

Prevention and Management of Intrathecal Drug Delivery and Spinal Cord Stimulation System Infections

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FULLY implantable devices or drug–device combinations, such as intrathecal drug delivery (DD) systems and spinal cord stimulation (SCS) systems, increasingly are used for the treatment of chronic intractable pain.[1,2] Another approved indication for intrathecal DD systems is the administration of intrathecal baclofen (ITB) to treat medically intractable spasticity of spinal or cerebral origin.[3–5] Although patients with cancer, spinal cord injuries, or cerebral palsy have a reduced life expectancy, the majority of intrathecal drug administration devices—and nearly all SCS devices—are implanted in patients with painful non–cancer-related disorders that are associated with a normal life span. Therefore, long-term implantable devices used for the treatment of pain and spasticity should have a relatively benign safety record.[6,7] Device-related infection is the most common, potentially reducible, serious adverse event associated with intrathecal DD or SCS devices.

Reducing the number of implantable DD and SCS device infections is important for various reasons. One is that treatment of an established infection often involves temporary or permanent removal of the device, which causes cessation of drug or stimulation therapy. Therapy cessation (with or without eventual device replacement) increases the risks, discomfort, inconvenience, and expenses of patients who experience infectious complications. Abrupt cessation of intrathecal drug therapy may precipitate drug withdrawal symptoms and, in the case of ITB, can have fatal consequences.[8] In rare cases, device-associated infections can progress to fatal sepsis, meningitis, or both.

Available data indicate that implantable DD and SCS device infections share important features with other surgical site infections (SSIs), including those that affect cerebrospinal fluid (CSF) shunts and electrophysiologic cardiac devices such as implantable pacemakers and cardioverter–defibrillators (ICDs). Management of infections associated with DD and SCS systems typically involves administration of antibiotics and explantation of the devices. Measures that reduce the incidence of other SSIs also should reduce the infection rate associated with the implantation of SCS and intrathecal DD devices.

Materials and Methods

Sources of Data and Literature Reviewed

The authors reviewed data pertaining to infections associated with DD and SCS. Sources of data included published[1] and unpublished clinical study data, postmarket and medical device reporting (MDR) data, published meta-analyses, US Centers for Disease Control (CDC) guidelines and other selected publications about prevention of SSIs,[9,10] and pertinent studies from the CSF shunt infection literature[11–42] and from the ICD infection literature.[43–51] Clinical study data included information about implanted DD and neurostimulation systems marketed by Medtronic, Inc. (Minneapolis, MN). Information regarding device-related infections was available from three monitored multicenter device studies (model 8709 catheter, SynchroMed® 10-ml pump, and IsoMed® pump) and one monitored multicenter study of an investigational intrathecal drug. The 8709 catheter study results were published previously.[1] Results of the two pump studies and one intrathecal drug study are unpublished to date.

The postmarket and MDR data included information about implanted DD and neurostimulation systems reported to the device manufacturer (Medtronic, Inc.), information which is reported also to the US Food and Drug Administration. The DD and SCS infection data analyzed in this review were reported between September 1, 2000, and July 1, 2002. Because of confidentiality regulations and voluntary reporting practices, it was not possible to audit postmarket surveillance data by comparing the information voluntarily reported by healthcare professionals, patients, or both to original medical records. Such limitations undoubtedly caused cases of DD or SCS device–related infections to go unreported.

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Reasons for considering DD and SCS devices together and for including a focused review of the recent CSF shunt and ICD infection literature include the following: Allowing for the differences in patient populations, underlying disease states, and other factors—CSF shunts and DD devices both involve catheterization of the subarachnoid space with a fluid-conduit system and, like SCS, involve tunneling a portion of the implanted system subcutaneously between two anatomical sites. Neurosurgeons implant and manage virtually all patients with CSF shunts and implant a substantial proportion of DD and SCS devices. In general, neurosurgeons use similar methods to minimize the occurrence of infections associated with each type of implant surgery. ICD and SCS devices are similar to each other in size and appearance but are smaller than DD pumps. ICD implantation also involves tunneling from one anatomical site to another. Infection is a frequent, serious, and potentially reducible complication associated with implantation of all of these devices (DD, SCS, CSF shunts, and ICD). Reported infection rates for the various devices are comparable.[1,2,4–6,11–51] Despite the differences between DD and SCS devices and therapy, a review of the postmarket infection surveillance data presented in this article revealed similarities in most of the factors that were examined.

The risks, prevention, and management of infections associated with implantable DD and SCS systems have not been explored in detail. In contrast, the CSF shunt and ICD infection literature is substantial. The CSF shunt infection literature contains reliable, high-level evidence regarding patient-related risk factors and methods to minimize the incidence of infection. Given the similarities among the various kinds of device-related infections, information from the medical literature and data from clinical trials and postmarket surveillance can be used to formulate general guidelines and recommendations for the prevention and management of DD and SCS infections.

Definition of Device-related Infections

The diagnosis of an implantable device–related SSI is established definitively by identification or culture of microorganisms (most commonly bacteria) 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 CSF involvement. Most cases reported in the postmarket and clinical studies reviewed in this article met those strict criteria. However, the need to begin treatment of suspected infections that involved device components implanted within the spinal canal sometimes prompted physicians to begin antibiotic therapy, to remove devices without waiting for the results of cultures or stains, or both. It is possible that some device infections reported by clinicians and investigators were misdiagnosed (false–positives).

