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Management of vagal nerve stimulator infections: do they need to be removed?

Clinical article

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Object. Vagal nerve stimulators (VNSs) have been used successfully to treat medically refractory epilepsy. Although their efficacy is well established, appropriate management of infections is less clearly defined. In the authors' experience, patients who have gained a benefit from VNS implantation have been reluctant to have the device removed. The authors therefore sought conservative management options to salvage infected VNS systems.

Methods. The authors performed a retrospective review of 191 (93 female and 98 male) consecutive patients in whom VNS systems were placed between 2000 and 2007.

Results. They identified 10 infections (5.2%). In 9 of 10 patients the cultured organism was *Staphylococcus aureus*. Three (30%) of 10 patients underwent early removal (within 1 month) of the VNS as the initial treatment. The remaining 7 patients were initially treated with antibiotics. Two (28.6%) of these patients were successfully treated using antibiotics without VNS removal. Patients in whom conservative treatment failed were given cephalexin as first-line antibiotic treatment. All patients recovered completely regardless of treatment regimen.

Conclusions. This study confirms the low rate of infection associated with VNS placement and suggests that, in the case of infection, treatment without removal is a viable option. However, the authors' data suggest that oral antibiotics are not the best first-line therapy. (DOI: 10.3171/2008.10.PEDS08294)

KEY WORDS • complication • in situ treatment • infection •
intractable epilepsy • vagus nerve stimulator

VAGAL nerve stimulation has been used over the past decade as a safe and effective treatment for medically intractable seizures. Long-term results have shown mean seizure frequency reductions of 45–81% in the first 1–3 years following VNS placement, with high patient and family satisfaction.^{1–3,9,19,21} Serious side effects have been rare, and most patients have complained of dysesthesias or vocal symptoms, which improve over time and with adjustment of the electrical stimulation. Infection is a relatively uncommon complication, occurring in 1–7% of surgeries.^{5,9,10,17} The majority of these infections have been diagnosed in the immediate postoperative period, and the remainder have been diagnosed in the 3–6-month postimplantation period.¹ Particularly for deep infections, removal of the device is typically recommended and performed.^{11,12,16} In our experience, this recommendation has been met with reluctance by patients and their families when a significant improvement

was noted in the patient's quality of life as a result of the VNS. Several of our patients have expressed a desire to retain the device despite infection. The objective of this study was to identify factors that played a role in the success or failure of VNS infection management. Additionally, we wanted to assess whether removal of hardware is a prerequisite for successful treatment of antibiotic therapy, and to determine the relative costs of the treatment regimens.

Methods

We searched the departmental clinical database and identified all patients who had undergone VNS placement between 2000 and 2007. These charts were reviewed to identify those patients in whom an implant-related infection was diagnosed. Age, presenting symptoms, comorbidities, allergies, culture results and treatment, timing and duration of antibiotic therapy, and whether the device was removed and/or replaced were extracted from

Abbreviation used in this paper: VNS = vagal nerve stimulator.

the available clinical data. Billing records for the hospital stays associated with VNS implantation and infection treatment were obtained from the Cincinnati Children's Hospital Medical Center office of Budget and Financial Analysis and reviewed for each of the 10 patients studied. All dollar values were inflation-adjusted to reflect fiscal year 2007 rates. Approval for this study was obtained from the institutional review board.

Results

Between 2000 and 2007, 191 patients underwent VNS placement by 4 pediatric neurosurgeons and were included in this analysis. Ninety-three were female and 98 male. Infection was diagnosed in 10 patients (5.2%), and all infections occurred at the site of the generator placement. The time from implantation to diagnosis of infection ranged from 2 to 93 days (mean 29.8 days, median 18 days) (Table 1). Half of the patients (5 patients) initially presented with erythema or edema of the wound, 1 with fever, 2 with fluctuance beneath the incision, and 2 with wound breakdown and hardware exposure. At the time of presentation, each device was tested and documented to be working properly. The wound region was evaluated using ultrasonography to detect any underlying fluid collection that was then drained by needle aspiration and cultured. Open wounds were cultured. *Staphylococcus aureus* was identified in all but 1 patient (1 oxacillin-resistant and 8 pan-sensitive). This remaining patient presented with wound breakdown and fluid drainage on postoperative Day 2, although cultures remained negative. No concurrent systemic infections were present in any of the 10 patients with VNS infection. No other

comorbidities that could predispose one to an infection were present in any patient.

