

# Infection and Erosion Rates in Trials of a Cranially Implanted Neurostimulator Do Not Increase with Subsequent Neurostimulator Placements

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## Keywords

Complications · Epilepsy · Stimulation · Surgery

## Abstract

**Background/Aims:** The RNS<sup>®</sup> System utilizes a cranially implanted neurostimulator attached to leads placed at the seizure focus to provide brain responsive stimulation for the treatment of medically intractable partial onset epilepsy. Infection and erosion rates related to the cranial implant site were assessed overall and by neurostimulator procedure to determine whether rates increased with additional procedures. **Methods:** Infection and erosion rates were calculated as (1) chance per neurostimulator procedure, (2) incidence per patient implant year, and (3) rates for initial and each subsequent neurostimulator implant (generalized estimating equation). **Results:** In 256 patients followed for an average of 7 years, the infection rate was 3.7% per neurostimulator procedure ( $n = 31/840$ ), and the rate of erosions was 0.8% per neurostimulator procedure ( $n = 7/840$ ). Rates did not increase with subsequent neurostimulator procedures ( $p = 0.66$ , infection;  $p = 0.70$ , erosion). A prior infection or erosion at the implant site did not significantly increase the risk at a later procedure ( $p \geq 0.05$  for all combinations). **Conclusion:** These data indicate that the risk for infection compares fa-

vorably to other neurostimulation devices and suggest that rates of infection and erosion do not increase with subsequent neurostimulator replacements.

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## Introduction

Brain responsive stimulation using the RNS<sup>®</sup> System is approved in the USA as an adjunctive treatment for medically intractable partial onset seizures in adults. Unlike currently available open loop deep brain stimulation systems that utilize a pectoral implant for the pulse generator, the RNS System neurostimulator is cranially implanted. Experience from prospective clinical trials provides data regarding the risk of infection and erosion related to the cranial implant approach.

## Methods

The RNS System provides targeted responsive neurostimulation via a cranially implanted programmable neurostimulator connected to 1 or 2 depth and/or subdural cortical strip leads placed at 1 or 2 previously identified seizure foci [1]. Each lead contains 4 electrode contacts, through which the neurostimulator continu-

ously senses electrocorticographic activity. The device is programmed by the physician to detect specific patterns in the electrocorticogram and to deliver brief stimulation pulses in response. Recording and stimulation occur on the same electrodes. The physician adjusts detection and stimulation parameters for each patient as needed for seizure reduction. The typical patient receives brief bursts of high-frequency stimulation with a total cumulative stimulation time of less than 6 min a day [2].

Patients were implanted with the RNS Neurostimulator and NeuroPace Leads while enrolled in either a primarily open-label safety study or in a randomized double-blind controlled trial [3]. Two years after the neurostimulator implant, patients were able to transition into a 7-year long-term open-label follow-up study. The studies are registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT00079781, NCT00264810, NCT00572195). All patients gave informed written consent.

Data were collected on infections and erosions associated with any neurostimulator procedure (i.e., initial implant, replacement, or explant). Any mention of an infection or erosion on a case report form was examined, regardless of culture or use of antibiotics. Patients who had a neurostimulator explanted without a replacement were followed for 6 weeks after the surgery and contributed data to the analysis. Included in the analysis were all serious adverse events (SAEs) related to infection or erosion that were identified by the investigator as device related or of uncertain device relation, and were not due to seizure-related injuries. An SAE was defined as one requiring hospitalization or a surgical procedure. An independent data-monitoring committee reviewed all adverse events.

The relationship between infection or erosion rate and procedure number (first to fourth) was assessed using a logistic generalized estimating equation (GEE) method. GEE is an extension of generalized linear modeling that appropriately accounts for the correlation of multiple measures from the same subjects [4]. The model used logistic regression to fit a linear model with procedure number (1–4) as a linear independent variable to predict infection or erosion probability. An additional constant cohort analysis was performed, in which only patients with at least 4 procedures were included in the analysis. Paired differences across subsequent procedure numbers were compared using the McNemar test.

## Results

Patients treated with the RNS Neurostimulator and NeuroPace Leads ( $n = 256$ ) were followed for an average of 6.9 years (10 days to 11 years). Twenty-eight patients had a total of 31 events related to infection over 1,715 patient implant years (0.018 per implant year). The rate of SAEs related to an incision or implant site infection was 3.7% per neurostimulator procedure ( $n = 31/840$ ).

