Francisco Carmona-Torre[1]
Marta Rua[2]
José Luis Del Pozo[1,2]

Non-valvular intravascular device and endovascular graft-related infection

[1]Division of Infectious Diseases. Clinica Universidad de Navarra. Pamplona, Spain.
[2]Department of Clinical Microbiology. Clinica Universidad de Navarra. Pamplona, Spain.

ABSTRACT

In the last few years there has been an increase of implantable cardiac electronic device and vascular graft related infections. This is due in part to a higher complexity of some of these procedures and an increase in patient's comorbidities. Despite wide diagnosis methods availability, early stage diagnosis usually constitutes a challenge as often patients only denote insidious symptoms. In most confirmed cases, removal of the infected device is required to resolve the infection. This is mostly explainable because of bacterial ability to grow as biofilms on biomaterial surfaces, conferring them antimicrobial resistance. If removal is not possible, chronic suppressive antimicrobial therapy could be an option.

Key words: Prosthesis-related infections. Vascular graft. Bacterial infection.

Infecciones relacionadas con dispositivos intravasculares no valvulares e injertos endovasculares

RESUMEN

En los últimos años se ha producido un aumento de las infecciones relacionadas con los dispositivos electrónicos cardíacos implantables y los injertos vasculares. Esto se debe en parte a la mayor complejidad de algunos de estos procedimientos y al aumento de comorbilidades en los pacientes tratados. A pesar de la amplia variedad de métodos diagnósticos disponibles, la detección de las infecciones asociadas a estos biomateriales constituye un reto. En la mayoría de los casos es preciso retirar los dispositivos para lograr la curación. Esto se debe en gran medida a la capacidad de las bacterias para desarrollar biopelículas sobre su superficie, lo cual les confiere una enorme resistencia a los antibióticos. Si la retirada no es posible, el tratamiento antibiótico supresor crónico podría ser una opción.

Palabras clave: Infecciones protésicas. Injerto vascular. Infección bacteriana.

INTRODUCTION

In the recent years an increasing number of medical devices have being placed in our hospitals[1]. Despite surgical advances and improvements in biomaterials and design of implantable cardiac electronic devices and vascular grafts, related infection continues to be a major related complication[2]. Ability of bacteria to form biofilms on the biomaterial surface represents one of the main issues involved in the pathogenesis of these infections. Biofilms confers microorganisms a great resistance to innate host defences and antimicrobial agents, making necessary in most cases to explant the infected device to solve the infection[1].

We will review infections related to implantable cardiac electronic devices (ICEDs) [permanent pacemakers (PPM), implantable cardioverter defibrillators (ICD), cardiac resynchronisation therapy devices (CRT)] and vascular grafts.

EPIDEMIOLOGY

Implantable cardiac electronic devices (ICEDs). Implantation rates of ICEDs in developed countries are increasing as a consequence of new technological advances and wider patient eligibility criteria[3]. Likewise, an increase in ICED related infections has been reported[4] in relation with a rise in the performance of more complex procedures and in the proportion of patients with severe comorbidities, including organ system

Correspondence:
José Luis Del Pozo
Division of Infectious Diseases. Clinica Universidad de Navarra. Pamplona, Spain.
E-mail: jdelpozo@unav.es

failure (i.e., renal, respiratory or cardiac) or diabetes[3]. Overall, incidence of related infection is estimated to range between 0.5% and 5.7%, being more frequent among ICD/CRT when compared to PPM, and for revision procedures when compared to primary implantation[2,3]. Implantation of devices in the abdominal wall or by a thoracotomy route represent other factor related to a higher incidence of infection, in comparison with those devices implanted at the pectoral site or transvenously[3]. Several studies have evaluated the potential risk factors for ICEDs related infection. Among the most consistently identified risk factors are the number of prior procedures, their complexity and the lack of antimicrobial prophylaxis[3]. Microbial epidemiology of ICED infections is characterized by a predominance of gram-positive bacteria (67.5-92.5%), with coagulase-negative staphylococci (CoNS) representing the most common isolated bacteria followed by *Staphylococcus aureus*. Gram-negative bacilli are isolated in 1% – 17% of patients, with fungal infections representing less than 2% of patients. Polymicrobial infections range from 2% to 24.5%. Culture negative infections range from 12-49%[3].

