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Salvage therapy for vagal nerve stimulator infection; Literature review and report of a delayed recurrence

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ABSTRACT

Background: Vagal Nerve Stimulation (VNS) is one of the most common neuro-modulation based approaches for the treatment of medically intractable epilepsy. Despite advances in technology and surgical techniques, hardware infection remains a recognized and feared complication in VNS placement. Management of such infections is scarce in the literature with the majority of data available in case reports. It ranges from immediate removal of the VNS device to conservative treatment with antibiotics in an attempt to salvage the device, particularly in patients who demonstrated significant improvement in seizure frequency and quality of life.
Methods: We performed a review of the literature in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to identify reported cases of salvaged VNS infection. A literature search for relevant English articles was conducted using Medline. References of relevant articles were also reviewed. Articles that comprised an attempt to salvage an infected VNS were included.
Results: We obtained 12 articles describing an attempt to salvage an infected VNS. Out of a total of 62 reported VNS infections and 43 salvage attempts using a variety of antibiotic-based approaches, 17 cases were successfully salvaged and 26 cases failed the salvage attempt and had to be explanted eventually. Moreover, we report a case of an 18-year-old male with Lennox-Gastaut syndrome who presented21 days after VNS placement with a MRSA deep tissue infection. An attempt was made to treat the infection with long-term culture-based intravenous antibiotics, but it recurred three years later with neck wound dehiscence and positive wound culture for the same organism, and ex-plantation was thus performed.
Conclusion: The management of VNS infections remains a dilemma for neurosurgeons. Although the idea of salvaging an infected VNS seems appealing, hardware removal seems to be inevitable despite adequate antibiotic treatment.

1. Introduction

Vagal Nerve Stimulation (VNS) is one of the most common neuro-modulation based approaches for the treatment of medically intractable epilepsy. This system, approved by the FDA in patients 4 years and older, is a battery powered device that consists of a pulse generator usually placed in a subcutaneous pocket in the anterior chest wall, along with a set of wire leads that wrap around the vagus nerve in the carotid sheath by means of a wire coil [1]. This approach has been shown to be beneficial in reducing seizure frequency and improving quality of life [1–3].

Minor transient complications of VNS in children and adults are common, and they include cough, hoarseness, dysphagia, numbness or tingling sensation in the throat, dyspnea, voice alteration, headache and nausea. However, despite being relatively rare, VNS pocket infections remain one of the most important complications associated with increased morbidity [1,4–8]. Because specific evidence-based treatment guidance for VNS infection is lacking, treatment of such infections has been debatable. Some authors tried to propose a management algorithm based on their small retrospective case series [9]. In particular, many of the disciplines in management of hardware infection in neurosurgery are extrapolated from established and clinically validated concepts in orthopedic and trauma surgery [10].

Because all hardware-associated infections involve biofilms that tend

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to be difficult to eradicate [10], removal of the device is typically recommended and performed [9,11]. However, when it comes to VNS, this approach can be arduous in terms of its high financial burden [9], further reduction in patient's quality of life [10], increased risk of vagal nerve injury upon coil removal, and finally, loss of the efficacious seizure control that the patient usually experiences following VNS placement. Therefore, salvaging an implanted VNS with antibiotics is attractive to the treating physician. In addition, successful treatment of VNS infection without removal of the device has been reported in superficial [12] and deep infection cases [13–15].

In this review, we provide a comprehensive pass over all the reported salvage attempts of an infected VNS, summarizing the reported risk factors of a VNS infection, ways to avoid infection, and success rates of reported attempts. We also report a case of MRSA deep tissue infection that has been treated with long term culture-based intravenous antibiotics, only to recur three years later with neck wound dehiscence and positive wound culture for the same organism necessitating explanting the device.

2. Methods

We performed a review of the literature in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to identify reported cases of salvaged VNS infection. A literature search for relevant English articles was conducted using Medline.A search flow diagram is provided in Fig. 1. The search strategy combined various search terms for vagal nerve stimulation and surgical or hardware infections using multiple versions of relevant medical subheading (MeSH) terms and text words. An effort was made to account for synonyms, acronyms, plurals, and variations in spelling. We utilized a combination of controlled vocabulary terms (MeSH terms in Medline) as well as keywords. The search terms were as follows:(Postoperative Complications [MeSH] OR surgical infection or surgical wound infection or hardware infection or postoperative infection) AND (Vagus nerve stimulation [MeSH] OR vagal nerve stimulation). Titles and abstracts were screened by two reviewers (C.A.F. and K.A) for eligibility. Non-English articles and those not reporting a VNS infection were excluded. Full text revision was then done, selecting all articles that comprised an attempt to salvage an infected VNS. References of relevant articles were also reviewed for potential papers to be included in our review.We eventually obtained 12 articles, including single case reports, case series, and retrospective studies, which met our inclusion criteria. Data were extracted independently by two reviewers (C.A.F. and K.A).