Fourteen of the 31 infections (45%) were reported to have occurred within the first postoperative month; 3 of these were asymptomatic infections discovered during a routine neurostimulator replacement procedure. The remaining 17 infection SAEs had reported onsets that

ranged from 35 days to 3.5 years after the neurostimulator procedure.

All patients with infections were treated with antibiotics, and debridement was performed in 61% of cases. Twenty-one percent of patients (6/28) continued to receive responsive therapy with no change in the neurostimulator or leads. Another 21% (6/28) had the neurostimulator replaced with no change to the leads, and continued to receive responsive therapy thereafter. The remaining patients (57%, 16/28) had the neurostimulator explanted, and 13 had leads explanted as well. Two of these patients were subsequently reimplanted with the neurostimulator and leads. None of the 3 patients with leads remaining reported any instance of meningitis or needed a subsequent surgery to remove remaining leads (duration of follow-up: 59, 461, and 1,336 days after device removal).

Infections in all but 1 of the 28 patients involved only soft tissue; there were no instances of meningitis. One patient developed osteomyelitis after a single hospitalization that included explantation of the neurostimulator and leads followed by 7 days of subdural grid mapping, a frontal lobe resection, and reimplantation of the RNS Neurostimulator and leads.

There were 5 patients with a total of 7 SAEs related to erosion over the 1,715 patient implant years (0.004 erosions per implant year). Two of the 5 patients had the neurostimulator implanted with the inner table of the skull intact, so that the neurostimulator protruded above the skull. The overall rate of erosion was 0.8% per neurostimulator procedure. All patients were treated with antibiotics. One patient continued to receive responsive therapy with no change to the neurostimulator or leads. Four patients had the neurostimulator explanted, and 2 had leads explanted as well. Of these, 1 patient had the neurostimulator and leads replaced at a later date. For the 2 patients with abandoned leads, there were no reports of meningitis or subsequent surgery to remove the leads (duration of follow-up: 250 and 754 days after device removal). One of these patients with a history of prior intracranial monitoring had a cranioplasty 20 months after the device had been explanted.

No cultures were provided for 4 of the events related to infection or erosion, and 1 culture was negative. Other cultures were as follows (cultures for a single infection or erosion event could be positive for more than 1 type of bacterium): gram-positive cocci – *Staphylococcus* (*S. aureus* 11, *S. epidermis* 1, other 9), not further specified (1); gram-positive rods – *Propionibacterium* (7), not further specified (1); gram-negative rods – *Enterobacter* (3),

**Table 1.** Number of patients reporting infections or erosions after each neurostimulator procedure

Procedure	Total of patients, <i>n</i>	Patients reporting infection <sup>1</sup> , <i>n</i>	Infection events, <i>n</i>	Patients reporting erosion <sup>1</sup> , <i>n</i>	Erosion events, <i>n</i>
1st	265	6	8	2	2
2nd	236	8	8	1	1
3rd	188	8	8	0	0
4th	100	2	2	2	2
5th	37	2	2	0	0
6th	14	2	2	0	0
7th	7	1	1	2	2
8th	2	0	0	0	0

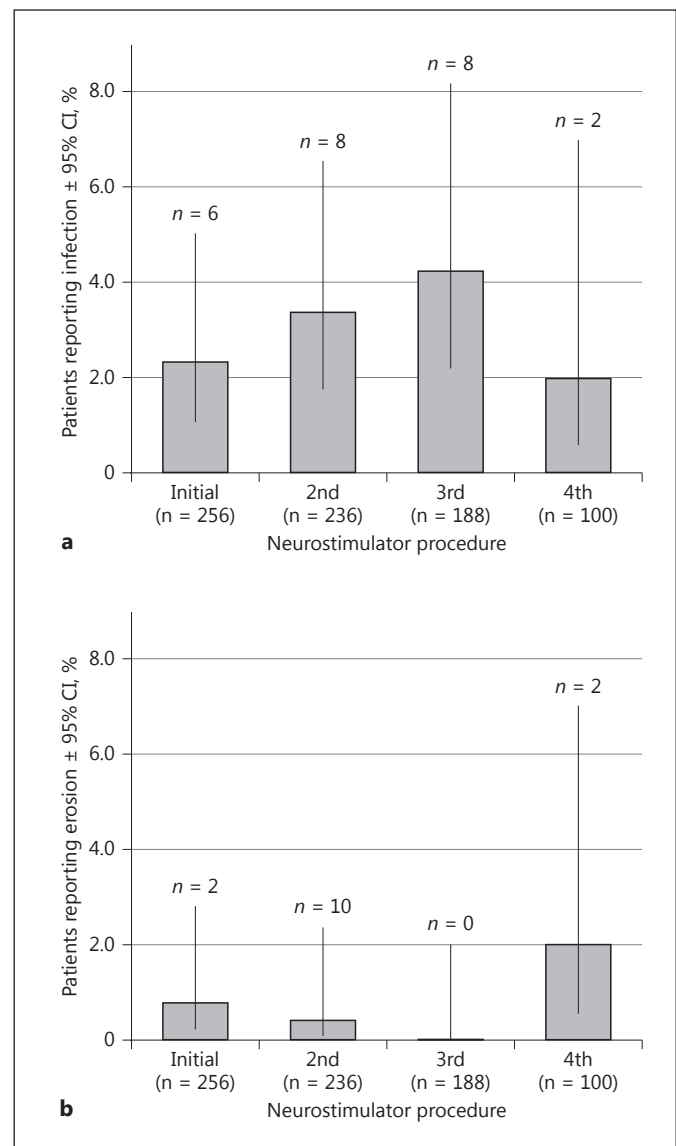
All serious adverse events related to infection or erosion were identified by the investigator as device related or of uncertain device relation, and were not due to seizure-related injuries. Data as of November 1st, 2015.

