

Can We Prevent Cochlear Implant Recipients from Developing Pneumococcal Meningitis?

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The restoration of hearing to persons with severely or profoundly impaired hearing by means of a cochlear implant is one of the great achievements of bionics applied to medicine. However, pneumococcal meningitis in implant recipients has received high profile public attention as a result of the US Food and Drug Administration's public health notification and recent media attention. Worldwide, 118 of the 60,000 people who received cochlear implants over the past 20 years have acquired meningitis, causing deep concern in the international medical community. This review provides answers to pediatricians, internists, and infectious diseases doctors who have patients with cochlear implants and who have questions about the safety of the cochlear implant from both the clinical and scientific research perspectives. Both clinical and laboratory research support the notion that pneumococcal meningitis is more likely in patients who receive cochlear implantation, and that the surgical insertion technique and the cochlear implant design should be nontraumatic, and that all cochlear implant recipients should be offered vaccination against *Streptococcus pneumoniae*.

A cochlear implant is a device for providing hearing sensations and speech understanding in severely-to-profoundly deaf individuals who receive little or no benefit from a conventional hearing aid. Hearing is achieved by direct electrical stimulation of the auditory nerve, with an electrode array implanted in proximity to the auditory nerve in the inner ear (cochlea). The procedure has had a very good safety record, but in 2002, there were numerous reports of meningitis among people with cochlear implants, including a number of deaths worldwide [1]. This review describes the most recent development by examining the scientific literature, which provides insights into fundamental questions concerning the pathophysiology of pneumococcal meningitis, as well as a method for minimizing the risk in clinical practice.

MENINGITIS AFTER COCHLEAR IMPLANTATION

Ninety-one cases of postimplantation meningitis, including a total of 17 deaths, were reported to the US Food and Drug Administration (FDA) in 2002 [1]. By September 2003, the total number of reported cases worldwide had increased to 118 (55 cases in the United States and 63 cases from other parts of the world) [1]. The age of patients with cochlear implant-related meningitis ranged from 13 months to 81 years. The onset of meningitis ranged from <24 h to >6 years after implantation.

The most common organism identified was *Streptococcus pneumoniae* [1, 2], and the cases of meningitis were attributed to a new electrode technology that had recently been released to market, known as an implant with positioner, which is a small, silastic wedge inserted next to the implanted electrode array to push it closer to the auditory nerve within the center of the cochlea (the modiolus) [1–3]. However, other risk factors that were also associated with postimplantation meningitis included inner-ear malformations, with and without CSF leak, the presence of a CSF leak after cochlear implantation, a history of ventriculoperitoneal shunt placement, and otitis media [2–4].

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The incidence of pneumococcal meningitis was found to be greater than that of an age-matched cohort in the general population [2]. To quantify continuing risk of meningitis, an additional study was conducted that involved the 4264 children who were followed up from 16 September 2002 through 1 December 2004 [5, 6]. Twelve new episodes of meningitis were ascertained among 12 children, 11 of whom received a cochlear implant with a positioner. The incidence of meningitis 24 months after cochlear implantation for children with a positioner implant was 450 cases per 100,000 person-years [6]. However, it remains to be determined whether cochlear implantation without the positioner device increases the risk of meningitis in subjects with no preexisting risk factors for acquiring the disease. Even if the implant increases the risk of meningitis, the exact mechanism of how it contributes to the risk of acquiring meningitis remains unknown.

CURRENT SCIENTIFIC RESEARCH

The increased incidence of meningitis that followed implantation of this device serves as a timely reminder that new implant technologies carry potential risks. However, on the basis of the current clinical literature, it remains unclear whether cochlear implantation increases the risk of meningitis in subjects with no existing risk factors for acquiring this disease. The question cannot be answered in humans because of ethical considerations, so the study of implant-related infection must involve living animals for the research findings to be applicable to a real-life clinical situation. The current success of cochlear implants is a result of many years of testing in the animal models.