Because of surgeon preference for immediate exploration and removal, 2 patients underwent removal of the VNS within 1 week of infection diagnosis. Five patients were initially treated with antibiotics but subsequently had their device removed. Of these 5 patients, 2 had the device removed within 1 month of diagnosis and 3 received prolonged courses of antibiotic treatment with device removal occurring 3.5, 4.5, and 16.5 months after diagnosis. The latter patient had 2 incision-and-drainage procedures and 5 separate courses of antibiotics with intervening periods of apparent wellness before eventual VNS removal. The initial choice of antibiotic therapy in each of these 5 cases was oral cephalexin. The patient for whom no organism was identified was observed clinically for 3 weeks without antibiotic treatment. Ultimately, the wound broke down, the hardware was exposed, and the wound became grossly contaminated. The VNS was then removed. At the time of removal, 7 of the 8 patients had complete removal of the hardware, including removal of the helical contacts around the nerve. In the remaining patient, there was significant scarring around the nerve preventing complete hardware removal. Therefore, wires were cut adjacent to the helical leads, which were left in place around the nerve, and the remainder of the hardware was removed. No patient suffered a vagal nerve injury secondary to VNS removal. All 8 of these patients received postremoval antibiotics: 7 received intravenous antibiotics and later switched to oral antibiotics, and 1 received oral amoxicillin clavulanate. Five of the 8 patients who underwent device explantation ultimately underwent reimplantation after the infection was eradicated without further complication.

TABLE 1: Clinical course summary of patients with VNS infections*

Case No.	Culture Results	Time to Infection (days)	Presentation	Treatment	Outcome
1	Oxacillin-resistant <i>S. aureus</i>	93	stitch abscess led to drainage	ceph, removal, vanco/ctx, PO cipro	removed/replaced
2	<i>S. aureus</i>	37	fever, purulent drainage	removal, ctx/cl, ceph	removed
3	<i>S. aureus</i>	20	wound breakdown, VNS exposed	ceph, removal, cf	removed/replaced
4	<i>S. aureus</i>	8	fluid collection	aspiration, removal, vanco	removed/replaced
5	<i>S. aureus</i>	45	erythema, wound breakdown, lymphadenopathy	ceph, wound revision, removal, IV to PO cipro	removed/replaced
6	<i>S. aureus</i>	16	drainage, chest fullness	ceph, vanco, removal, vanco/rif	removed/replaced
7	no growth	2	wound breakdown, VNS exposed	exploration, wound revision, removal, vanco	removed
8	<i>S. aureus</i>	16	erythema, drainage	ceph, removal, PO AC	removed
9	<i>S. aureus</i>	13	fluid collection	aspiration, IV cl then PO TMP/SMX	not removed
10	<i>S. aureus</i>	48	swelling, wound dehiscence	PO AC, IV ctx, then PO ceph	not removed

* AC = amoxicillin/clavulanate; ceph = cephalexin; cf = cefazolin; cipro = ciprofloxacin; cl = clindamycin; ctx = ceftriaxone; IV = intravenous; PO = by mouth; rif = rifampin; TMP/SMX = trimethoprim-sulfamethoxazole; vanco = vancomycin.

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Two patients were successfully treated with antibiotics and did not require explantation of the VNS. The first was started on oral amoxicillin clavulanate, which was changed to intravenous therapy after 10 days. The second was immediately started on a 3-week course of intravenous clindamycin after an ultrasonography-guided aspiration and culture of fluid collection. In total, the patients received 8 and 9.5 weeks of antibiotics, respectively.