<sup>1</sup> This column represents the number of unique patients who had an infection or erosion in the time period between the *n*th and the *n* + 1st procedure. The sum of patients in this column does not reflect the number of unique patients who ever had an infection/erosion, because any patient having an adverse event in more than one *n*th procedure bin would be represented multiple times. ©2017 NeuroPace Inc.

*Pseudomonas* (3), *Serratia* (3), *Escherichia coli* (1), not further specified (1).

To assess whether the risk of infection or erosion changed with subsequent neurostimulator procedures, the rate of infection or erosion by the *n*th procedure was analyzed through 4 procedures (Fig. 1); there were not sufficient numbers of patients with more than 4 procedures to extend the analysis beyond this point (Table 1). Note that this analysis includes data from the first-generation neurostimulator, which had a median battery longevity of 2.2 years [5], as well as a later-generation neurostimulator with an estimated battery longevity of 3.9 years [6]. Development of a next-generation device with substantially increased battery life has been completed [NeuroPace Inc., pers. commun.].

Rates of infection did not statistically significantly increase or decrease with more procedures ( $p = 0.66$ ) nor did the rates of erosion ( $p = 0.70$ , GEE, Fig. 1). A constant cohort analysis in the 100 patients who had at least 4 neurostimulator procedures indicated that an infection or erosion at a prior procedure did not significantly increase the risk of having an infection or erosion at a later procedure ( $p \geq 0.05$  for all combinations, McNemar exact test).



**Fig. 1.** Percentage of patients reporting an infection (a) or erosion (b) after a neurostimulator procedure. Rates of infection and erosion were analyzed for all patients who had at least 4 procedures; there were not sufficient numbers of patients with more than 4 procedures to extend the analysis further. Neither the percentage of patients with infections ( $p = 0.66$ , GEE) nor that of patients with erosions ( $p = 0.70$ , GEE) increased over time. ©2017 NeuroPace Inc.

## Discussion

The RNS System is demonstrated to be safe and effective as an adjunctive treatment for medically intractable partial onset seizures in adults based on the results of clinical trials conducted in 256 patients across 32 comprehensive epilepsy centers in the USA [3, 7]. These data indicate

that the risk of infection or erosion related to the crani-ally implanted neurostimulator is not higher than is expected with comparable epilepsy procedures in which a stimulating device is implanted pectorally, and that there is not an increased risk with additional neurostimulator replacement procedures.

The advantages of a crani-ally implanted neurostimulator are both technical (there is an excellent signal-to-noise ratio, which is important to a responsive system) and cosmetic (the neurostimulator is not apparent to the patient and others). Anticipated advantages over a pectoral implant are a lower risk for lead or device migration [8]. Considerable prospective data from clinical trials of the RNS System indicate that the risk of infection or erosion with the cranial implant compares favorably with other neurostimulation systems that utilize a pectorally implanted pulse generator, such as vagal nerve stimulation [1] and deep brain stimulation for Parkinson disease [9] or epilepsy [8], and that this risk does not increase with subsequent routine neurostimulator replacements. These data support the hypothesis that a crani-ally implanted stimulator may offer several technical advantages over one placed pectorally without increasing the risk of infection or erosion.

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