initial set that do not grow MRSA; defervescence within 72 hours of initiating effective therapy; and no evidence of metastatic sites of infection), vancomycin (**A-II**) or daptomycin 6 mg/kg/dose IV once daily (**A-I**) for at least 2 weeks. For complicated bacteremia (defined as patients with positive blood culture results who do not meet criteria for uncomplicated bacteremia), 4–6 weeks of therapy is recommended, depending on the extent of infection. Some experts recommend higher dosages of daptomycin at 8–10 mg/kg/dose IV once daily (**B-III**).
- For adults with infective endocarditis, IV vancomycin (**A-II**) or daptomycin 6 mg/kg/dose IV once daily (**A-I**) for 6 weeks is recommended. Some experts recommend higher dosages of daptomycin at 8–10 mg/kg/dose IV once daily (**B-III**).
- Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis (**A-II**).
- Addition of rifampin to vancomycin is not recommended for bacteremia or native valve infective endocarditis (**A-I**).
- A clinical assessment to identify the source and extent of the infection with elimination and/or debridement of other sites of infection should be conducted (**A-II**).
- Additional blood cultures 2–4 days after initial positive cultures and as needed thereafter are recommended to document clearance of bacteremia (**A-II**).
- Echocardiography is recommended for all adult patients with bacteremia. Transesophageal echocardiography (TEE) is preferred over transthoracic echocardiography (TTE) (**A-II**).
- Evaluation for valve replacement surgery is recommended if large vegetation (>10 mm in diameter), occurrence of ≥1 embolic event during the first 2 weeks of therapy, severe valvular insufficiency, valvular perforation or dehiscence, decompensated heart failure, perivalvular or myocardial abscess, new heart block, or persistent fevers or bacteremia are present (**A-II**).

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- **What are the recommendations for vancomycin dosing and monitoring?**
- These recommendations are based on a consensus statement of the American Society of Health-System Pharmacists, the IDSA, and The Society of Infectious Diseases Pharmacists on guidelines for vancomycin dosing (Rybak et al., "Therapeutic monitoring," 2009; Rybak et al., "Vancomycin therapeutic," 2009).
- **Adults**
- IV vancomycin 15–20 mg/kg/dose (actual body weight) every 8–12 hours, not to exceed 2 grams per dose, is recommended in patients with normal renal function (**B-III**).
- In seriously ill patients (e.g., those with sepsis, meningitis, pneumonia, or infective endocarditis) with suspected MRSA infection, a loading dose of 25–30 mg/kg (actual body weight) may be considered. (Given the risk of red man syndrome and possible anaphylaxis associated with large doses of vancomycin, one should consider prolonging the infusion time to 2 hours and use of an antihistamine prior to administration of the loading dose.) (**C-III**).
- Trough vancomycin concentrations are the most accurate and practical method to guide vancomycin dosing (**B-II**). Serum trough concentrations should be obtained at steady state conditions, prior to the fourth or fifth dose. Monitoring of peak vancomycin concentrations is not recommended (**B-II**).
- For serious infections, such as bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe SSTI (e.g., necrotizing fasciitis) due to MRSA, vancomycin trough concentrations of 15–20 micrograms (mcg)/mL are recommended (**B-II**).
- For most patients with SSTI who have normal renal function and are not obese, traditional doses of 1 gram every 12 hours are adequate, and trough monitoring is not required (**B-II**).
- Trough vancomycin monitoring is recommended for serious infections and patients who are morbidly obese, have renal dysfunction (including those receiving dialysis), or have fluctuating volumes of distribution (**A-II**).
- Continuous infusion vancomycin regimens are not recommended (**A-II**).