3. Results

We obtained 12 articles, summarized in Tables 1 and 2, which comprised an attempt to salvage an infected VNS with the majority of the cases being at the pulse generator site. Out of a total of 62 reported VNS infections and 43 salvage attempts, 17 cases were successfully salvaged using a variety of antibiotic-based approaches.26 cases failed the salvage attempt and had to be explanted eventually.

3.1. We also report our experience with salvaging a VNS deep pocket infection describing the following case

An 18-year-old male with Lennox-Gastaut syndrome (LGS) presented to a tertiary care center with medically intractable epilepsy. Physical

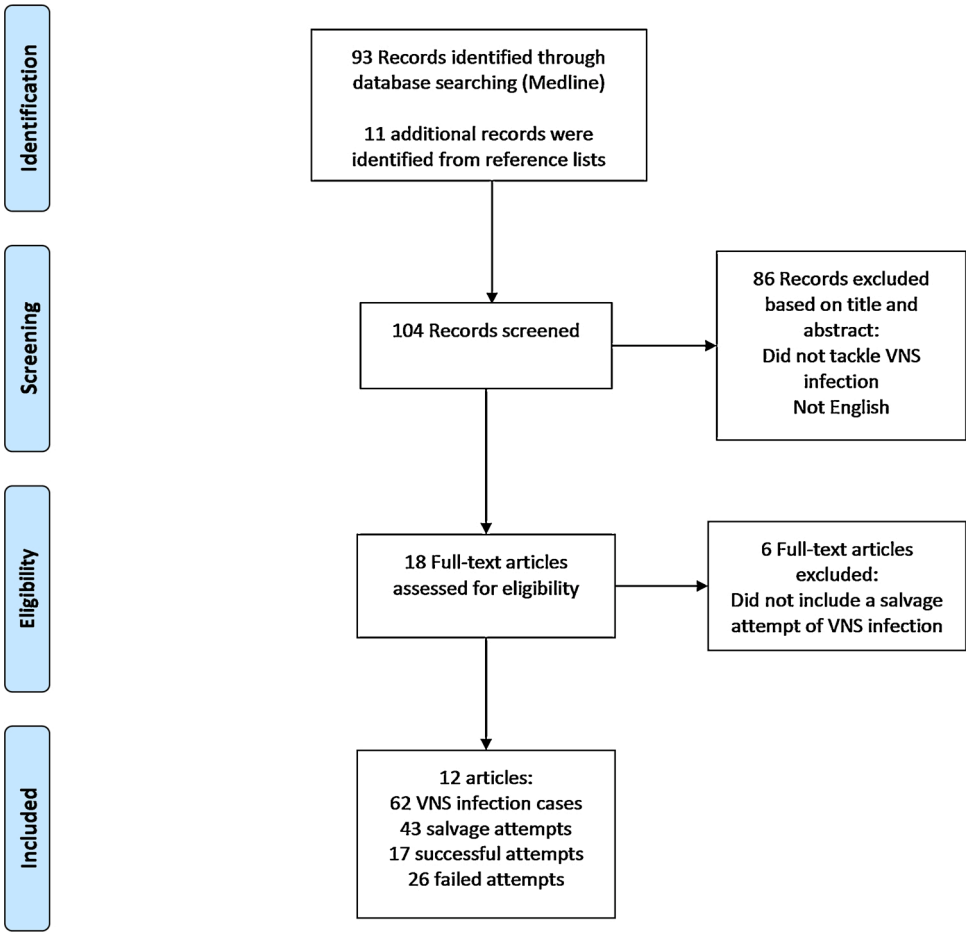

Fig. 1. PRISMA search flow diagram showing our literature search.

Table 1
Summary of case reports/series that attempted to salvage VNS infections with demonstration of different successful and failed methods of salvage [8,9,11–17,19–21].