Results

Intrathecal Drug Delivery

Clinical Studies. The device-related infections that occurred in four DD device or drug–device clinical studies are summarized in table 1. The aggregate total period at risk for the occurrence and detection of an infection in those studies was 7,620.8 device-months. Limitations include different data collection periods in each study (mean follow-up varied from 6.4 to 14.1 months) and the fact that none of the studies specifically was designed to investigate device-related infections. Another limitation was that the diagnosis of an infection in each study did not have to meet all of the criteria defined in the previous section. However, all cases had clinical signs, bacteriologic evidence of infection, or both. In addition, the studies were mandated by the US Food and Drug Administration and were monitored in accordance with US Food and Drug Administration and international standards (table 1).[1] Those features increase the likelihood that all device-related infections were identified and reported. The infection rates, based on the number of infections that occurred and the number of patients that were enrolled in each study, varied from 2.5 to 9.0% of implanted patients. The highest infection rate, 9%, occurred in the 10-ml SynchroMed® pump study. That study cohort consisted of pediatric patients with spasticity of cerebral origin, predominantly spastic cerebral palsy (n = 90 of 100 patients). The lowest infection rate, 2.5%, occurred in the trial of intrathecal recombinant methionyl human brain-derived neurotrophic factor (BDNF) to treat amyotrophic lateral sclerosis. Combining all studies, 36 infections involving 35 separate patients were reported in a total of 700 patients (5% overall infection rate).

Device infections reported in the various clinical studies shared common characteristics. The majority of infections in each study (57–80%) involved the pump pocket site. The aggregate proportion of cases that were treated with complete or partial device removal also varied from 57 to 80%. The individual investigators made the decision to explant all or part of the device in each case. The small numbers of cases precluded further meaningful analysis, and differences between the proportions that predominantly involved the pump pocket in each clinical study did not seem to be remarkable. The available data also did not allow us to determine whether the 57–80% figures for pocket site involvement and device removal among the clinical trials were the same or different individuals. All of the patients experienced resolution of their infections by the time each study or observation period had ended. No deaths or episodes of drug withdrawal were reported.

Table 1. Comparison of Drug Delivery Device–Related Infections in Multicenter Studies

Devices	Pump Studies		Catheter Study: 8709 One-piece Catheter	Drug Study: BDNF and 18-ml SynchroMed Pump‡
	10-ml SynchroMed® Pump*	IsoMed® Fixed Rate Pump†		
Indications and No./% of patients	Spastic CP 90/90%	Noncancer pain 103/93.6%	Noncancer pain 152/73%	ALS
	Brain injury 5/5%	Cancer pain 7/6.4%	Cancer pain 10/5%	
	Other etiology 5/5%		Spasticity 47/22%	
	Total 100	Total 110	Total 209	Total 281
No. of infections/infection rate	9/9%	5/4.5%	15/7%§	7/2.5%
Patient age, mean (range), yr	8.1 (1–16)	51 (26–88)	51 (21–94)	53.2 (22–76)
Duration of follow-up				
Mean/range, months	11.8/0.5–17	6.4/0.1–14.5	8.4/0–24.8	14.1/0–22.8
Cumulative device-months	1,178	704.8	1,764	3,973
Implanter specialty	Neurosurgery	Anesthesiology and neurosurgery	Anesthesiology and neurosurgery	Neurosurgery
Infected sites, No./% of infections				
Pump pocket	6/67%	4/80%	11/73%	4/57.1%
Lumbar site	3/33%‖	1/20%	2/13%	2/28.6%
Meningitis	1/10%‖	—	2/13%	1/14.3%
	1 lumbar + meningitis‖			
Device explantation, No./% of infections				
Total	5/55%	4/80%	9/60%	4/57%
Partial	—	—	1/7%	—
Not explanted	4/45%	1/20%	5/33%	3/43%
Time: implantation to infection, No./% infections				
≤ 1 month	3/33%	4/80%	11/73%	6/86%
≤ 2 months	3/33%	—	1/7%	—
> 2 months	3/33%	1/20%	3/20%	1/14%
Infections resolved, No./%	9/100%	5/100%	15/100%	7/100%

All pediatric patients with cerebral origin spasticity had at least two risk factors for infection; all adult patients with amyotrophic lateral sclerosis (ALS) had at least one risk factor for infection (debilitated status). Risk factors are enumerated in the text.

* SynchroMed® model 10-ml pumps, post-approval study, protocol No. D97-062, final report, January 24, 2002. † Medtronic IsoMed® Implantable Fixed Rate Infusion System, P990034/Amendment 3. November 19, 1999. ‡ Device Safety Information, protocol 970278: A randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of recombinant methionyl human brain-derived neurotrophic factor (r-metHuBDNF) when given by intrathecal infusion to subjects with amyotrophic lateral sclerosis (ALS), Device Objective Study Report. November 8, 2001. § 14 patients experienced 15 infections in the 8709 catheter study (one patient had two infections at 4.5 and 13.3 months after enrollment). ‖ One patient in the 10-ml pump study simultaneously had meningitis and an infected lumbar site.

BDNF, recombinant methionyl human brain-derived neurotrophic factor; CP, cerebral palsy.

Apparent differences between the 10-ml pump study cases *versus* the other three studies included a relatively lower proportion of infections diagnosed within 1 month compared with those diagnosed longer than 2 months after implantation. Data from the 8709[1] and BDNF studies were analyzed to detect differences in the rate of device-related complications after implant procedures by individual implanters or at different centers. Although the overall rate of implant-related device complications varied from 0 to 100% among centers and implanters in those two studies, there were no implanter- or implanter specialty–related (anesthesiology *vs.* neurosurgery) differences in the device infection rate. None of the studies summarized in table 1 specifically collected information related to underlying risk factors for device-related infection, and none were designed to enroll enough patients to detect differences in the infection rate among the different implanters or investigative centers.

Postmarket Data and Medical Device Reports. The results of postmarket surveillance and MDR analyses of 116 infections that involved Medtronic, Inc., intrathecal DD devices and that were reported to the company between September 1, 2000, and March 1, 2002, are summarized in the center column of table 2. Because of the limitations associated with postmarket MDR, the incidence of device-related infections could not be estimated or calculated from these data. The percentages shown in table 2 refer only to the proportion of infected cases that shared the particular feature or factor addressed in each row of the table.

