Retrospective Review

Medical Device Related Pressure Injury in the Treatment of Chronic Pain: An Early Sign of Explantation in Suspected Infection

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Background Chronic back pain is a prevalent disease and has a high impact in daily life. Implantable devices (IDs) for chronic pain management include spinal cord stimulation (SCS) systems and intrathecal drug delivery (ITDD) pumps. The number of ITDD implants have increased exponentially in the last decade. The number of complications, such as infections, are also more prevalent. Infection management guidelines are needed to standarize our clinical practice and define protocols of explantation.

Objectives: The primary outcome is to define the likelihood of device explantation regarding some covariates related to the patient, antibiotic therapy or surgerical procedures. The secondary outcome is to evaluate performance compared to the results published in the literature.

Study Design: Retrospective study.

Setting: Hospital General of Valencia. Valencia. Spain.

Methods: A retrospective study of 288 implantable device surgeries was conducted at the Hospital General Universitary of Valencia (Spain) from 1994 to 2015. Demographical and infection data were collected. We have followed the "guidelines for the diagnosis, prevention and management of implantable electronic cardiac device infection" due to the lack of a specific guideline in our field.

Results: Forty-three out of 288 procedures were identified as suspected device-infected interventions. Half of the patients had microbiologically confirmed infection after wound, blood or lumbar fluid culture. The odds ratio (OR) for explantation of the device was 19 for the presence of decubitus, a sign of medical device related pressure injury ($P < 0.0005$) and 5 for positive wound culture ($P < 0.0452$). Medical indication leading to device implantation and the antibiotics on discharge also played a role in the decision of device explantation.

Limitations: Lack of external validity and others.

Conclusion: In this study, presence of decubitus is the defining variable for device explantation when a infection is suspected rather than waiting to culture results. Due to a high variability in infection rates, multidisciplinary guidelines are needed to provide an approach that focuses on accurate data monitoring, rigurous implantation technique and standardized protocols.

Key Words: Chronic pain, spinal cord stimulation infection, neurostimulator, intrathecal drug delivery pump, complication, infection, explantation

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Implantable devices (IDs) for chronic pain management include spinal cord stimulators (SCS) and intrathecal drug delivery (ITDD) pumps. The main advantage of ITDD devices is that the direct infusion into the cerebrospinal fluid supplies the minimal dose needed to obtain a therapeutic effect

reducing systemic toxicity and providing stability in drug levels (1, 2) .

The indications for IDs in cancer and non-cancer patients is pain. SCS is a standard in the treatment of chronic pain in several pain syndromes and one of the current primary indications of SCS is the treatment of failed back syndrome (3-6). ITDD pump implantation has increased in the last decade. In adults, ITDD are used in the treatment of benign diseases, dystonia, and cancer related chronic pain, while in children the main disease is cerebral palsy (7-10). The indications are mainly for chronic pain and spasticity, associated with opioids or baclofen, respectively.

Approximately 14% of patients with cancer, do not achieve significant pain relief with the standard medical management (4) and IDs may be able to provide a therapeutic benefit.

Although SCS and ITDD are different techniques, one of the most important complications, which can be prevented in both, is infection of the subcutaneous pocket where the generator is placed. This could lead to more serious conditions, such as neuroaxial´s abscess or meningitis. For this reason, cases of suspected infection should be studied in order to establish and define a unified diagnostic protocol. Infection from IDs increases morbidity and mortality, especially in immunocompromised patients (11). Risk factors for infection include: neutropenia associated with cancer or cancer treatments, diabetes mellitus, poor nutritional status, smoking, treatment with corticosteroids, chemotherapy, and radiotherapy (12).

Several complications have been reported in the literature, but IDs infection remains the most serious complication, posing challenges to clinicians, aggravating morbidity and mortality, and raising health care costs. IDs infection is particularly relevant in immunocompromised patients (13).

The incidence rates of IDs infection reported in the literature varies between 3 to 21.8% (10,14-18) (Table 1) and it's an important cause requiring explantation (Table 2). As inert elements, the immune system is incapable of controlling the infection in these "foreign materials." Once it´s contaminated, the biofilms grow on its surface and the infection becomes difficult to control. This situation usually leads to treatment failure and requires the removal of the IDs.