Vascular graft infections (VGIs). Advances in surgical techniques and graft design (e.g., use of native venous or arterial tissues) have leaded to a reduction in frequency and severity of VGI. However the number of vascular grafts procedures has risen, especially among patients with multiple comorbidities, increasing the risk of related infections and complications. Major complications of VGI are sepsis developement, disruption of infected anastomotic suture with rupture or pseudoaneurysm formation, vascular-enteric fistulae, embolization of infected thrombi, bacteraemic spread of infection, amputation and death[5].

VGIs can be categorized in two groups based on their location: extracavitary (primarily in the groin or lower extremities) and intracavitary (primarily within the abdomen or thorax). Despite this initial classification, frequency of VGI for each group changes in relation with graft anatomic location. For most extracavitary grafts the infection rate is 1.5% to 2%, however it rises to 6% for groin grafts. For intracavitary grafts, infection rate ranges from 1% to 5%, with 1% to 2% of aortic graft erosion or fistulisation to the bowel[5].

Evidence about risk factors associated with VGIs is scarce. *S. aureus* nasal colonization, end-stage renal disease, groin incision, lower limb arterial bypass grafting, postoperative bacteraemia and wound infection have been identified in some studies[6].

Distribution of microorganism responsible for VGIs is as follow: Gram-positive cocci 75%, Gram-negative 9%, polymicrobial infection 7% and culture negative infections 7%. Among Gram-positive cocci infections, CNS are the most common isolation, followed by *S. aureus*. The most common cause of Gram negative-infection is *Pseudomonas aeruginosa*[5].

DIAGNOSIS

Implantable cardiac electronic devices (ICEDs). Diagnosis of ICED infections constitutes a challenge as patients often show insidious symptoms that are usually disregarded. Any combination of the generator pocket, device leads and endocardial structures can be a clinical presentation, being those affecting endocardial structures those associated with a higher mortality[4].

a) Clinical diagnosis. Current guidelines categorized ICEDs infections as early post-implantation inflammation, uncomplicated and complicated generator pocket infections, ICED-infective endocarditis (ICED-IE) and ICED-lead infections (ICED-LIs)[3,4] (table 1).

b) Imaging diagnosis.

Chest radiography/CT scanning. Both tests could contribute to diagnosis providing additional information as the presence of embolic foci of infection or generator migration[3].

Echocardiography. It should be carried out as soon as possible if endocarditis o lead involvement is suspected. This technique is able to establish the presence of endocardial or lead involvement and consequent complications (e.g., new valve regurgitation, abscess formation, etc.). Despite transeoesophageal echocardiography (TEE) has a higher sensibility to diagnose ICED-LI or ICED-EI than transthoracic echocardiography (TTE), both techniques are complementary. Information provided by echocardiography should be interpreted in conjunction with clinical data because masses can be present in non-infected leads and infection could be present in the absence of vegetations[3].

FDG positron emission tomography/computed tomography (PET/CT). Current guidelines discourage routinely use of FDG PET/CT in clinical practice[3] until strong evidences are obtained. Hybrid PET/CT imaging allows a correct fusion of both sets of metabolic and anatomical data, contributing to an easier interpretation[7]. Several studies have evaluated accuracy of FDG PET/CT to diagnose ICED related infections suggesting a substantial improvement in sensibility and specificity. Scarce utility has been suggested for this technique if associated native valve infection is suspected because of the high false negative results in some series[8].

c) Microbiological diagnosis. Blood cultures are the main microbiologic tool for diagnosis of ICED infections during the initial evaluation. Blood cultures are positive in 15-30% of generator pocket and device leads related infections. However, when endocardial structures are involved, this percentage increases[2]. Cultures obtained from pus or tissues from a generator pocket wound are recommended in generator and leads device infection. At the time of device removal, lead fragments (ideally distal and proximal), lead vegetation, generator pocket tissue and the explanted device should be cultured after sonication in order to retrieve biofilm bacteria. If the results are negative, specimens should be submitted for fungal and mycobacterial cultures or amplification and sequencing of bacterial 16S ribosomal RNA genes in order to detect atypical causes not detected by routine cultures[2-4,9].