Fifty-two percent of DD cases had noncancer pain, 1% had cancer pain, and 42% had spasticity, and in 5%, the underlying diagnosis was not reported. Seventy percent of DD cases had concomitant illnesses or medical conditions that may have increased the risk for an SSI (table 2). These risk factors were identified retrospectively at the time of the initial report. Information was supplied

Table 2. Postmarket Surveillance Data: Drug Delivery and Spinal Cord Stimulation Device–related Infections

	Drug Delivery, Postmarket Data, September 1, 2000–March 1, 2002, No./% of 116 Cases with Infection	Spinal Cord Stimulation, Postmarket Data, September 1, 2000–July 1, 2002, No./% of 114 Cases with Infection
Device models	Pumps: 18 ml: 113/97% 10 ml: 3/3%	Power source: IPG: 106/93% RF coupled: 8/7%
Indication		
Noncancer pain	60/52%	114/100%
Cancer pain	1/1%	—
Spasticity	49/42%	—
Not reported	6/5%	—
Perioperative antibiotics		
Antibiotics used	90/78%	99/87%
Antibiotics not used	6/5%	1/1%
Unknown or not reported	20/17%	14/12%
Infected sites or components		
Pocket (IPG or pump)	84/72%	61/54%
Tract (lead or catheter)	10/9%	19/17%
Lumbar site	6/5%	9/8%
Multiple sites	8/7%	16/14%
Other, or site not reported	8/7%	9/8%
Any site plus meningitis	10/9%, in addition to other sites	—
Bacterial cultures		
Cultures performed	94/81%	95/83%
Cultures not performed	3/3%	5/4%
Unknown or not reported	19/16%	14/12%
	No./% of 94 Cultures Performed	No./% of 95 Cultures Performed
Culture results		
Staphylococcus species	55/59%	46/48%
Pseudomonas species	3/3%	3/3%
Multiple or other species	7/7%	6/6%
No growth	10/9%	17/18%
Unknown or not reported	19/20%	23/24%
Antibiotic treatment		
Intravenous	50/43%	46/40%
Oral	5/4%	18/16%
Intravenous and oral	41/35%	45/39%
Not reported	20/17%	5/4%
Device explantation		
Total	110/95%	94/82%
Partial	3/3%	14/12%
Not explanted	2/2%	4/4%
Not reported	—	2/2%
Interval: implantation to explantation, range, months	1–43	1–104
$\leq$ 1 month	46/40%	43/38%
$\leq$ 2 months	15/13%	21/18%
$>$ 2 months	39/34%	39/34%
Device not explanted	—	1/1%
Interval not reported	10/9%	10/9%
No. of risk factors*		
Zero	35/30%	71/62%
One	55/47%	34/30%
Two	19/16%	7/6%
Three or more	8/7%	2/2%
Outcome		
Resolved, no complications	88/76%	104/91%
Resolved, drug withdrawal	15/13%	—
Event ongoing at time of report	3/3%	3/3%
Death (cause)	1/1% (meningitis and sepsis)	—
Outcome not reported	8/7%	7/6%

* Risk factors for infection or poor wound healing included diabetes, debilitated status, malnutrition, extremely thin body habitus, obesity, autoimmune disorder, corticosteroid use, decubitus ulcers, preexisting infection, poor hygiene, urinary or fecal incontinence, and malabsorption syndrome.

IPG = implantable pulse generator; RF = radiofrequency.

most often by the treating physician or another healthcare professional—but sometimes from patients or family members. Because of limitations described above, data could not always be confirmed. Within the limitations of postmarket data collection and analysis, implanter specialty (anesthesiology *vs.* neurosurgery) did not seem to correlate with the number of reported infections or with any other factors that were examined.

Seventy-eight percent of DD patients were given perioperative antibiotics, and the pump pocket was the most common site of infection. Cultures of infected sites grew *Staphylococcus species* in 59% of DD cases (85% of cases with positive cultures); no growth was reported in 9% of cases. Most reports did not specify whether the cultured *Staphylococcus* organisms were *S. aureus* or *S. epidermidis*. *Pseudomonas*, the second most frequently cultured organism, accounted for only 3% of infections. No positive fungal cultures were reported.

Forty-three percent of DD cases received parenteral (intravenous) antibiotics, and 36% received parenteral and oral antibiotics to treat their infections. Physicians elected to remove the devices completely or partially to clear the infections in 98% of cases (table 2). The majority of device infection and explantation events occurred within 2 months after implantation. The aggregate proportion of infected DD systems removed within the first 2 months after implantation was 53% (40% at $<$ 1 month, 13% at 1–2 months). Seventy-six percent of cases resolved without sequelae, but in 13% of cases, patients experienced nonfatal drug withdrawal symptoms as a consequence of device removal and therapy interruption. One DD patient died from generalized sepsis and meningitis.

Spinal Cord Stimulation

Postmarket Data and Medical Device Reports. We are not aware of published clinical studies of SCS devices that are comparable to the ones described for DD devices. The results of postmarket surveillance and MDR analyses of 114 infections that involved Medtronic, Inc., implantable SCS devices, and that were reported to the company between September 1, 2000, and July 1, 2002, are summarized in the right-hand column of table 2. All SCS cases had noncancer pain, and 38% had medical conditions that may have placed them at increased risk for an infection (table 2). These risk factors were identified retrospectively in the same manner as for DD cases.

As was the case for DD clinical trial and postmarket data, implanter specialty (anesthesiology *vs.* neurosurgery) did not seem to influence the number of reported infections or to be associated with any other infection-related factors. Eighty-seven percent of patients were given perioperative antibiotics, and the implantable neurostimulator or receiver pocket was the most common site of infection. Cultures of infected SCS device sites also yielded *Staphylococcus species* in a plurality of cases (48% of infected cases; 84% of cases with positive cultures). No growth was reported in 18% of SCS cases, double the proportion reported for DD. Again, growth of *S. aureus versus S. epidermidis* usually was not specified; *Pseudomonas* also caused 3% of SCS device infections; and no cultures were positive for fungi.

Forty percent of SCS patients received intravenous antibiotics, and 39% received intravenous and oral antibiotics to treat their infections. Physicians decided to completely or partially remove the infected SCS devices in 94% of SCS cases. The percentage of infected SCS systems removed during the 2-month postimplantation interval was 56% (38% at $<$1 month, 18% at 1–2 months). Ninety-one percent of SCS cases experienced successful resolution of their infections; no patients died.