Table 1. *Percentage of infection for ITDD and SCS systems.*

Authors	Year of publication	Type of ID	N	Infection rate (%)
Sydney et al (13)	2012	ITDD	207	18.7
Taira et al (15)	2013	ITDD	12	3
Ghosh et al (16)	2013	ITDD	119	21.8
Motta et al (7)	2014	ITDD	430	9.3
Malheiro et al (17)	2015	ITDD	145	6.4
May et al (41)	2002	SCS	59	18.6
Rudinger et al (6)	2011	SCS	84	4.8
Engle et al (12)	2013	SCS	59	3.4
Follet et al (27)	2004	SCS	114	-
Turner et al (60)	2004	SCS	830	4.6
North et al (59)	2005	SCS	45	6
Taylor et al (57)	2006	SCS	554	4
Taylor et al (58)	2006	SCS	3427	6
Kumar et al (5)	2006	SCS	410	3.4
Kumar et al (52)	2008	SCS	42	10
Hayek et al (53)	2015	SCS	234 of 345 implanted	4.3
Al-Kaisy et al (54)	2014	SCS	72	6
Van Buyten et al (55)	2013	SCS	72	4.8
Kemler (56)	2004	SCS	24	4
Sanchis, Romero et al {Ref #}	-	SCS+ITDD	228	8

Table 2. I*nfections according to causative organism and subsequent treatment.*

Author, year of publication	Type of device	N	Microorganism	Treatment
Sydney et al 2012 (13)	ITDD	1	GroupB Staphylococcus	ABT
		5	MSSA	ABT+explant
		1	MSSA	ABT+explant
		3	P. aeruginosa	ABT+explant
		1	MRSA, Acinetobacter	ABT+explant
		1	Negative	ABT+explant
Boviatsis et al 2004 (49)	ITDD	1	S. epidirmidis	ABT+explant
		2	S. aureus	ABT
		3	S. epidirmidis	ABT
		2	P. aeruginosa	ABT
Rudiger et al 2011 (6)	SCS	1	S. aureus	Explant
		1	MRSA	ABT
		2	Skin flora	ABT
Engle et al 2013 (12)	ITDD+SCS	1	Not collected	ABT
		1	MRSA	Explant
		1	P. aeruginosa	Explant
		1	No growth	ABT
Sanchis, Romero et al	ITDD+SCS	8	S. epidermidis	
		2	S. aureus	Explant
		1	P. aeruginosa	ABT
		1	Corynebacterium	Explant
		1	S. mitis	Explant
		1	S. epidermidis + Corynebacterium	Explant
		1	*S. epidermidis + S. lugdonensis*	Explant

MSSA:Methicillin-susceptible staphylococcus aureus
MRSA:Methicillin-resistant staphylococcus aureus.

Although the literature is enough to report the incidence of infection related to the use of neuromodulation systems in the treatment of chronic pain; however, it is scarce providing standards for the prevention, management and monitoring of infection of implanted systems (19,20). Defining criteria for suspected device-infection would be very helpful in order to prevent and minimise the risk of future device explantation and clinical worsening. We suspected that first clinical signs could be related with the alteration of skin integrity ,which might be found in medical device related pressure injuries, as first signs of suspected infection device-related (21,26).

Objectives

The primary objective was to define the likelihood of device explantation related to some covariates related to the patient, antibiotic therapy, or surgical procedures. The secondary objective is to evaluate our performance compared to the results published in the literature.

Methods

A retrospective study was conducted, including all patients who were evaluated in the Multidisciplinary Pain Management Unit of the Hospital General Universitario of Valencia (Valencia, Spain) during the years 1994 to 2015. This study was authorized by the Ethics Committee (IRB was approved).

Reasons for considering SCS and ITDD devices together are the same as the ones explained by Follett (27). Both involve neuroaxial catheterization with a fluid-conduit system. SCS involves tunneling a portion of the implanted system subcutaneously between 2 anatomical sites.

Preoperative data were collected in the first visit to our unit, including demographic data, patient comorbidities, diagnosis leading to implantation and years of follow-up. After the implatantion of the device, the type of surgery performed, type of device implanted and prophylactic antibiotic agents used were also recorded. If the type of device requiered a second procedure, the same variables were recorded again. In the follow-up visit the wound was inspected following the recommendations published by the National Pressure Ulcer Advisory Panel (NPUAP) related to long term care of IDs. First, a visual inspection was made and cushioned the skin with dressings in high risk areas, being aware of the presence of oedema under device and potential for skin breakdown (23-25). The definition of decubitus and the rating of the severity of the skin process was describe according to NPUAP stages; Stage 1 Pressure Injury: Non-blanchable erythema of intact skin, Stage 2 Pressure Injury: Partial-thickness skin loss with exposed dermis, Stage 3 Pressure Injury: Full-thickness skin loss and Stage 4 Pressure Injury: Full-thickness skin and tissue loss (24).