The development of both an experimental model for pneumococcal meningitis and interventional strategies to reduce implant-related infection will depend upon the route of spread of bacteria from the middle ear to the CNS. The exact routes by which the bacteria reach the meninges in the presence of a cochlear implant are still unclear [7]. As a result of the potential breakdown in both mucosal soft tissue and bony barriers between the inner and middle ear as a result of cochlear implantation, the direct spread of infection from the middle to the inner ear and then to the CNS has been proposed as a major route of infection (figure 1) [8] and has been the main focus in the study of infection-prevention strategies in implant-related meningitis [9]. The presence of a peri-implant fibrous tissue seal has been considered to be an important barrier that will resist the spread of infection from the middle ear to the inner ear [8, 10, 11]. Others have postulated that pneumococcal meningitis is caused by the bacteremia that follows colonization of the upper respiratory tract (figure 1) [7, 12–14]. An experimental model was recently designed to study several of the

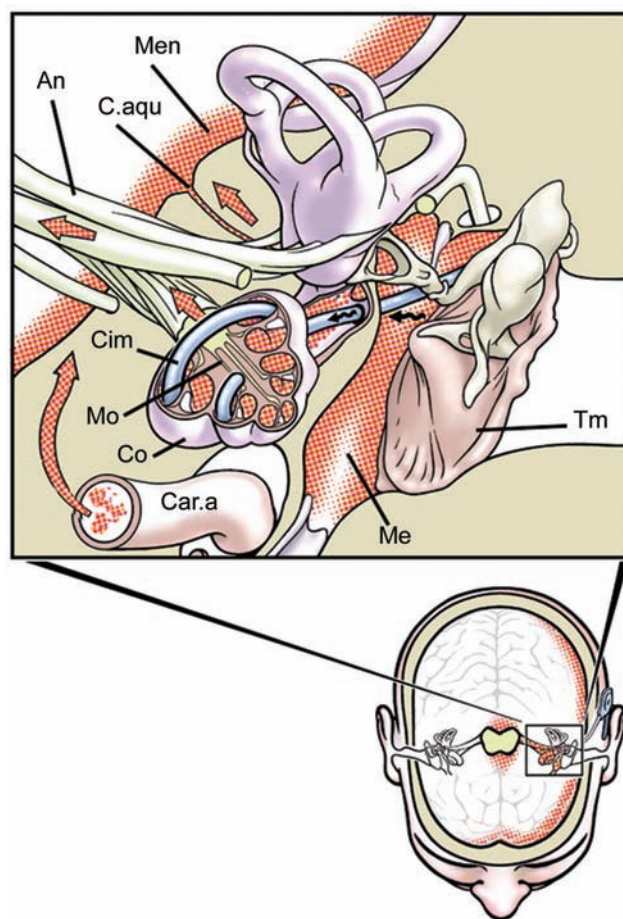


Figure 1. The patterns of spread of pneumococcal infection. Infection is represented as red stippling. Infection can spread from the blood (red stippled arrow originating within the carotid artery [CAR.A]) to the CNS. Alternatively, pneumococci can spread into the adjacent cochlea (CO) along the cochlear implant (CIM) when present (black arrows). Once the infection reaches the inner ear (i.e., the CO), it can then spread to the CNS along either the cochlear aqueduct (C.AQ) or the auditory nerve (AN; red arrows). In the presence of acute otitis media, it is possible that the bacteria can reach the CNS via the 2 described routes (directly via the inner ear or via blood circulation). MEN, meninges; ME, middle ear; MO, modiolus (i.e., the center of the CO that contains the AN); TM, tympanic membrane.

main potential routes of infection leading to meningitis [15, 16].

THRESHOLD MODEL FOR PNEUMOCOCCAL MENINGITIS

Previous work investigating meningitis caused by the bacterium *Haemophilus influenzae* in the rat demonstrated that a threshold number of bacteria were required to induce meningitis after intranasal inoculation of bacteria [17, 18]. It was considered that threshold measurements for *S. pneumoniae* in the rat would

be an effective method for investigating the anatomical and pathological mechanisms leading to meningitis in patients with implanted cochleas.