Discussion and Recommendations

Surgical Site Infections: Literature and Data Review

CSF Shunt Literature. Cerebrospinal fluid shunts share common features with DD and SCS systems. The devices are implanted by neurosurgeons who most likely use similar infection prevention and management techniques for each type of implant surgery. Principles and methods that are effective to reduce the incidence of and to manage CSF shunt infections also should apply to DD and SCS systems. Findings from a selective review of the CSF shunt literature that are pertinent to DD and SCS device infections are listed and referenced in table 3. Other possible shunt infection–related factors that do not apply to adults implanted with DD or SCS systems were not included. A history of previous device revisions or infections seemed to increase the risk for subsequent infection only under limited circumstances that included multiple revisions, an interval of less than 6 months between repeated operations, or both.[17,30,36] Postoperative CSF leakage[26] increased the risk of infection in some series but not in others.[14,33] Analysis of the responsible surgeon's skill or experience and the duration of the implant operation, factors which may be interrelated, were significant in some studies[13,23,24,39] but not in others.[20,22,30,36]

Perioperative antibiotic administration emerged as a significantly effective prophylactic measure predominantly when the infection rate in the control group or study period was relatively high[23,27,29,37] or when data from different studies were combined in meta-analyses.[21,28] Determining the efficacy of perioperative antibiotics in reducing shunt infection rates is difficult to accomplish in a statistically significant manner because of the relatively low overall infection rate. No study to date strongly supports the use of one particular perioperative antibiotic regimen over another, but a major determinant for effective prophylaxis may be administration of the antibiotic before the actual skin incision.[9,10]

Table 3. Selected Factors Studied for Association with Cerebrospinal Fluid Shunt Infections and for Applicability to DD and SCS System Infections

Factors Evaluated	References That Found a Significant Association	References That Found Minimal or No Association
Patient-related factors		
CSF leakage	26	33
Poor skin condition	33	—
Intercurrent infection	33	—
Urinary tract infection	35	29
Seizures	—	30
Surgery-related factors		
Primary implant *vs.* first revision	—	13, 14, 20, 42, 30, 33
Multiple revisions	17, 30 (especially within < 6 m), 36	—
Surgeon or duration of surgery	13, 23, 24, 39	20, 22, 30, 36
Perioperative antibiotics	21, 23, 27–29, 37	20 24, 36, 41
Specific antibiotic	—	21, 28, none superior
Shaving of scalp	22 (worse)	—
Restrict operating room	42 (plus other measures)	—
Time of day (first case or other)	—	12, 23
Breached surgical gloves (retrospective)	26	—
Other factors		
Shunt design (one piece)	20, 30, 38, 40	15, 16, 24, 29, 36
Infectious agent		
Staphylococcus species	14, 17, 23, 24, 25	—
S. epidermidis >> *S. aureus*	16, 19, 23, 29	—
Interval from implantation to infection		
15–60 days	18, 28	—
50–70% within 1 month	12	—

CSF = cerebrospinal fluid; DD = drug delivery; SCS = spinal cord stimulation; >> = much greater than.

Another common practice, shaving the patient's scalp before surgery, seem to increase the risk of infection.[22] Scheduling surgery as the first morning case, limiting operating room entry or egress during surgery, and other personnel management strategies have not reduced shunt infection rates unless those measures were part of a larger infection reduction program.[12,23] A few studies have found a correlation between one-piece shunt designs and lower infection rates,[20,30,38,40] whereas other studies found no correlation.[15,16,24,29,36]

As was the case for implantable DD and SCS system–related infections, most shunt infections occurred relatively soon after implantation and were caused by *Staphylococcus* species. The majority occurred within 60 days after implantation in case series and meta-analyses[18,28] and within 1 month after implantation in another published series.[12] *Staphylococcus* species accounted for 50–92% of infections in several series,[14,17,23–25] and *S. epidermidis* was the single most commonly identified organism.[16,19,23,29]

Implantable Electrophysiologic Cardiac Devices. Despite the differences in patient populations, indications for device implantation, and medical specialties of the implanting physicians, ICDs share features that are relevant to infection reduction and management with DD and SCS devices. Estimated infection rates for ICDs varied from 1 to 7%.[43] Factors associated with higher ICD infection rates included complex operative techniques and longer operating times (*e.g.*, thoracotomy *vs.* transvenous placement),[44,46,47] lead insertion in a procedure room rather than in a formal operating room, or both.[44] Infections were more common after battery end-of-life device replacement than after the initial implantation.[44] The most commonly cultured organisms were *Staphylococcus* species, and treatment in most cases involved explantation of the system in conjunction with antibiotic administration.[43–48] Efforts to eradicate the infection without device removal or with partial device removal were associated with lower success rates and higher relapse rates.[43–48] To date, small studies have not shown lower infection rates after prophylactic antibiotic administration at the time of initial device implantation.[49,50]

Infection Prevention Guidelines and Recommendations. Pertinent information from the most recent version of SSI prevention guidelines published by the CDC is summarized in table 4. Additional recommendations derived from a review of the CSF shunt literature and from postmarket surveillance data on DD and SCS device infections are included among the class II recommendations in table 4 as well. The original document and a subsequent review applied broadly to the practice of general surgery and other surgical specialties.[9,10] Guidelines on preoperative bowel preparation and other factors not relevant to the current review are omitted from the table.