Concerning infection of the devices, there is a lack of consensus. Usually, infection is defined by identification or culture of microorganism or both on specimens from a clinically suspect surgical wound or implant site. Clinical signs of wound infection can include fever, redness, swelling, pain, wound exudate, poor healing, or skin erosion at the implant site. Meningismus indicates cerebrospinal fluid (CSF) involvement (26).

We have established also, that devices exposed through the skin were counted as infected because it was assumed that an implanted system that contacts the body surface becomes contaminated; as the device is an inert material, it is difficult to eradicate the microorganism given the biofilm effect exerted by them on the surface of the foreign material.

In the group of patients with infection, variables such as number of surgeries performed, time to diagnose the infection, laboratory and microbiology results, and clinical signs of infection were also recorded. The number of days to explantation and antibiotic administered were also collected when a device removal procedure was indicated. In patients with subsequent reimplantation, the variable number of days to reimplantation was recorded.

In all cases of infection of the device, surgical procedure for the explantation was conducted as follows: implantation was performed in an operating room under strictly aseptic conditions. Antibiotics were administered 60 minutes preoperatively with 2 additional doses 8 hours and 16 hours following the first dose. In all cases, the cefazolin dosing schedule used was 30 mg kg--1(maximum 2000 mg) given intravenously (IV) , in pediatrics 2 g, and 3 g for patients weighing > 120 kg, which was consistent with the antibiotic hospital policy and the recommended doses and redosing intervals for commonly used antimicrobials for surgical prophylaxis in the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA) (27).

The outcome variable, time to explantation, had 2 time periods. An early period was defined when the explantation was performed within the first 120 days and the late period was from 121 days to the last day of follow-up.

Data were analyzed using R software (28) and the libraries HMISC (29,30), MASS (31) and VCD (32). Descriptive analysis were performed. Ordered logistic regression (OLR) was adjusted for the dataset to establish main variables concerning infection of the dispositive. OLR is a case of multinomial logit models in which the categories are ordered. The polr command is used from the MASS package to estimate an OLR model. The command name comes from proportional odds assumption in the model. Suppose we have J ordered categories and that for individual i, with ordinal response Y_i, p_{ij} = P (Yi=j) for j=1,…, J. With an ordered response, it is often easier to work with the cumulative probabilities, γ_{ij} = P (Yi ≤ j). The cumulative probabilities are increasing and invariant to combining adjacent categories. Furthermore, γ_{iJ} = 1, so we need only model J-1 probabilities. At the end of the process, γ_{ij} s would be linked to covariates x. The specific model considered is the proportional odds model. To calculate a *P*-value, we compared the t-value against the standard normal distribution, like a z test.

The outcome variable is "days to explantation", which has 3 ordered levels: no explantation, early explantation (less than 4 months after implantation), and late explantation. It makes more sense to treat them as ordered rather than unordered. The remaining variables are our covariates, which will be used as predictors (33,34).

Results

A total of 288 surgeries were performed; 247 SCS (63%) and 39 ITDD (37%) systems were implanted at

the General University Hospital of Valencia during the period between 1994 and 2015.

The mean age and standard deviation was 54 (±13) years. 47% were male and 54% of the total had no comorbidities. Diabetes Mellitus and Stroke were present in the 9% of the group. Also viral infections as human inmunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) were found in the 7%. Other less common comorbidities were spinal tumours and cerebral palsy representing a 5%. Least frequent were alcoholism and poliomyelitis (2.3%).

Conditions leading to implantation in the SCS group were failed back syndrome (44%), vascular diseases (5%), and complex regional pain syndrome (2%). In the subgroup of ITDD, spasticity was the main cause (30%) and benign pain in complex regional pain syndrome (12%).