The average cost of initial VNS implantation was \$31,806 (10 patients, range \$25,149–\$36,525). The average cost of a VNS removal was \$13,293 (8 patients, range \$7329–\$19,869). The average cost of a VNS reimplantation was \$37,032 (5 patients, range \$27,076–\$52,037). The average cost of nonoperative management was \$19,432 (2 patients, range \$5840–\$33,024). The average total cost for patients who had their VNS removed was \$69,130 (8 patients, range \$37,475–\$97,791). The total average cost for patients who did not have their VNS removed was \$47,693 (2 patients, range \$30,988–\$64,396). The difference between treating a patient with a VNS removal versus conservative antibiotic management was \$21,438 ($p = 0.22$) in favor of conservative management.

Discussion

The current study reports the infection rate and treatment results of patients with intractable seizures who required VNS implants at our institution. To our knowledge, we are reporting the largest pediatric group from a single institution.^{3,9,12,22} The low rate of infection among these patients is consistent with results from prior studies.^{5,11,12,22} As in prior studies, the majority of infected patients underwent removal of their device, although primary conservative management with in situ antibiotic treatment was attempted in most of our patients. *Staphylococcus aureus*, predominantly pan-sensitive, was cultured in all patients in whom an organism was identified. This finding is in agreement with other published studies.^{16,20}

Reported Treatment for VNS Infections

Patel and Edwards¹⁶ described the need to remove all infected VNS implants in their patients because of the failure of in situ treatment. The authors described 3 patients with battery site infections. One patient underwent immediate device removal. Two patients were initially treated in situ, but ultimately required device removal as well. Murphy et al.¹⁴ encountered 3 infections in their patient population post-VNS implantation, and all 3 cases required device explantation, antibiotic treatment, and eventual reimplantation. Other studies have shown that infections may be successfully treated with in situ antibiotic therapy.^{1,13,15} Liechty,¹³ Ortler,¹⁵ and their colleagues described single-patient case reports regarding the salvaging of a VNS system using open wound treatment with continuous or recurrent irrigation. Although this treatment was successful in these 2 cases, it is labor intensive and requires strict vigilance in wound care. Alexopoulos and colleagues¹ reported on 1 patient who was successfully treated with intravenous antibiotics without open wound care. Another study in children reported 6 cases of infection, 2 of which were superficial wound infections

unrelated to the device and were resolved with antibiotics alone. One of the 6 cases of infection was managed with operative debridement and antibiotics, and the remaining 3 eventually required explantation.²⁰ In this paper, we have reported 2 more cases of complete infection resolution using antibiotics alone.

A closer look into our data and at the treatment regimens for those devices successfully salvaged and those requiring explantation revealed one consistent factor: the patients in whom antibiotic treatment failed and who eventually required VNS explantation had initially received cephalexin treatment. This failure may be because of the biofilm-producing nature of *S. aureus*. Formation of a biofilm on the VNS device allows for viable bacteria to persist after obvious signs of infection have gone, and it has been shown to require more aggressive antibiotic treatment to eliminate it.⁴ The increasing incidence of resistant organisms¹⁶ argues for treatment with a stronger antibiotic than oral cephalexin, although the incidence of oxacillin-resistant *S. aureus* in this study remained low. The choice of cephalexin for the initial treatment was made based on the clinical assessment that the presenting symptoms represented a superficial process. However, as the clinical course of these patients has demonstrated, all such cases must be considered to involve the deep space and hardware. Although 1 of the 2 patients in whom the VNS was salvaged initially was treated with oral amoxicillin clavulanate, short-interval recurrence of her symptoms prompted the transition to intravenous antibiotics. Although medical treatment was ultimately successful, her clinical course may have been shortened if intravenous antibiotics were started initially. Therefore, we believe the best approach is upfront treatment with broad-spectrum intravenous antibiotics.