Similarities between DD and SCS System Infections and Other SSI. In contrast to patients with different indications or surgical infection risks or both, the results of device and drug–device clinical studies, post-

Table 4. Recommendations for the Prevention and Management of DD and SCS Device Infection

Patient selection, preparation, surgical planning, and preoperative hand and forearm antisepsis
- Category IA
  - Identify and treat all remote infections before elective operation; postpone surgery until treated.
  - Do not remove hair unless removal is necessary to facilitate surgery.
  - If hair is removed, do so immediately before surgery, preferably with electric clippers.
- Category IB
  - Control serum blood glucose perioperatively.
  - Patients should discontinue tobacco use 30 days before surgery.
  - Do not withhold necessary blood products to prevent SSI.
  - Require patients to shower or bathe with an antiseptic agent at least the night before surgery.
  - Perform surgical scrub for at least 2–5 min with an appropriate antiseptic.
  - After scrub, keep hands up and away from body, dry hands with sterile towel; don sterile gown and gloves.
  - Wash incision site before performing antiseptic skin preparation with approved agent.
- Category II
  - Prepare skin in concentric circles from incision site.
  - Keep preoperative stay in hospital as short as possible.
  - Device implantation may proceed, albeit at increased risk, in patients—especially those with spasticity or cancer pain—in whom remote infections or other risk factors cannot be eradicated or resolved completely.
  - Select device or model suitable for patient's size and body habitus.
  - Consider surgical scars, ostomies, seat belt or wheelchair use, and clothing or belt line in selection of device pocket site.
  - If practical, mark the device pocket site preoperatively with the patient in the standing position.

Surgical and operating room management
- Category II
  - Perform implant surgery in an operating room rather than a procedure room.
  - Minimize operating room traffic during implant surgery.
  - Use sterile draped fluoroscope to expedite case and to avoid contamination by portable x-ray equipment.

Antimicrobial prophylaxis
- Category IA
  - Administer antimicrobial agent only when indicated, and with efficacy against most common pathogens.
  - Use intravenous route to achieve adequate serum concentrations during surgery and for at most a few hours after incision is closed.
- Category IB
  - Do not routinely use vancomycin for antimicrobial prophylaxis.

Surgical procedure
- Category II
  - Use double glove and minimal-touch or no-touch surgical techniques.
  - Avoid placing devices directly under incision lines.
  - Close the implant site incisions in anatomical layers, consider subfascial placement in small or underweight patients.

Postoperative care
- Category II
  - Apply occlusive, antiseptic wound dressings; perform the initial dressing change using sterile technique.
  - Treat threatened incisions and external CSF leaks promptly and aggressively.

Treatment of established infection
- Category II
  - Remove infected components or entire system as indicated.
  - Taper intrathecal drugs or administer substitute medication systemically or both to prevent or treat intrathecal baclofen or opioid withdrawal when a drug delivery system is removed because of infection.
  - Administer antibiotics directed at the responsible organism as determined by wound cultures and stains.

Device reimplantation after treatment of infection
- Category II
  - Ensure complete and permanent eradication of the infection off antibiotic therapy before device reimplantation.
  - Implant the new device in a site that was not involved in the previous infection.

Surveillance
- Categories IB and II
  - Use CDC definitions and a combination of direct and indirect case finding methods to identify SSI among inpatients and outpatients.
  - Prospectively record surgical wound classification and other factors associated with SSI risk.
  - Periodically calculate risk-stratified, operation-specific SSI rates, and report the results to surgical team members.

Definitions of category rankings (category IA and IB recommendations are adapted from Mangram *et al.*[9] and Nichols[10]): IA = strongly recommended for implementation and supported by well-designed experimental, clinical, or epidemiologic studies; IB = strongly recommended for implementation and supported by some experimental, clinical, or epidemiologic studies and strong theoretical rationale; II = suggested for implementation and supported by suggestive clinical or epidemiologic studies or theoretical rationale. Category II recommendations have not necessarily been validated by controlled studies.

CDC = Centers for Disease Control; CSF = cerebrospinal fluid; DD = drug delivery; SCS = spinal cord stimulation; SSI = surgical site infection.

market surveillance and MDR data, and literature regarding surgical site, cardiac device, and CSF shunt infections all support the notion that DD and SCS system infections share common features with other SSIs. A substantial body of evidence and theoretical reasoning support the use of practical approaches aimed at reducing the incidence of such infections and also provide a rational basis for infection management strategies.

Drug delivery and SCS system infections tend to occur relatively early after implantation, predominantly involve the abdominal pocket site (largest device component), and are caused by *Staphylococci*, specifically *S. epidermidis*, which arises from the skin of the patient or operating room personnel.[52] The data strongly suggest that most DD and SCS system infections arise from surgical wound contamination at the time of device implantation. By inference, the postmarket data also suggest that perioperative antibiotic prophylaxis in the absence of other infection-control measures is insufficient to prevent device-related infections. However, the number of infectious complications might be reduced by conscientious adherence to the established principles of surgical antisepsis that appear in the recent CDC recommendations.[9,10]

Recommendations to Minimize the Risk of Infection

Patient-related Factors, Surgical Preparation, and Preoperative Planning. The majority of DD implants and virtually all SCS implants are performed electively in adult patients and are intended to improve the patient's quality of life. In most cases, ample time is available preoperatively to follow the guidelines and recommendations that are summarized in table 4. However, certain patients or situations present exceptions to the recommended practices that govern preparation and planning for elective surgery. Some patients with cancer pain or intractable spasticity have underlying medical conditions that cannot be improved or resolved completely before implantation of DD devices. For example, CDC recommendations (table 4) to "identify and treat all remote infections before elective operation; postpone surgery until treated" and to "keep preoperative stay in hospital as short as possible" may be unrealistic for hospitalized patients with severe cancer pain or spasticity who also have any of the risk factors identified in table 2 (diabetes, debilitated status, malnutrition, extremely thin body habitus, obesity, autoimmune disorder, corticosteroid use, decubitus ulcers, preexisting infection, poor hygiene, urinary or fecal incontinence, malabsorption syndrome).

Another potential patient-related risk factor, nasal colonization with *S. aureus*, can be eliminated by the application of mupirocin nasal ointment preoperatively, postoperatively, or both. However, the results of open studies and controlled trials were either contradictory or not as robust as anticipated.[9,10,53,54] None of the studies specifically addressed DD or SCS device implantation, although neurosurgical cases were included in the largest controlled trial.[53] One important finding that limited the efficacy of mupirocin was that a majority of *Staphylococcal* SSI were caused by different strains of bacteria than the ones that had colonized the patients' nares.