Forty-three cases of suspected infection were identified, which represents 15% of the patients. The main location of clinical infection was the subcutaneous pocket, representing 72%. Decubitus (Fig. 1), which is defined as a medical device related injury, was found in 44%. Other less common signs observed were seroma collection within the pocket, superlative or dehiscence wound, and fever.

Leukocytosis was present in 42%. Culture confirmed infections were found in 23 patients (53%), selecting those with positive blood culture, positive wound culture, or positive lumbar fluid culture.

Wound culture was performed in 51% of the patients with a suspected device infection, blood culture in 9%, and spinal fluid culture was obtained in 5%. Negative wound culture results were obtained in 65%, staphylococcus epidermidis was observed in 18%, staphylococcus aureus in 5% and other microorganisms were found in 12%.

The modelization of the data was made following the formula: *time to explantation ~ decubitus + wound culture + indication + discharge antibiotic;* following an ordered logistic regression. The model shows (Table 3) that the covariates decubitus, wound culture, and indication for implantation are statistically significant, explaining the outcome variable time to explantation. The presence of decubitus has an odds ratio (OR)determining the time to explantation of 19 and the OR for a positive wound culture is 5. Both variables were statistically significant.

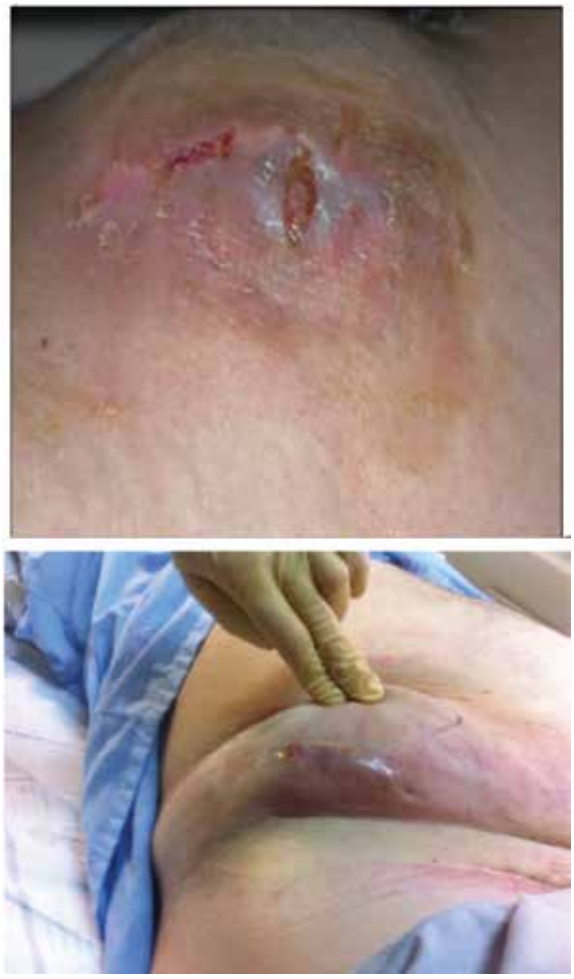

Fig. 1. *Decubitus after implantable device surgery seen in the follow-up visit.*

Limitations

This is a retrospective single center study, so it lacks external validity. There are also several physicians acting as implanters in our unit, so it could be a source of heterogeneity. Our team has different grades of experience, which we defined as the time of technical implantation experience of IDs and time to clinical diagnose and infection of the device. The surgical time keeps a direct correlation with the infection rate also, but we did not record the surgical time of each surgery implant. This is one of the most significant factors in the appearance of surgical infection, so it is a major limitation.

There is an absence of monitoring in the patients who had the IDs implantation after 2015. While some patients have been followed for more than five years,

Table 3. *OLR for time to explantation*.

	β coefficient	OR	IC	*P*-value
Decubitus	12	19	(3 , 125)	0.0005***
Wound culture	4	5	(1 , 21)	0.0452*
Indication	13	1	(0.3 , 5)	0.0041**
		2,637e-9	(2,635e-9 , 2,639e-9)	
		7	(0.8 , 67)	
Discharge antibiotic	5	5	(0.8 , 28)	0.0673·
		1	(1.1 , 110)	

Decubitus: No/Yes.
Wound culture: Negative/Posittive.
Indication for implantation: back surgery, spasticity, pain and others.
Discharge antibiotic: ciprofloxacin, augmentin and others.

others have been followed for only one year.