New Algorithm for Treating Suspected VNS Infections

Based on our results, we propose an algorithm for treatment of suspected postimplantation infections (Fig. 1). Initial evaluation should include serum studies to assess infectious and inflammatory markers and ultrasonography of the VNS generator site to identify any underlying fluid collection and allow for aspiration. Patients should be started on broad-spectrum intravenous antibiotics while awaiting culture results. Vagus nerve stimulator removal should be performed if the device is exposed or malfunctioning. Antibiotic treatment should be further tailored after identification of the organism. The patient should then be followed clinically and with serial blood work to assess for improvement in inflammatory markers and response to treatment. If clinical and laboratory improvement is still not demonstrated beyond this point, VNS removal is appropriate. In those patients for whom cultures are negative, antibiotics should be discontinued to reduce the potential for drug toxicity and limit the promotion of antibiotic resistant organism development.¹⁸ These patients must continue to be followed closely and the algorithm reinitiated if signs of infection recur.

Cost Analysis

In addition to the noted health benefit of VNS place-

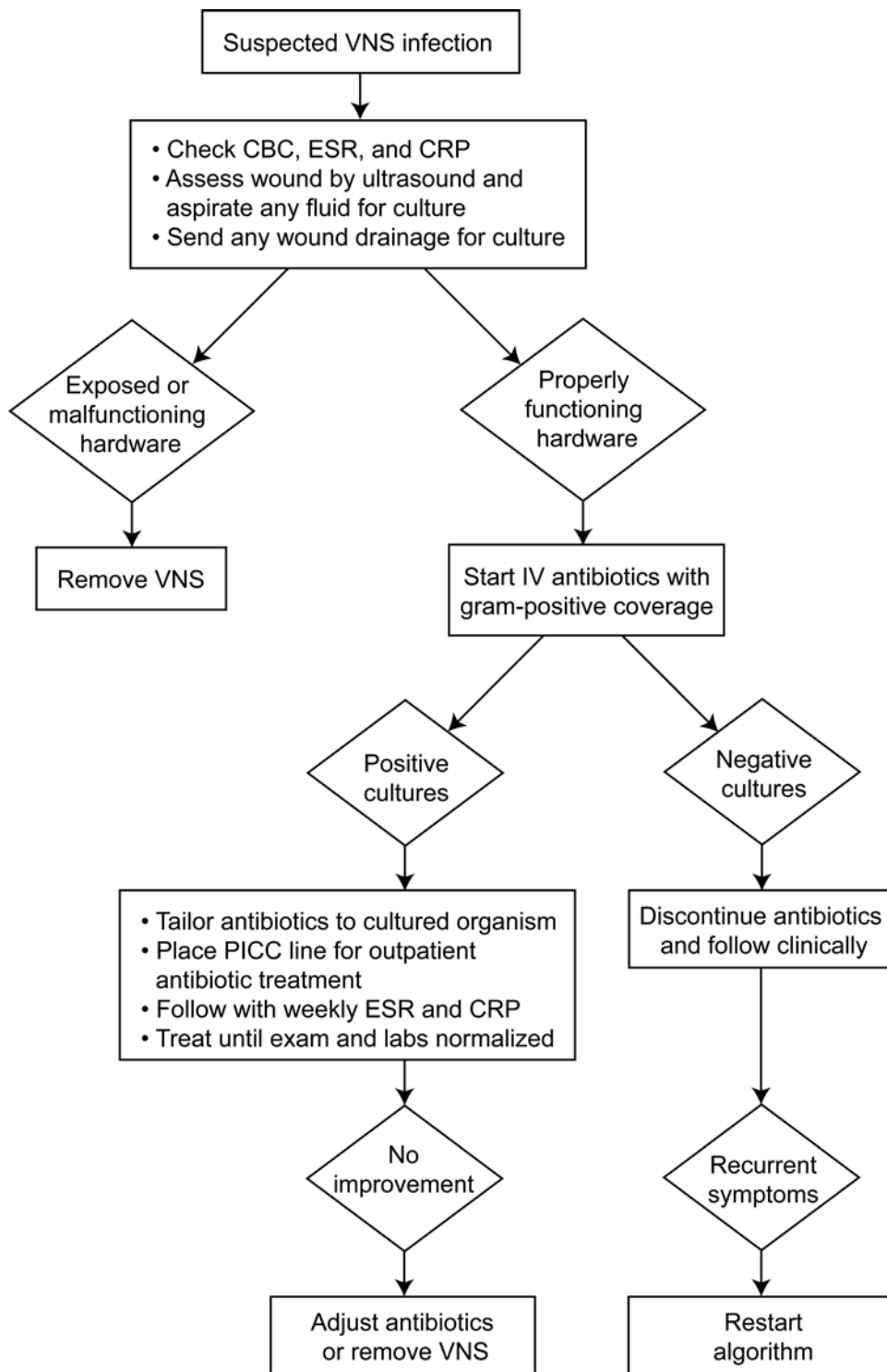


FIG. 1. Algorithm for treatment of VNS infections. CBC = complete blood count; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; PICC = peripherally inserted central catheter.

ment for appropriate patients, a significant reduction in healthcare expenditures has also been attributed to device placement. Boon et al.⁷ evaluated overall epilepsy-related direct medical costs across different treatment regimens, both surgical and nonsurgical, and found a significant decrease in epilepsy-related direct medical costs in VNS-

treated patients compared with those treated with anti-epileptic medications alone. Their report suggests that long-term cost savings resulting from the success of VNS therapy may offset the cost of the device and its initial implantation operation. This finding has been supported by 2 other studies that investigated per-patient annual medi-

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cal costs before and after VNS implantation. In 1 study, annual medical costs dropped from \$8830 preimplantation to \$4215 postimplantation.⁸ A second study showed an approximate savings of \$3000 per patient per year following VNS implantation.⁶

Given the long-term financial benefit of initial placement, we sought to determine whether efforts to maintain the device in situ during infection treatment might also cost less. Although this issue has not been addressed previously in the published literature, it may be an important factor when evaluating treatment options. In this small group of patients, the average cost savings associated with in situ treatment with antibiotics was \$21,438. This difference is approximately equivalent in cost to replacing the device once the infection resolved. This is in addition to the avoidance of the surgical risk associated with both removal and replacement surgeries.