Vascular graft infections (VGIs).

a) Clinical diagnosis. Clinical presentation of VGIs de-

Table 1 **Definitions of ICEDs infections.**

Early postimplantation inflammation	Erythema affecting the box implantation incision site, without purulent exudate, dehiscence, fluctuance or systemic signs of infection within 30 days of implantation. Includes a small, localised area (<1 cm) of erythema and/or purulence associated with a suture ('stitch abscess').
Uncomplicated generator pocket infection	Any one of: Spreading cellulitis affecting the generator site. Incision site purulent exudate (excluding simple stitch abscess). Wound dehiscence. Erosion through skin with exposure of the generator or leads. Fluctuance (abscess) or fistula formation. AND no systemic symptoms or signs of infection AND negative blood cultures.
Complicated generator pocket infection	As for uncomplicated generator pocket infection but with any one of: Evidence of lead or endocardial involvement. Systemic signs or symptoms of infection. Positive blood cultures.
ICED-lead infection (ICED-LI)	Symptoms and signs of systemic infection without signs of generator pocket infection but with: Definite ICED-LI—either: Echocardiography consistent with vegetation(s) attached to lead(s) and major modified Duke microbiological criteria or Culture, histology or molecular evidence of infection on explanted lead. Possible ICED-LI—either: Echocardiography consistent with vegetation(s) attached to lead(s) but no major modified Duke microbiological criteria or Major modified Duke microbiological criteria but no echocardiographic evidence of lead vegetation(s).
ICED-associated infective endocarditis (ICED-IE)	All of: ICED in situ. Modified Duke criteria for definite infective endocarditis. Echocardiographic evidence of valve involvement.

Adapted from Harrison et al[4].
ICED: Implantable cardiac electronic devices; ICED-LI: ICED-lead infection; ICED-IE: ICED-associated infective endocarditis.

pends on location of graft infection, time since surgery and microorganism responsible for the infection[5]. Several classifications of VGIs have been proposed. One of the most used was proposed by Samson et al[10] (table 2).

Extracavitary

· *Early onset VGIs (<2 months post-surgery)*

It is characterized by an acute presentation with fever, chills and other signs of systemic sepsis, wound erythema, erosion of the graft through the wound, abscess, sinus tract drainage, graft occlusion, peripheral septic emboli, pseudoaneurysm formation, anastomotic rupture with haemorrhage and poor tissue incorporation of the graft[5].

· *Late onset VGIs (>2 months postoperation)*

The clinical course use to be indolent associating local groin erythema, pain, swelling, sinus tract drainage, pseudoaneurysm at the anastomosis or skin erosion[5].

Intracavitary

· *Intraabdominal VGIs*

The clinical presentation includes fever, abdominal pain, failure to thrive, erosion with fistulous enteric communication and sepsis. No obvious physical findings could be identified[5].

· *Intrathoracic VGIs*

In cases of infection affecting aortic roof, symptoms could mimic an infectious endocarditis with fever, chills and heart failure. Other clinical presentations may include septic emboli or sudden massive haemorrhage secondary to anastomotic rupture, oesophageal or bronchial fistula[5].

b) Radiologic diagnosis

Ultrasound. It constitutes a cheap and innocuous imaging procedure of interest especially in patients with suspected extracavitary VGIs. Ultrasound can be performed at patient´s bedside allowing puncture of potentially cultivable collections and identification of pseudoaneurysms. A low utility for intracavitary VGIs has been reported. Echocardiography should be indicated for patients with suspected intrathoracic VGIs[5].