The ITDD infection also shows 2 different problems. One of them is directly in relationship with the implant itself, and the second one, is related directly with the pump refill. Each manipulation can lead to infection, even years after the implantation was done. This complication is not related to the experience of the team or linked with the antiseptic measures of the intervention.

Discussion

Infection following the implantation of ITTD and SCS systems is one of the most feared complications due to the high morbidity and potential of mortality.

Our results are consistent with the assessment by Engle et al (12) of infectious complications in ITDD and SCS implants in cancer patients, as the rate of infectious complications are similar compared to the rest of the patients. Most infectious events (43.58%) were found for ITDD pumps, whereas SCS systems accounted for only 10% of all recorded cases. In our opinion, the fact that the majority of infected systems were ITDD pumps relates not only to the surgery, but also to the frequent manipulation for refills. This was one of the reasons why we considered existing definitions to be inadequate, because a surgical site infection (implanted devices) is defined as an infection occurring within the first year after implantation, as long as the device has not been manipulated and the infection appears to be related to the operation (12,35). This diagnostic definition does not seem to fit our working system, because ITDD pumps are refilled from time to time (i.e., the device is manipulated periodically and frequently).

When assessing the site of the infection, the subcutaneous pocket was the most common source of infection. In keeping with this data, we found that the surgical time associated with higher rates of infection for SCS systems was the time when the generator is replaced (subcutaneous pocket area); for ITDD systems, results are high for almost all surgeries involving the subcutaneous pocket. One of the reasons for this may be the longer surgical times devoted to the subcutaneous pocket, paired with the invasiveness and trauma to tissue dissection. This is the major limitation of this study because we didn´t collect this information and longer durations of surgery is directly correlated with a higher incidence of infection. For the early surgical site infections (SSI) the NICE quality standard (QS49) (36) published in October 2013 identified 6 high priority areas that are amenable for quality improvement in the preparation of the patient. These are recommendations on hair removal; antibiotic prophylaxis in accordance with the local antibiotic formulary; maintenance of normothermia during general or regional anesthesia; maintenance of operating room best practice for all theatre staff; provision of information regarding wound care; early recognition of infection to patient and care providers and treating SSIs with appropriate antibiotics and the surveillance of rates of SSI (including post-discharge infections) and the provision of feedback to relevant staff and stakeholders for continuous improvement through adjustment of clinical practice. There were 2 peaks in the assessment of time to diagnosis, with one peak seen between postsurgical weeks 1 to 3 and a second peak after the second month. However, late cases of potential infection should be differentiated better between actual infections and allergic reactions to a foreign body with wound dehiscence (36). For these purposes, a pathological examination of the tissue should be undertaken. Delayed hypersensitivity reactions (i.e., foreign body reactions to any component of the implanted device) should be included in the dif-

ferential diagnosis of device infection. Excision of the affected tissue and histological examination is key for diagnosis (37). Not all infections without microorganism detected should be considered as potential infections.

Microbiological results

A potential infection may be a serious occurrence. Therefore, sampling for microbiological investigation should always be considered. Half of the patients show positive cultures. As for patients showing negative cultures, it should be borne in mind that the antibiotic treatment administered may alter the "false negative" results (i.e., if these patients were not under antibiotic coverage, the clinical value of culture yield would be higher). Yet profitability is always high and microbiological study recommended. Microbiologically, as in the cardiac implantable electronic devices (33,34), the most frequently found pathogens after clean surgery came from cutaneous flora like staphylococcus aureus and coagulase-negative staphylococci (i.e., S. epidermidis). Staphylococcus aureus colonizes skin and nasopharynx of humans in about 30 to 50% of the population and is a major cause of community and hospital acquired infection worldwide. It is the most commonly isolated human bacterial pathogen and is an important cause of skin and soft-tissue infections. Coagulase-negative staphylococci, particularly staphylococcus epidermidis is one of the most common pathogens associated with infections of surgical implants and other prosthetic devices owing to its adhesion and biofilm-forming ability on biomaterial surfaces. However, cases of multiple microbial infection were also recorded.

Pathogens responsible for surgical infections are evolving in recent decades. Data (ECDC - Point survey prevalence survey) show that the percentage of surgical site infection caused by Enterobacteriaceae and nonfermenting gram-negative bacilli in patients admitted to a hospital in Spain in 2012 was 51% compared to 40% of Gram-positive cocci, and among these, staphylococcus aureus was the most frequent pathogen (14.2%) (43% resistant to oxacillin) (38). Therefore, the initial empirical antibiotic coverage should target skin-dwelling microorganisms.