The experimental method was to inoculate adult Hooded-Wistar rats with a clinically relevant strain of *S. pneumoniae* via 3 different routes: the middle ear, the inner ear, and intraperitoneally [15, 16]. The intraperitoneal route of infection modelled blood-borne systemic infection (bacteremia). The main outcome was the development of meningitis occurring within a 5-day observation window. The animals were found to clear the infection if they had not developed meningitis 5 days after initial inoculation.

It was discovered that a threshold *S. pneumoniae* load is required to induce meningitis when the bacteria are delivered via any of 3 routes of administration [16]. The lowest threshold was obtained when *S. pneumoniae* were inoculated directly into the inner ear. Larger numbers of bacteria were required to cause meningitis after systemic inoculation, and the highest bacterial counts were required to cause meningitis after inoculation of the middle ear. Although it cannot be proven that threshold numbers of pneumococci are required to cause human meningitis, the experimental findings are consistent with some important clinical observations.

Patients with reduced immunocompetence (e.g., elderly persons and children aged <2 years) are known to be more susceptible to meningitis than the rest of the population [19, 20]. These patients presumably have a lower threshold. This can be understood within the context of a threshold model as an effective increase in the bacterial load mediated by a reduced capacity of the host to kill the inoculated pneumococci; greater numbers of bacteria survive per inoculum and the bacterial count required to cause meningitis is more easily exceeded. The rarity of meningitis in the healthy human population suggests that the bacterial thresholds for pneumococcal meningitis are not often reached, presumably because host immunity seldom fails even after infection with invasive serotypes of these bacteria. The threshold model gave us new insight as to how *S. pneumoniae* could potentially induce meningitis in human subjects. Extrapolating from this threshold model whether a healthy human subject acquires pneumococcal meningitis may depend on the route of infection and the bacterial load for each route (hematogenous or middle or inner ear route). It is important to understand that a quantitative threshold model can be established in animals but not in humans because of ethical reasons. Therefore, the animal model described in the recent literature [15, 16] is an alternative means to study human disease and is useful in that possible mechanisms behind pneumococcal meningitis in human subjects, with or without a cochlear implant, can be examined in a controlled laboratory environment.

EFFECTS OF THE COCHLEAR IMPLANT ON THE THRESHOLD FOR PNEUMOCOCCAL MENINGITIS

Next, we studied the effect of a cochlear implant procedure and electrode on an animal's susceptibility to develop meningitis. Cochlear implant electrodes were implanted into the inner ear 1 month before inoculation with *S. pneumoniae*, to model the human situation in which this period of time is required for the tissue surrounding the electrode to return to normal [21]. The bacteria levels inoculated via each of the 3 routes of administration were less than the threshold required to induce meningitis in nonimplanted control animals. Most of the animals implanted with a cochlear electrode developed meningitis, meaning that the implant is associated with a reduction in the threshold of bacteria required to induce pneumococcal meningitis, irrespective of the route of administration [22]. The increased infection rate associated with the implanted cochleae was significant for all routes of inoculation ($P < .05$, by 1-tailed Fisher's exact test) [22]. It was also shown that it was the presence of the implant and not the surgical entry into the inner ear that was associated with the increased risk of meningitis. The threshold for developing pneumococcal meningitis was not altered in a group of animals that received a cochleostomy (i.e., a small opening of the cochlea that is created surgically to allow insertion of a cochlear implant electrode array) but did not have an electrode implanted [22]. The thresholds were also not lowered when the electrode was inserted using a standard insertion technique and immediately withdrawn after insertion [22].