Study Limitations

Several limitations of this retrospective investigation should be noted. Four different surgeons placed the devices, and treatment of postoperative infections was not standardized, but based on individual practices. However, the use of oral cephalosporin antibiotics was prevalent as first-line treatment. The overall number of infections was low, and the number of patients who were successfully treated was conservatively small. Given the large number of patients included in this analysis, this reflects the relative safety of VNS implantation. We believe that with increased awareness as more infections are treated conservatively improved treatment success will occur in the future.

The cost analysis was limited by the retrospective nature of the data collection and by the variable approaches to treatment of these patients. Therefore, a formal cost-benefit analysis could not be performed. Our cost analysis is also limited by the overall number of patients and changing costs during a 7-year period. To address this issue, we evaluated cost based on inflation-adjusted rates to fiscal year 2007. Our financial analysis suggests a cost benefit if a given patient experienced a positive seizure outcome from the original device implantation. Further study is required to determine the true cost-effectiveness of each treatment approach.

Conclusions

In this paper, we have presented the infection rate, treatment results, and cost analysis from the largest cohort of pediatric patients following VNS implantation from a single institution. In this population, we found that VNS can be placed with a low risk of infection. In patients who developed an infection, oral cephalexin proved to be an inadequate therapy for treating infection and resulted in the need for VNS removal. In situ treatment was successful, however, when a more aggressive antibiotic regimen was started immediately. Therefore, a VNS site infection may be successfully treated without hardware removal, and instead with immediate and aggressive antibiotic therapy and close clinical follow-up in an appropriate patient population. Such salvaging of the VNS device

may afford the patient the benefit of fewer surgeries and the continuation of quality of life enhancements gained from the VNS implantation and the resulting attenuation of seizures. It may also serve as a more cost-effective strategy in the care of these patients. The algorithm we present herein is meant to provide possible options in the treatment of infections. Our observation that all patients harboring infections presented with localized infections demonstrates that conservative treatment should be attempted as first-line therapy unless the VNS is clearly malfunctioning or exposed. However, it must be emphasized that, despite the localized presentation of these infections, oral antibiotics provided inadequate treatment. All patients must be treated as having a deep infection and be given broad-spectrum intravenous antibiotics as first-line treatment.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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