Number	Literature	Nb. of reported VNS infection cases	Salvage success rate	Salvage attempt Successful/ Failed	VNS infection location	Microorganisms detected	Mechanism of salvage	Follow up duration (if failed attempt, follow up duration is from attempt to VNS removal)
1	Ortler 2001 [15]	1	1/1	Successful	Cervical wound infection deep under superficial cervical fascia **Presentation: 5 weeks post-implantation**	*S. aureus*	Open wound treatment without removal of stimulating electrodes + IV fosfomycin 4 g t.i.d. and cefmenoxim 2 g t.i.d. for 14 days + daily wound rinsing Wound closed on postoperative day 13 after obtaining a negative wound culture	1 year
2	Smyth 2003 [12]	6	3/6	Successful	Pulse generator pocket: superficial **Presentation: Within 4 weeks post-implantation**	MSSA in 4/6 patients Unknown in 2/6 patients	**2/3 patients with superficial wound infection and no infection of device:** antibiotics alone (oral cephalexin for 10 days) **1/3 patients with superficial wound breakdown at stimulator site:** debridement and antibiotics (cefazolin followed by oral cephalexin for unspecified duration)	Not specified
3	Wozniak 2011 [11]	6/206	3/6	Successful	Pulse generator pocket	MSSA	Lead salvage protocol	7.5 years
					Pulse generator pocket	MSSA	Lead salvage protocol	5.5 years
					Pulse generator pocket	S. viridans	Lead salvage protocol	10 months
				Failed	Initially at pulse generator pocket only **Presentation: 3 weeks post-implantation**	MRSA	After a trial of systemic antibiotic treatment, the entire VNS system was infected 11 weeks post-implantation	8 weeks
					Pulse generator pocket	MSSA and P. mirabilis	Lead salvage protocol	6 weeks
4	Leichty 2005 [14]	1	1/1	Successful	Deep pocket infection	*S. epidermidis*	Sump antibiotic irrigation system at 15 mL/hr for 7 days + IV vancomycin followed by oral antibiotics for 2 weeks post-discharge	Not specified
5	Alexopoulos 2006 [13]	5/46	1/5	Successful	Pulse generator pocket **Presentation: within 1 week to 6 months post-implantation**	Not specified	IV antibiotics	33 months (after which VNS battery was replaced)
6	Air 2009 [9]	10/191	2/10	Successful	Pulse generator pocket	MSSA	Aspiration + IV clindamycin then PO TMP-SMX for a total of 9.5 weeks	Not specified
							PO amoxicillin-clavulanate + IV ceftriaxone then PO cephalexin for a total of 8 weeks	Not specified
							2 patients had prompt removal within first week of infection diagnosis	
				Failed	Pulse generator pocket	1 MRSA and 6 MSSA	5 patients had a trial of antibiotics prior to removal (of these, one patient had 2 incision and drainage procedures and 5 separate courses of antibiotics with intervening periods of apparent wellness)	2 patients: 1 month Others: 3.5, 4.5, and 16.5 months
7	Kuroda 2019 [17]	9/208	2/9	Successful	Surgical site	Not specified	Debridement and antibiotics	Not specified
				Successful	Wound	Not specified	Oral antibiotics	Not specified
8	Murphy 1998 [19]	3/24	2/3	Failed	Pulse generator pocket **Presentation: 3 months post-implantation**	Not specified	A trial of parenteral antibiotics was attempted for abscess formation	Not specified
9	Revesz 2016 [16]	10/260	2/10	Successful	Superficial infection	Not specified	Oral antibiotics	Not specified
				Failed	Not specified	Not specified	8 cases: Trial of oral antibiotics given but infection persisted	Duration ranged from 26 days to

(*continued on next page*)

Table 1 (*continued*)

Number	Literature	Nb. of reported VNS infection cases	Salvage success rate	Salvage attempt Successful/ Failed	VNS infection location	Microorganisms detected	Mechanism of salvage	Follow up duration (if failed attempt, follow up duration is from attempt to VNS removal)
								186 days for first reoperation
10	Patel 2004 [8]	3	0/3	Failed	Deep pocket infection at pulse generator site	MSSA	**Steps of unsuccessful salvage:** 1 Patient completed a 21-day course of antibiotics with cefazolin and rifampin 2 Surgical wound dehiscence one week after therapy 3 Battery removed, cleaned, and replaced 4 4 week course of cefazolin and rifampin 5 Recurrent infection → battery pack removed 6 3 week course of cefazolin and rifampin followed by cephalexin as suppressive therapy 7 Recurrent infection 8 weeks after cessation of IV therapy → wire leads removed	1 week
						MRSA	6 weeks of vancomycin + TMP-SMX prophylaxis	3 months
11	Gigliotti 2018 [20]	4/216	0/4	Failed	Not specified	MRSA	Antibiotic treatment suppressed but did not resolve infection	Not specified
12	Horowitz 2012 [21]	4/100	0/4	Failed	Wound Infection	2 MSSA 2 negative cultures	Failure to resolve with antibiotic treatment	Two lasted <1 month One lasted for 10 months One lasted for 13 months