In cases in which risk factors such as malnutrition or thin body habitus cannot be altered, selection of the implantable device can take the patient's body size and soft tissue dimensions into account. Preoperative considerations to minimize the likelihood of long-term hardware erosion through the skin and other implant-related complications have been described previously.[6] For example, an infusion pump with a smaller reservoir and lower profile may be better suited for the pediatric patient population than the larger pump customarily implanted in adults. Other preoperative considerations that might reduce the incidence of wound breakdown and infection include preoperative consideration or examination of the patient for surgical scars and existing or anticipated ostomy sites, considerations of automobile seat belt use, wheelchair use, clothing styles or belt locations, and avoidance of pump impingement on the rib cage or iliac crest.[6] Failure to take such factors into consideration can result in device malposition, which may lead to excessive pressure on the surgical incision, increasing the potential for wound breakdown or infection. If the anticipated benefits of the proposed therapy are substantial, one may decide to proceed with device implantation in high-risk patients after discussing the potentially increased risk of infection with the patient, the family, or both.

Surgical and Operating Room Management. The broad CDC SSI guidelines did not address specific operating room management factors that were investigated in some studies of CSF shunt infection rates.[13,14,20,24,30,33] None of the studies confirmed that the time of day at which an operation was performed influenced the likelihood that an infection would occur. However, two studies found that restricting nonessential personnel from entering the operating room during surgery (as part of a larger concerted effort to reduce the shunt infection rate) seemed to make a positive contribution.[12,23] The incidence of infection of cardioverter devices is lower when implantation is performed in a formal operating suite rather than in a procedure room, and as part of a larger infection reduction effort.[44] Such practices seem to be prudent and justified on theoretical grounds.

Spinal cord stimulation device implantation procedures nearly always involve intraoperative fluoroscopy to guide or confirm proper lead placement, and some implanters of DD devices routinely use intraoperative fluoroscopy. It seems prudent, based on theoretical grounds, that whenever use of intraoperative imaging is anticipated, physicians should drape the fluoroscopy unit within the sterile operative field at the start of the procedure. This maneuver should help to reduce the potential for contamination of the surgical field and implantable devices.

Surgical Procedure and Postoperative Care. The efficacy of perioperative prophylactic antibiotics remains unsettled in the CSF shunt and ICD literature. Nonetheless, the available evidence indicates that it is reasonable to administer perioperative antibiotics for DD and SCS implantation procedures. The specific antibiotic

should be selected according to the experience and preference of the implanting surgeon, taking into consideration institutional variations in the antibiotic sensitivity of organisms that are responsible for most postoperative infections. In general, a single dose of an antibiotic effective against gram-positive skin flora should be administered within 1 h before the skin incision. More potent or later generation antibiotics or both may be considered in special cases, *e.g.*, in patients with drug allergies or previous infections with resistant organisms. Available data do not support the use of additional postoperative antibiotics.[6]

Careful preparation of the surgical sites with antiseptic agents and careful sterile draping are important parts of any surgical procedure. These steps are especially critical in the setting of device implantation. No data indicate a clear superiority of any preparation agent or technique over other available techniques.

Given the finding of a relatively high incidence of breached surgical gloves in a recent study,[26] the use of double gloves and some variant of minimal-touch or no-touch surgical techniques may reduce the incidence of device related infections. No-touch surgical technique refers to handling the implantable device only with surgical instruments, not with gloved hands. Other techniques to minimize device handling include the selection of devices and components that require the fewest number of connections or implant accessories (*e.g.*, anchors, connectors, screws, strain-relief sleeves).

Placement of surgical incisions to avoid suture lines crossing over the implanted devices, and the closure of incisions in anatomic layers with obliteration of dead space are standard practices among many CSF shunt and DD or SCS implanters. Careful hemostasis is important. Inadequate hemostasis, especially at the pump or stimulator pocket site, may predispose to seroma formation, infection, or both, although there are no data that indicate the technique used to form the subcutaneous pocket (*i.e.*, sharp *vs.* blunt dissection) influences the likelihood of seroma formation or the incidence of pocket infection. The results of one *in vitro* and *in vivo* laboratory study of various suture materials "showed that immobile bacteria can propagate inside multifilament materials. The spreading was correlated to the capillary properties of the threads. A similar result was obtained in an *in vivo* study in the muscle of the rat."[55] These findings and practices have a sound theoretical basis, especially for the most frequently infected sites: the DD pump and SCS neurostimulator pockets. Creation of an adequately sized pocket minimizes the tension placed on wound closure. Anatomically layered closure of an adequately sized pocket may reduce the incidence of skin erosion or wound dehiscence around the largest component of the implantable system. Investigators recently have published a detailed description of the subfascial (rectus sheath) implantation technique for use in small or underweight patients with spasticity who are candidates for ITB therapy.[56] Placement of the pump in a tissue layer deeper than the usual subcutaneous location may prevent some instances of wound dehiscence or skin erosion.

In the event that threatened wound dehiscence, skin erosion, or external CSF leakage (in DD systems) is identified, prompt and aggressive medical and surgical intervention is appropriate. No data exist regarding the likelihood of success if one attempts to salvage a threatened DD or SCS implant with nonoperative measures. Successful treatment of CSF shunt infection most often requires explantation of the shunt, and the ICD infection literature indicates that treatment regimens that attempt to salvage the implanted device usually fail.[43,44,48] However, anecdotal reports and clinical experience suggest that wound repair and, if indicated, parenteral antibiotic administration are most likely to be effective when instituted as early as possible in the patient's clinical course.

Because device programming often is required during the early postoperative period (*e.g.*, in the recovery room) and because the programmer head is not sterile, application of a sterile, occlusive dressing immediately after closure of the surgical incision may reduce the likelihood of wound contamination. Dressings should cover the incision line and should not be so bulky that they interfere with device programming. The timing and details of the first postoperative dressing change may vary with surgeons' preferences as long as the procedures avoid contamination of the surgical wound.