CT/CT angiography (CTA). It is useful in cases of extravascular VGIs suspicious, representing the elective procedure in

Table 2 Samson classification for extracavitary VGIs

Grade	Definition
Samson I	Infection (purulence and bacteria) extended no deeper than the dermis of the wound containing the arterial prosthesis.
Samson II	Infection (abscess, fluid collection) involved subcutaneous tissue but did not come in grossly observable direct contact with the graft.
Samson III	Infections involved the body of the graft but not an anastomosis.
Samson IV	Infections surrounded an exposed anastomosis but bacteraemia or anastomotic bleeding had not occurred.
Samson V	Infections involved a graft-to-artery anastomosis and were associated with septicemia with positive blood cultures and/or anastomotic bleeding at the time of presentation or, at the time of wound excision, by evidence of arterial wall softening such as loose sutures or discoloration of the artery at the anastomosis.

Adapted from Samson et al[10].

cases of intracavitary VGIs. CTA is useful to define extend of infection, to evaluate vascular anatomy (providing valuable information for surgical planning) and to identify fluid collection eligible to be puncture for culture[5]. Suggestive signs of VGIs include ectopic gas present beyond 4-7 weeks and perigraft fluid with fat stranding beyond 3 months after implantation[6].

CT/CTA require iodinated contrast iv administration with a potential kidney toxicity, so it should be avoided in patients with renal failure despite loose of diagnostic capacity. Otherwise implantable medical devices induce image degradation, making harder to evaluate the image. In case of suspicion of gastrointestinal bleeding related to intra-abdominal VGI performance of CTA in combination with esophagogastroduodenoscopy are recommended[5].

Magnetic resonance image (MRI). It is indicated if CTA result inconclusive. It is more expensive and requires more time to be done but offers higher soft tissue resolution. MRI may differentiate between hematoma, inflammation and infection, identifying potential mycotic aneurisms, bleeding or aortic fistulas. MRI requires infusion of gadolinium iv contrast that may cause a fibrosing dermopathy in patients with pre-existing renal failure. As disadvantages, guide punctures collections could not be done and its use is limited in patients with intracardiac electronic devices[5].

Nuclear medicine studies. Characterized by high cost and scarce availability.

· *Indium labelled white blood cell scan (In-scan)*

It is recommended in combination with other imagine techniques (e.g., MRI) when previous radiologic test result indeterminate. There is no risk of renal impairment after contrast administration. It requires more than 24 hours to obtain results. It is less sensitivity if patient is under or recently received antibiotic treatment, with high risk of false positive results in early postoperatory patients[5].

· *FDG PET/CT*

It may be indicated if previous radiologic exams are indeterminate. Scarce evidences are available about its role for VGIs diagnosis but it seems to be useful. Among proposed predictors of VGIs, focal FDG uptake on the PET component and irregular graft boundary on CT has been related to a positive predictive value of 97%. False positive results have to be considered, especially if no other clinical or laboratory evidence of infection is present (i.e., aseptic inflammatory reaction to synthetic grafts)[5,7].

c) Microbiological diagnosis

Efforts to obtain a representative culture should be done in these cases. Perigraft fluid collection obtained through ultrasound or computed tomography-guided aspiration are usually diagnostic. Cultures from wounds or sinuses must be avoided because isolates may just represent skin-colonizing microbiota and might not accurately reflect the causative microorganism. Blood cultures are often negative in these cases. Intraoperative specimens and complete or partial device are recommended to be cultured after a sonication procedure or analysed with molecular techniques[2,5,6].