examination revealed a bedridden patient with severe scoliosis and generalized spasticity. Evidence of cognitive delay was also present. VNS was placed in the usual fashion with pulse generator in subclavicular site. He presented 21 days later, however, with high grade fever, erythema, and swelling of the surgical wound site. Inflammatory markers were elevated including a CRP level of 121.6 mg/L. CT chest with contrast showed swelling and fat stranding overlying the pulse generator in the left upper chest wall with 2.6 × 1.4 cm phlegmon and early abscess formation at its deep superior aspect. No collections were seen in the neck. The chest wall collection was drained and cultures grew methicillin resistant *Staphylococcus aureus* (MRSA).

He was thus started on intravenous cephalexin 500 mg for 1 week. He was then discharged on intravenous ceftaroline 600 mg for 2 weeks. In the light of clinical and laboratory response to treatment, he was kept on two more weeks of oral doxycycline 100 mg and clindamycin 300 mg. Follow up CT scan 4 weeks later showed near resolution of all signs of infection. The infectious diseases specialist preferred to keep the patient on extended term of oral ciprofloxacin 500 mg b.i.d. and rifampin 450 mg once daily completing a total duration of 14 weeks of antibiotics.

The patient was consistently following up with his neurologist and remained clinically stable with clean and healthy looking wound sites and no fever, until he was referred back to our service three years later when the family noticed neck wound localized area of dehiscence with exposure of one of the anchoring tie-downs from the VNS device. The chest wound, on the other hand, was well healed. After discussion with the family, the device was entirely explanted and deep tissue cultures taken operatively from the neck woundgrew, once again, MRSA.

4. Discussion

Our literature search uncovered many reports that describe possible risk factors for a VNS infection with ways to avoid them. Children with cognitive delay are at a higher risk of hardware infection due to increased potential manipulation at the surgical site [17,18]. Smyth et al. recommended using layered and well secured dressings to prohibit these children from manually manipulating the device or the associated incision [12]. Another author went as far as using interscapular placement, instead of the usual subclavicular location, of the pulse generator as a protective measure against wound infection in children at increased risk of VNS infection [18]. Another risk factor that Kuroda et al. found in their series was low BMI as it is associated with malnutrition, emaciation, and hypoalbuminemia [17].

Although randomized controlled studies are unavailable in the literature, our search yielded multiple case reports and series with recommendations ranging from strongly opposing infected VNS salvage to advocating various methods of salvage therapy with different degrees of success. These are summarized in Tables 1 and 2.

Patel and Edwards [8] described their failed trials to salvage VNS deep pocket infections with antibiotics.They concluded that salvage attempts only prolong the morbidity andrecommended explanting the device to achieve cure [8]. On the other hand, other authors described their various salvage attempts with variable success rates [9,11,13–15]. Alexopouluset al. reported successful treatment of 1 out of 5 infection cases in his series with intravenous antibiotics without open wound care [13]. Ortler et al. described a single successful case of VNS salvage in which they undertook debridement of an infected generator pocket, leaving the entire VNS system in place. The wound was then packed with 3 % iodoform gauze and lavaged daily with 1.5 % hydrogen peroxide and systemic antibiotics were given for two weeks. The wound was sutured on postoperative day 13 after obtaining a negative wound culture without further wound complications after 1 year of follow-up [15]. Furthermore, Leichty et al. also salvaged an infected VNS via the use of a sump irrigation system for 7 days. Their approach consisted of inserting

Table 2
Summarized Table 1 [8,9,11–17,19–21].