Special Situations and Risks

Drug Delivery. Early or delayed DD system infections in pediatric patients with spasticity of cerebral origin warrant special consideration. Although prospective data are lacking, anecdotal reports and information from the 10-ml SynchroMed® pump study suggest that patient-related risk factors may make such children particularly vulnerable to both early and late infections. In retrospect, many pediatric patients with spasticity of cerebral origin had comorbidities potentially associated with early device infections, including debilitated status, malnutrition or extremely lean body habitus, decubitus ulcers, preexisting infection, poor hygiene, and urinary or fecal incontinence. Even use of the relatively thin 10-ml pump in that study did not eliminate pocket infections. Among the nine reported infections, six (67%) involved the pump pocket, six occurred approximately 2 months after implantation, and the other three occurred between 4 and 13 months after device implantation (table 2). Data were not collected on the use of subfascial implant techniques in that study, so it remains unknown whether that measure would have reduced the infection rate. Still, implanters should strongly consider the use of smaller devices and subfascial placement to ameliorate infectious risk factors that may be present

in pediatric spasticity patients.[56] Another potential risk for device infection in the 10-ml pump study was that an unknown number of patients had temporary intrathecal catheters placed for use with external pump systems to allow an extended trial of continuous ITB administration over several days before permanent device implantation. Such procedures may have caused subclinical bacterial contamination of the surgical site or CSF before the final implant operation.

Some adult patients with cancer pain and underlying nutritional deficiencies or remote infectious conditions also may be at increased risk for device-related infections. When assessing such individuals for device implantation, especially if the therapy is expected to provide palliative benefits or improve the patient's quality of life, strict adherence to the recommendations to "identify and treat all remote infections before elective operation; postpone surgery until treated" and to "keep preoperative stay in hospital as short as possible" may not be possible or practical. In fact, in the case of spastic adults or children with contaminated decubitus ulcers, ITB therapy may facilitate local measures to cleanse or heal the skin lesions or both.

Spinal Cord Stimulation. Another infectious risk may apply to percutaneously inserted SCS leads, which constitute the majority of stimulation leads marketed in the United States (R. Coffey, Medtronic, Inc., Minneapolis, Minnesota, 2003). Postmarket surveillance data revealed that the aggregate total proportion of lumbar site plus multiple site infections was 22% of reported SCS device infections compared with 12% of reported DD device infections. Such comparisons of attributable risks should not be overstated because of limitations that include completeness of the data and potential differences between the data sets. However, implantation of percutaneous stimulation leads necessarily involves monitoring the procedure under fluoroscopic guidance and recording the awake patient's responses to test stimulation using different electrode selections, device settings, or both—a process that is more complicated and time consuming than implantation of intrathecal catheters. In most instances, percutaneous SCS electrodes are brought out directly through skin, or extension wires are attached temporarily to implanted SCS leads and tunneled externally to allow testing of efficacy of therapy for a few days before permanent device internalization during a second procedure. The duration and complexity of the lead implantation procedure, the use of a percutaneous lead or extension during a trial period that lasts for days or weeks, and the need for a second-stage implant operation all might contribute to the spinal and multiple-site infections observed in SCS patients. Avoidance of the potentially contaminated temporary lead–extension tract when internalizing SCS leads after the trial period and placement of the neurostimulator pocket on the side of the body opposite the location of the temporary lead or extension wire tract are ways to mitigate those risks. If the permanent electrode or extension wire or both must be implanted at the same cutaneous/subcutaneous site used for the temporary trial, a delay between removal of the trial system and implantation of the permanent SCS system may reduce the risk of contamination of the new system. In addition, the permanent internalization of percutaneously inserted SCS trial leads during a second-stage neurostimulator implant operation requires removal of the temporary extension wires. Those wires should be withdrawn by having a nonscrubbed assistant pull on the external (nonsterile) extension from outside the sterile operative field after the implanter has disconnected it from the extraspinal end of the stimulation lead.

Surveillance. The DD or SCS team can know their infection rate—and how it compares to that of other institutions— only if they establish prospective methods to capture eligible patients at the time of implantation (denominator) and cases with infections (numerator) at the time of diagnosis or treatment. The trend toward short postoperative hospital stays, the division of care among various outpatient clinic and office settings, and the fact that most infections are diagnosed after discharge from the surgical center mean that effective surveillance requires cooperation among personnel at different venues. CDC guidelines recommend a combination of direct observation and case finding methods (*e.g.*, hospital readmission) to detect cases.[9] Case loads and the results of initial surveillance efforts can help centers to determine how often to calculate their infection rate and report the results to members of the implant team. The lowest DD device infection rate among the audited clinical studies reviewed in this article, 2.5% in the BDNF study, may be considered a benchmark against which to compare the results at one's own institution.

Management of DD and SCS Infections. Available data for DD and SCS systems, as well as for CSF shunts and cardiac devices, indicate that treatment of most infections involved inpatient hospitalization, parenteral antibiotics or oral plus parenteral antibiotics, and complete (or rarely partial) removal of the implanted devices. Antibiotic treatment alone rarely cured an established DD or SCS device–related infection (tables 1 and 2). The same held true for CSF shunts and ICDs.[43–45,47,48]

Insufficient data were available in our review of DD and SCS infections to determine how or why a few reported infections were treated successfully with only partial device removal or without device removal. Those cases may represent a few successes among many failed attempts to salvage infected devices, or they may reflect the genuine rarity of circumscribed, individual component involvement. Isolated cases exist in which shunt infections or cardiac device infections have been cured without device explantation. However, the lowest success

rates and the highest relapse rates for ICD infections occurred in patients treated without device explantation.[43–45,47,48]

The duration of hospitalization for nonoperative treatment of ICD infections was similar to or longer than that required when treatment included device explantation.[43] With the possible exceptions of superficial stitch abscesses or skin inflammation without confirmed infection, prompt removal of all infected device components and concomitant administration of parenteral antibiotics is recommended. Antibiotic choice, duration of therapy, and the decision whether to include an oral antibiotic depend on the responsible organism and the clinical details of each case. In the event that device explantation is necessary, tapering the intrathecal drug dose before device removal (if practical) or administration of substitute medications systemically or both may be indicated to prevent or treat ITB or opioid withdrawal.