The organisms identified in patients who had conservative antibiotics were Staphylococcus epidermidis in three patients and Pseudomona aeruginosa in one patient. We are not suggesting, however, that these pathogens cause less severe infections than others, or that device explantation should not be seen as the only solution when there is a documented infection. Our microbiological results are consistent with the infectious agents found by other authors. In the report by Eldabe et al (39), staphylococcal infections were the most frequent. These authors have also reported up to 24 % of unknown germs and 18 % of absence of growth. These data are consistent with the lack of standardization of infection definitions and the absence of a definition for infection with an isolated pathogen.

Despite being labeled as infections, these cases may actually constitute allergic reactions to the system components or infections masked by the antibiotic treatment. This factor appears to be directly related to surgical time and the rate of infection. Rudiger et al (6) describes a clear correlation between the rate of infection and the number of previous implantations performed by the implanting physician. The number of years of experience of the implanting physicians was not taken into account. This could be a limitation of our work, however, it seems clear that long procedures causing tissue trauma may increase the risk of infection. Based on this idea, according to Henderson et al (40), the influence of the implanting physician's experience on patient selection, surgical technique, and standardization of training in SCS implantation, are important for achieving better outcomes. The patient's contribution to the decrease of infection rates may be more relevant than currently thought. According to the data published by May et al (41), health-related patient education for hygiene and proper handling of temporary electrodes during the test phase could help reduce infection rates.

Of patients who had positive microbiological results, the system was removed in a total of 11 patients (73.3%), whereas conservative ABT was chosen for 4 patients (26.6%). This data shows that the therapeutic algorithm is not fully established in our unit as well as in the literature reviewed. It seems that individualized treatment continues to be the most used therapeutic strategy.

The introduction of control measures for IDs infection in chronic pain improves patient's adherence to the therapy, and improves daily clinical practice. A proper diagnostic protocol will help physicians to closely follow highly suspicious cases. Laboratory values are good indicators, but in our opinion 2 points are key: 1) isolation of the causative organism and 2) initiation of antibiotic treatment adjusted to the prevalent flora or to the specific organism, if susceptibility testing has been conducted. According to the study of Zhu et al (42), the most important item is selecting an appropriate prophylactic antibiotic regimen, which covers the expected

endogenous flora, as well as the anticipated organisms. The antibiotic approach consisted, for the majority of our patients, of 3 doses of cefazolin, with the first one administered 60 minutes before the incision and the subsequent 2 doses, 8 hours and 16 hours later. Antibiotic coverage was subsequently maintained for at least 7 days. The guidelines of the British Pain Society published in 2005 (43) recommend single doses of a cephalosporin or a combination of vancomycin and gentamycin, or teicoplanin and gentamycin 30 minutes before the incision. Routine use of vancomycin is not recommended; however, its indications include patients with documented contamination by methicillin-resistant staphylococcus aureus (MRSA) or patients who are allergic to penicillin.

Based on the antibacterial spectrum and low incidence of allergy and side effects, cephalosporins have traditionally been the drugs of choice for the vast majority of operative procedures, especially for SCS implant (41). According to the clinical laboratory standards institute (CLSI) guidelines (44), penicillin should be used to test susceptibility of staphylococci. It is also advisable to perform a test to detect ß-lactamase production on staphylococci, for which the penicillin minimal inhibitory concentrations (MIC) are < 0.12 µg/mL.

The pharmacokinetic–pharmacodynamic (PK–PD) factor, most closely associated with the antibacterial effectiveness of cephalosporins, is the amount of time the concentration of the free drug exceeds the MIC for bacterial growth (fT > MIC); therefore, this value was calculated using relevant minimum inhibitory concentrations required to inhibit growth of 90% of bacteria (MIC90) values (46). Clindamycin and vancomycin may be used for patients with a confirmed beta-lactamic allergy. Vancomycin may be used in patients with known colonization with MRSA.

One of the most important consensus committee in neuromodulation's infection is the Neuromodulation Appropriateness Consensus Committee (NACC) guides. We have wanted to compare our clinical practice with NACC guides (19) but we only compared but we only show the match with the CDC or National Institute for Health and Care Excellence NICE recommendations. We can improve our results because we don't apply all the statements recommendated. For example, we didn't remove hair with electric clippers (Consensus Strength strong) (Table 4).