No.	Salvage Technique	Papers reporting on salvage technique	Salvage success rate in the literature	Time to Salvage Failure*
1	Antibiotics alone (IV or oral)	Murphy 1998 [19] Smyth 2003 [12] Patel 2004 [8] Alexopoulos 2006 [13] Air 2009 [9] Wozniak 2011 [11] Horowitz 2012 [21] Revesz 2016 [16] Gigliotti 2018 [20]	9/35	1 week to 3 months (Patel 2004) 1 month to 16.5 months (Air 2009) 8 weeks (Wozniak 2011) <1 month to 13 months (Horowitz 2012) 26–186 days (Revesz 2016)
2	Open wound treatment + daily wound rinsing + IV antibiotics with wound closure two weeks later	Ortler 2001 [15]	1/1	–
3	Operative debridement + IV and oral antibiotics	Smyth 2003 [12] Kuroda 2019 [17]	3/3	–
4	Lead salvage protocol	Wozniak 2011 [11]	3/4	6 weeks
5	Sump antibiotic irrigation system	Leichty 2005 [14]	1/1	–

*Follow-up duration starting from salvage attempt until VNS device removal (i.e. failed attempts).
IV: intravenous.

a 7 F Jackson-Pratt drain below the battery and placing a Foley catheter over the battery with inflation of the balloon to increase flow space throughout the pocket. A diluted vancomycin solution passed through the drain perfusing the pocket at a flow of 15 mL/hr. Outputwas maintained through the Foley catheter and into an external collecting system. During this period, systemic vancomycin was also administered, and this was followed by a subsequent 2 weeks of outpatient oral antibiotics [14].

Air et al. proposed a treatment algorithm based on 10 cases of deep pocket infections out of his series of 191 patients [9]. They proposed that in case of an exposed or malfunctioning hardware, removal of the device is necessary. However, in case the hardware is properly functioning, intravenous antibiotics should be attempted as first line treatment option. Initial evaluation should include serum studies to assess infectious and inflammatory markers and ultrasonography of the VNS generator site to identify and aspirate any underlying fluid collection. Patients should be started on broad-spectrum intravenous antibiotics while awaiting culture results and this should be further tailored after identification of the organism. The patients should then be followed clinically for signs of improvement and with serial blood tests to assess for improvement in inflammatory markers. If no improvement is demonstrated beyond this point, VNS removal is warranted. Moreover, in case of negative cultures, antibiotics should be discontinued unless signs of infection recur in which case the algorithm can be reinitiated [9].

In addition, Wozniak et al. proposed and demonstrated the successful use of lead-salvage protocol in patients with VNS infection in 3 of 4 attempted cases [11]. This protocol entails disconnecting the lead from the pulse generator, irrigating both with 1−2 L of bacitracin-containing sterile saline, tucking and securing the exposed lead in a newly created medially located generator pocket, removing the generator, and finally tailoring a course of intravenous antibiotic therapy for 3–4 weeks according to culture results. At least 4 weeks were allowed post antibiotic cessation before the generator was re-implanted again. The end goal of this protocol is to avoid repeated dissections in the carotid sheath and thus risking injuring the vagal nerve and further scarring [11].

In our case, the patient had two risk factors described in the literature for VNS postoperative infection, namely cognitive delay due to increased potential manipulation of surgical site [12,17,18], and low BMI [17]. It is interesting to note that pediatric cases have a higher infection rate at 3–8 % [12,16] compared to 2.1 % in adult cases. We were tempted to salvage our VNS as it was functional without wound dehiscence. The antibiotics regimen was culture-based specifically targeting MRSA that grew in the aspirate of the pocket wound collection. The regimen we followed was also longer than that reported by other authors in the literature. This gave us a false security that we were able to control the infection. Of note, choosing cephalexin as initial treatment of a MRSA infection was noted by Air et al. to be associated with treatment failure and eventual removal of hardware. They related this finding to the biofilm-producing nature of S. aureus.

When the patient presented three years later with wound dehiscence, we feared that this might represent an indolent infection. When we explanted the device, the deep tissue cultures taken intraoperatively revealed the same organism again (MRSA). Revesz et al. [16] reported a case of delayed recurrent infection 6 months following attempted salvage with oral antibiotics alone, and Air et al. [9] reported removal of a VNS device 16.5 months following two incision and drainage procedures and five antibiotic courses. In both of these papers, the organism was not specified. We wrote this report to stress on the fact that even if initial salvage therapy is met with success, one has to remain vigilant as this does not exclude the possibility of late recurrence of an indolent infection.

5. Conclusion

Even though successful conservative management has been demonstrated in multiple cases in the literature, we report a deep pocket infection case managed conservatively with initial success, but ending in late recurrence of the infection. We conclude that VNS hardware removal seems to be inevitable in case of deep pocket infection despite adequate antibiotic coverage since this infection can be indolent for years before it reappears again. Further studies are needed to better assess and compare the various reported approaches to VNS infection.

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