Meningitis is uncommon but may occur in association with the initial implantation procedure or during the course of long-term therapy with intrathecal DD. Maintenance of intrathecal therapy requires the pump reservoir to be refilled percutaneously at intervals that can vary from days to months. Each refill procedure provides an opportunity for the drug to become contaminated during preparation and handling or for the reservoir to become contaminated with resident skin flora during needle penetration of the refill port. Extra precautions may be warranted during the early postoperative period to avoid the entry of skin flora into the nutrient-rich environment of a fresh, postoperative pocket that may still contain small amounts of blood and tissue fluids. Relevant to the diagnosis of meningitis in patients with implanted intrathecal DD systems, the presence of a chronic indwelling intrathecal catheter does not seem to have any effect on CSF leukocyte or erythrocyte counts, protein, or glucose concentrations (M. Wallace and T. Yaksh, American Pain Society, Chicago, Illinois, 2003).

Many intrathecal drug infusion pumps, including all models marketed by Medtronic, Inc., contain a 0.22-μm bacterioretentive filter in the fluid pathway between the drug reservoir and the catheter outlet. However, the fluid pathway from the catheter access port to the spinal canal (in pumps that have that feature) lies downstream from the filter. Physicians should not rely on the presence of a bacterioretentive filter to prevent implant- or refill-related infections for several reasons: All of the DD device infections listed in tables 1 and 2 occurred after implantation of devices that contained such filters, all of the infections listen in table 2 that included meningitis also involved one or more extraspinal sites, and the single case of isolated meningitis listed in table 1 may have been implant related rather than refill or reservoir related. Finally, bacterial growth within the drug reservoir eventually may overcome the antibacterial filter and grow through it to reach the CSF. In cases of isolated CSF infection (meningitis), the addition of preservative-free antibiotics to the other drugs in a pump reservoir has been described a few times in the medical literature.[57–61] That novel, unlabeled use of the pumps and antibiotic drugs seemed to be most useful when refill procedures or nonsterile drugs contaminated the interior of the pump reservoir. This kind of treatment is seldom indicated because of the rarity with which isolated meningitis has been reported in the absence of other soft tissue or device component involvement. Physicians also should remember that antibiotic drugs administered into the CSF *via* the pump reservoir do not reach other potentially infected sites, such as the abdominal wall pocket, the lumbar insertion site, or the catheter tract.

Elective Reimplantation of DD and SCS Devices. No DD or SCS data are available on which to base recommendations for timing of elective device reimplantation after successful treatment of a previous infection. Most patients with CSF shunt infections undergo implantation of a new shunt system within 2 weeks of initiation of antibiotic therapy, provided the infection has resolved based on clinical and laboratory evidence. No consensus exists regarding the interval before ICD reimplantation after an infection.[44] Reimplantation after 7 days of antibiotic therapy following explantation of an infected ICD has been associated with a low risk of relapse.[43] However, other investigators have recommended a delay of 1–3 months before ICD reimplantation.[44,47] DD and SCS devices are not life-sustaining therapies, so reimplantation is not as urgent as for CSF shunts and ICDs. Most physicians would err on the side of caution and delay implantation of a new DD or SCS system until at least several weeks has elapsed without signs of recurrence after the completion of antibiotic therapy. At minimum, the CDC recommendations state that a new device should not be implanted until the active infection is under control and systemic signs of infection (*e.g.*, fever, increased leukocyte count) have resolved.

Regardless of timing, it is prudent, based on generally accepted surgical principles, clinical experience, and theoretical considerations, that reimplantation of a DD or SCS system should occur at a site that was not involved in the original infection. In a review of 117 patients who underwent device explantation to treat a variety of ICD infections, the single recurrence occurred after reimplantation of a new device into the previously infected pulse generator pocket.[43] Replacement pumps or neurostimulators may be placed in the contralateral abdominal wall. That technique also causes the catheter or lead to pass through a different tunnel around the patient's flank. Finally, the catheter or lead may be inserted into the spinal canal at a different vertebral level than the previously infected one.

Limitations of the Current Work, Future Developments, and Other Applications

The conclusions and recommendations in this article may apply to other kinds of implantable neurologic devices and to SCS or DD devices besides the ones mentioned herein. For example, one patient in a pilot study had bilateral intraparenchymal DD systems removed because of a postoperative infection.[62] However, the clinical studies and postmarket–MDR data described in this report involved only products currently marketed by Medtronic, Inc., and generalization of these conclusions to other devices or to products of other manufacturers may not yield sound conclusions. Other limitations arise from the inevitable undercounting of cases in postmarket surveillance reports and from the fact that the clinical studies discussed in this article were not designed to investigate device-related infections. The cardiac device and CSF shunt infection literature provided valuable insights about potential risk factors and how to reduce the incidence of device-related infections. Still, CSF shunt devices and hydrocephalic patients, and ICD systems and cardiac patients differ in important ways from DD or SCS devices and patients. As the CSF shunt infection literature suggests, it is both logical and likely that the largest percentage reduction in infections may be easiest to accomplish in institutions with the highest current infection rate. Similar or proportional reductions may not be achievable in settings with an already low infection rate.

New devices, indications, antibiotic drugs, and other advances undoubtedly will cause SSI reduction and management strategies to change over time. Impending device improvements may include the incorporation of antimicrobial agents into stimulation leads, drug administration catheters, and other system components. Antibiotic impregnated catheters for CSF drainage and other indications already exist.[63–65] Advances in surgical glove materials, operating room design, and environmental controls also may help to limit the entry of microbes into the sterile field.

Conclusions

Drug delivery and SCS device–related infections are potentially dangerous and costly. Although treatment of established infections is straightforward and almost always successful, the incidence of such infections should be reduced to the lowest achievable level in the first place. Exceptions may involve specific patient populations with concomitant underlying risk factors. Given the relatively small overall population in which DD and SCS therapies are used, randomized controlled studies of infection reduction measures are not likely to be undertaken. We conclude from the available data that the most effective antiinfection measures consist of adherence to published guidelines and recommendations that apply to SSIs in general.

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