The Problem of Biofilm

Common bacteria encountered for wound infections after SCS implant are similar to those encountered in orthopedic surgeries. The most frequent is staphylococcus aureus, followed by coagulase-negative staphylococci. In 4th and 5th place are streptococci and gram-negative rods/bacilli respectively (37).

Staphylococcus aureus and staphylococcus epidermidis biofilms are widely implicated in many implant-based and chronic infections. Biofilms are typically characterized by dense, highly hydrated clusters of bacterial cells, adhered to a surface and encased in a matrix that is primarily composed of exopolysaccharides, such as polysaccharide intercellular adhesin (PIA) in staphylococci (46).

When an infection from staphylococcus aureus and staphylococcus epidermidis occurs in an ID, we have an adverse therapeutic outcome owing to the reduced antibiotic susceptibility of biofilm bacteria compared with planktonic cultures. If we observe the diameters of the zones of inhibition obtained with antibiotics by CLSI, whose penetration was significantly decreased through staphylococcus aureus and staphylococcus epidermidis biofilms (cefotaxime, oxacillin, and vancomycin) (47)

The resistance of bacterial biofilms to antibiotics is multifactorial (47), and many mechanisms including reduced antibiotic penetration, slow growth of biofilm bacteria, spatial heterogeneity in the biofilm structure, and the presence of drug-resistant or drug-tolerant physiology, contribute to the observed resistance (40).

Alternative agents are novel antibiotics such as linezolid, tigecycline and daptomycin claimed to be highly effective against biofilms but these agents have some disadvantages, mainly the high cost (43,45).

In our institution, documented infection was treated with linezolid in 4 cases, but the results were inconclusive.

Standardized Diagnostic Criteria of Infection

The first step of our study was to obtain the rate of infection of our unit. We did a retrospective analysis of 288 IDs surgeries and this revision already showed differences between physicians in the diagnosis when a "suspicious infected device" was found. While a physician considered an infected device when it appeared a dehiscence, others considered it was infected when it showed clinical signs of infection such as erythema, purulent secretion, or when a microorganism grew up in culture. We observed that there were no clear diagnostic guidelines or specific times in performing diagnostic test.

A review of infectious signs and symptoms showed that in 12 cases the infection was diagnosed by ery-

Table 4. *The NACC recommended infection-management practices with defined origin of practice (19).*

Statements	Origin of recommended practice*	Application of NACC guidelines in the HGUV patient group
Preoperative practices		
Identify and treat all remote infections for neuromodulation trials and implant	CDC IA	Yes
Utilize preoperative antibiotics for neuromodulation and implants	CDC IA and NICE	Yes
Utilize preoperative weight-based antibiotics dosing for neuromodulation trials and implants	CDC IA and NICE	Yes
Use appropriate preoperative timing (within 1 hour prior to surgical incision excluding vancomycin) for prophylactic antimicrobial administration for neuromodulation trials and implants	CDC IA, NICE and SCIP	Yes
Remove hair (when required) with electric clippers immediately before the surgical procedure	CDC IA and NICE	Yes
Perform preoperative surgical scrub for a minimum of 2-5 min with an appropriate antiseptic prior to neuromodulation trials and implants	CDC IB and NICE	Yes
Keep nails short and do not wear artificial nails for neuromodulation trials and implants	CDC IB and NICE	Yes
Do not wear hand or arm jewelry for neuromodulation trials and implants	CDC IB and NICE	Yes
Intraoperative practices		
Double glove	CDC IB and NICE	No
Utilize chlorhexidine glucanate for preoperative skin antiseptic agent	CDC IB and NICE	
If an incise drape is used, then iodophor-impregnated drape for neuromodulation implants are recommended	NICE	No
Limit procedure room traffic for neuromodulation trials and implants	CDC II and NICE	Yes
Limit tissue trauma, maintain hemostasis, eradicate dead space, and avoid electrocautery at tissue surface	CD IB and NICE	Yes
Postoperative practices		
Apply an occlusive dressing following neuromodulation trials and implants for 24-48 hours	CD IB and NICE	Yes
Do not routinely use topical antimicrobial agents for surgical wound that are healing by primary intention	NICE	Yes
Educate patient and family on proper incision care, symptoms of SSI, and importance of reporting symptoms	CDC II and NICE	Yes
Use sterile technique for dressing changes	CDC II and NICE	Yes
When SSI is suspected, prescribe an antibiotic that covers the likely causative organism. Consider local resistance patterns and culture results in choosing an antibiotic	NICE	Yes