TREATMENT

Implantable cardiac electronic devices (ICEDs)

a) Early post-implantation inflammation. This entity does not constitute a confirmed infection. Device removal is not required, but a close follow up should be done. Empirical antimicrobial therapy may be started for 7-10 days based on clinical decision, although the role of antibiotics is unclear[3].

b) Uncomplicated and complicated generator pocket infection. Preferred treatment option includes removal of the whole system as soon as possible (i.e., <2 weeks from diagnosis) followed by a 10-14 days of antimicrobial treatment. In those patients with absolute ICED requirement, a temporary pacing should be used until reimplantation (i.e., once symptoms and sings of systemic and local infection are resolved). If lead removal is not an option because risk are considered too high or because patient declines, then, generator should be removed leaving leads in *situ* and followed by a 6 week iv

antibiotic course treatment. As it was previously mentioned, the role of persisting biofilms in the remaining biomaterial increases the risk of relapse. Patients with absolute requirement for ICED requiring a newly implanted system, are at high risk of re-infection. In case of terminally ill or exceedingly frail patients chronic suppressive antimicrobial therapy might be the best option[3].

c) ICED-lead infection (ICED-LI). Complete device removal followed by antibiotic treatment is the preferred option. Percutaneous procedures are preferred over open surgery for ICED removal. Duration of antimicrobials should be established based on clinical response. Short course of antibiotic therapy (2 weeks) should be considered, reevaluating therapy 1 week after device removal. In case of tricuspid valve lesions, ghost lesions after system removal, or an inappropriate clinical response, patient should be treated as having ICED-IE[3,4].

d) ICED-associated infective endocarditis (ICED-IE). As for previous ICEDs infections, prompt and complete device removal followed by iv antibiotic treatment constitutes the headstone of treatment. Duration of treatment vary according to the characteristics of the affected valve, ranging from 4 weeks for native valves to 6 weeks for prosthetic valves or extra-cardiac foci of infection (i.e., secondary brain abscess or spinal infection)[3].

For ICED-LI or ICED-IE in which device removal is considered too risky or refused by patient, salvage therapy with a prolonged course of iv antibiotic therapy could be attempted. Antibiotics should be discontinued after 6 weeks. Close follow up should be continued because the high risk of relapse of this treatment option. In case of relapse, long-term oral suppressive therapy should be started[3].

Vascular graft infections (VGIs)

a) Extracavitary VGIs. The absence of specific guidelines makes difficult a standardization of surgical therapy for extracavitary VGIs. Some authors propose the use of the Samson classification to define the extent of VGI, establishing specific medical and surgical recommendation for each group[5].

- Samson I

It should be treated as a soft tissue infection without involvement of graft tissue. Initial empiric antibiotic treatment should be initiated until specific microorganisms are identified with a 2-4 weeks antimicrobial course. Excision, drainage or debridement is not generally required[5].

- Samson II

Antibiotics should be used as for Samson I, but patients usually require surgical debridement including muscle flap or use of vacuum-assisted closure (VAC) device to promote wound coverage[5].

- Samson III

Better outcomes have been reported with graft preservation for patients with Samson III early onset VGIs, with graft resection and in situ reconstruction being recommended for Samson III late onset VGIs. Among in *situ* reconstruction techniques are rifampin-bonded or silver-coated synthetic vascular grafts, cryopreserved or fresh arterial allografts, and autogenous venous grafts. Antibiotic treatment should be accomplished for 4-6 weeks (oral or IV), considering a 6 weeks to 6 months period of additional oral therapy based on individual patient risk[5].

- Samson IV

Management of Samson IV VGIs depends on several factors including the involved microorganism and the status of the anastomotic suture. In patients with a failure attempt of graft preservation or in situ reconstruction, or when *P. aeruginosa* or a multidrug-resistant microorganism is involved, it is preferable to perform an extra-anatomic revascularization followed by graft excision. A muscle flap is recommended for wound coverage with or without use of VAC device for intermediate steps. The antibiotic regimen might be as for Samson III[5].

- Samson V

Extra-anatomic revascularization followed by graft excision is the preferred option for this group of patients, with the exception of those with a solid contraindication for the surgical procedure (i.e., high operative risk, no viable revascularization options, short life expectancy). A 4-6 weeks course of iv antimicrobials is recommended followed by at least 6 months of oral therapy[5].