*CDC: centers for disease control, SCIP, surgical care improvement project, MRSA, methicillin-resistant S. aureus; MSSA, methicillin-sensitive S. aureus; NICE National Institute for Health and Care Excellence; SCS, spinal cord stimulation; SSI, surgical site infection.

thema, pocket swelling, and cellulitis, but in 6 cases the physician only saw erosion through the skin, and it was labelled "suspicious infection." This is one of the reasons why we observed a lack of diagnosis consensus in our unit. In fact, we identified other diagnostic problems like false negatives. Some cases of infection presented diagnostic doubts because they met only some of the diagnostic criteria (for example, we had no bacteriological sample because they had previously received antibiotic treatment). When comparing our rate of infection to the infection rate in the literature we saw that there is a wide range. We considered this was due to the lack of well-established diagnostic criteria, rather than due to qualitative or technical differences. This is why we found contradictions in our infection rate. The lack of standardized diagnostic criteria showed that the high percentage refers to a false positive diagnosis and provide unifying diagnostic criteria.

A good comparative model for similar outcomes in terms of prevention and therapeutic management of infections would be implantable cardiac electronic devices (pacemakers and others). Strategies for the prevention and management of these infections are highly variable and based on limited evidence. We believe that it is a good option to compare and adapt specific guidelines to our IDs, beginning with the "guidelines for the diagnosis, prevention and management of implantable cardiac electronic device infection" published in 2015 by the British Cardiovascular Society (20,21). The introduction of measures of infection control for the implant device in the treatment of pain, improve adherence compliance in clinical practice in the management of infection (18). Lack of adequate data collection could hamper the daily practice of physicians (19).

The classification of SSI subtypes according to the CDC (35) does not provide diagnostic standardization to help us unify criteria. According to the CDC classification, SSIs can be classified as superficial incisional SSIs, deep incisional SSIs, and organ/space SSIs. Deep incisional and organ/space SSIs are considered to be invasive and require ABT with hospitalization and possibly explantation of the system.

The rate of "suspected infection" in these implanted devices at Hospital General Universitario of Valencia was 14.9%. However, when the number of actual infections with documented organisms was counted, the rate was considerably lower, down to 5.2%. Indeed, this rate is higher than recent studies, but we would like to remark that this is a 21 year period study, and although we can strongly assure recent implantation techniques, we suspect that procedures performed in earlier years may not have such high quality standards. Considering this fact, our data does not differ greatly from published reports due to the variability of diagnostic criteria among the studies reviewed. Therefore, it is necessary to standardize diagnostic criteria for infection of implanted devices. For this reason, we present a set of standard definitions adapted from the clinical guidelines for the diagnosis, management, and prevention of implantable cardiac electronic device infection (20,48). Our results go along with the results of Hoelzer's work (50), but in this study the infection rate was 2.45% out of a total of 2737 implants of SCS systems. We can assume they did not record those patients with "suspected infection" as we did. The conclusions are the same in recent publications from Deer's team (51) with 1.9% of infection rate.

Conclusion

In this study, the clinical sign decubitus was the most relevant in order to determine the explantation time. When decubitus was present, an early explantation of the device was preferred. Wound culture and indication were also relevant, mainly when the indication was due to pain. There is no evidence that we are aware of a prior quantitative analysis assessing the risk of early explantation.

Antibiotic therapy at the moment of discharge should be studied in more detail to enlighten which treatment is better for preventing infection.

Diagnosis of early infection has improved in our unit in recent clinical practice. There is a tendency of early explantation despite the results of the microbiological culture in our unit.

The inconsistency of diagnostic criteria and the absence of standardization of outcomes preclude comparability among different studies. For this reason, such highly variable infection rates are reported in the literature. Among potential risk factors described in the literature, none were found in our study to be directly associated with documented infections.

Multidisciplinary clinical guidelines are needed to provide an approach that prioritizes accurate monitoring of data, rigorous implantation techniques, standardized protocols, and more dynamic and aggressive management for the explantation of the IDs in selected cases.

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