Long-term suppressive antimicrobial therapy should be an option in cases of infection with difficult to eradicate microorganisms, emergency or multiple surgeries, graft preservation or in situ reconstruction with extensive perigraft infection or patients not eligible for reoperation[5].

b) Intracavitary VGIs

- *Intraabdominal*

Graft excision and in situ reconstruction with cryopreserved arterial allograft, venous autograft or rifampin-bonded synthetic graft constitute the preferred surgical option in patients with or without aortoenteric fistula. Recommended duration of parenteral antibiotic regimen after surgery is 6 weeks. Based on individual risk factors of patients, an additional course of oral antibiotic treatment should be considered for 3-6 months[5].

In those patients with extensive intraabdominal abscesses, perigraft purulence or VGIs caused by MRSA, *Pseudomonas* spp., or multidrug–resistant microorganisms, performance of an extra-anatomic bypass revascularization followed by graft excision represents the elective procedure. After a conventional course of antibiotic, lifelong suppressive antimicrobial therapy may be considered[5].

- *Intrathoracic*

Intrathoracic VGI without an oesophageal or bronchial fistula used to affect patients with a synthetic arterial allograft. In these cases, in *situ* repairment using cryopreserved or fresh arterial allografts is reasonable. To promote healing and

to reduce infection, coverage of the new allograft with a muscle flap or omentum is recommended[5].

Unstable patients with oesophageal or bronchial fistula usually require in *situ* graft replacement. In selected patients ascending aorta–to–upper abdominal aortic bypass could be an option, with removal of the infected graft, debridement of devitalized tissues and closure of the ends of the aorta. Extra-anatomic reconstruction is rarely an option. To cover the new graft or aortic stumps with omentum, muscle flap or other components are important surgical adjuncts[5].

Parenteral antibiotic treatment for 4-6 weeks is recommended. Based on the risk of infection recurrence, a prolonged course of antibiotic treatment (i.e., 3-6 months) or lifelong suppressive antimicrobial treatment should be considered[5].

REFERENCES

1. del Pozo JL, Patel R. The challenge of treating biofilm-associated bacterial infections. Clin Pharmacol Ther. 2007;82(2):204-9.
2. de Cueto-Lopez M, Del Pozo-Leon JL, Franco-Alvarez de Luna F, Marin-Arriaza M. [Microbiological diagnosis of medical device-associated infections]. Enferm Infecc Microbiol Clin. 2016;34(10):655-60.
3. Sandoe JA, Barlow G, Chambers JB, Gammage M, Guleri A, Howard P, et al. 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). J Antimicrob Chemother. 2015;70(2):325-59.
4. Harrison JL, Prendergast BD, Sandoe JA. Guidelines for the diagnosis, management and prevention of implantable cardiac electronic device infection. Heart. 2015;101(4):250-2.
5. Wilson WR, Bower TC, Creager MA, Amin-Hanjani S, O'Gara PT, Lockhart PB, et al. Vascular Graft Infections, Mycotic Aneurysms, and Endovascular Infections: A Scientific Statement From the American Heart Association. Circulation. 2016;134(20):e412-e60.
6. Leroy O, Meybeck A, Sarraz-Bournet B, d'Elia P, Legout L. Vascular graft infections. Curr Opin Infect Dis. 2012;25(2):154-8.
7. Keidar Z, Nitecki S. FDG-PET in prosthetic graft infections. Semin Nucl Med. 2013;43(5):396-402.
8. Granados U, Fuster D, Pericas JM, Llopis JL, Ninot S, Quintana E, et al. Diagnostic Accuracy of 18F-FDG PET/CT in Infective Endocarditis and Implantable Cardiac Electronic Device Infection: A Cross-Sectional Study. J Nucl Med. 2016;57(11):1726-32.
9. Baddour LM, Cha YM, Wilson WR. Clinical practice. Infections of cardiovascular implantable electronic devices. N Engl J Med. 2012;367(9):842-9.
10. Samson RH, Veith FJ, Janko GS, Gupta SK, Scher LA. A modified classification and approach to the management of infections involving peripheral arterial prosthetic grafts. J Vasc Surg. 1988;8(2):147-53.