This recent animal study suggested that the presence of a foreign body, such as a cochlear implant, may reduce the ability of the rats' immune system to fight pneumococcal infection [22]. Therefore, fewer bacteria are required to overwhelm the immune system, compared with the immune system in nonimplanted rats. Previous studies have illustrated that the presence of a rigid, perforated polytetrafluoroethylene tube in the subcutaneous tissue of animals increased the apoptotic activity of polymorphonuclear leukocytes and impaired their ability to phagocytose bacteria [23–25]. In human subjects, it is possible that a foreign body in the inner ear can also reduce the ability of the immune cells to eliminate *S. pneumoniae*, although the detailed molecular mechanism(s) of how the foreign body impairs the function of immune cells is still unknown. This will require additional laboratory research. However, the current animal model suggested that, with impaired local immunity around the implant, a smaller quantity of bacteria was required to induce meningitis in the implanted rats. Therefore, the threshold of pneumococcal infection had been lowered in the presence of a foreign body.

EFFECTS OF INNER EAR TRAUMA ON THE THRESHOLD FOR PNEUMOCOCCAL MENINGITIS

The surgical technique and the insertion trauma to the inner ear structures have also been proposed to be possible mechanisms for post-cochlear implantation meningitis [1]. In a recent clinical study, children receiving an implant with a positioner had 4.5 times the risk of developing meningitis than did children with other cochlear implant types [2]. In human temporal bone studies, a severe insertion trauma to the bony structures of the inner ear was observed when an implant device with a positioner was fully inserted into the cochlea [26–31]. This injury appeared to occur primarily because the device was too large to permit full insertion into the scala tympani. It has been postulated that a 2-part electrode system may increase the likelihood of trauma to bony structures (osseous spiral laminae and/or modiolus) in the inner ear [11], thereby allowing bacteria direct access to the subarachnoid space once they have entered the inner ear. With use of the same threshold principle developed in the animal study, a severe inner ear trauma as a result of surgery also reduced the threshold of bacteria required for meningitis via direct routes of infection ($P < .05$, by 1-tailed Fisher's exact test) but not for hematogenous infection [32]. The likely explanation is that a severe trauma to the inner ear structures created a more direct communication route between the inner ear and the subarachnoid space of the CNS but did not alter the pathway for the bacteria to reach the meninges via the hematogenous route—that is, the bacteria have greater access to the CNS once in the traumatized inner ear [32]. Therefore, it is important to minimize the insertion trauma in the cochlea. The ideal cochlear implant design and insertion technique should not cause trauma to the cochlea during implantation. This will reduce the risk of meningitis [32].

PROTECTIVE EFFECTS OF PNEUMOCOCCAL VACCINATION

There is an urgent need to prevent meningitis in patients with implants by immunization against *S. pneumoniae*. The efficacy of immunization in reducing the risk of meningitis was tested experimentally by repeating the cochlear implantation experiment on animals that had first been immunized against pneumococcus with a 23-valent polysaccharide vaccine (PPV23) [33]. Although bacteria inoculated by each of the 3 routes caused meningitis in animals with implants that had not received the vaccine, vaccinated animals with implants were protected from meningitis when inoculated via the middle ear ($P < .05$, by 2-tailed Fisher's exact test) or systemically ($P < .05$, by 2-tailed Fisher's exact test), demonstrating that immunization is an effective means of protection [33]. The protection was less effective when inoculation was made directly

into the inner ear ($P > .05$, by 2-tailed Fisher's exact test) [33]; this implies that the immune surveillance in the inner ear is lower than for extracochlear tissues, possibly because antibody levels in cochleae are 1000 times lower than are those in serum [34]. Furthermore, the presence of a blood-labyrinthine barrier partially isolates the labyrinth from systemic immunity [35] and may reduce the transit of antibodies from the serum into the inner ear [36].

The current recommendation from the FDA, the Centers for Disease Control and Prevention, and the Advisory Committee on Immunization Practices is that all current and future cochlear implant recipients should receive age-appropriate vaccination with either PPV23 or heptavalent pneumococcal conjugated vaccine (PVC7) [1]. The recent experimental data clearly support this recommendation. However, the animal data also have suggested that pneumococcal immunization may not protect subjects from meningitis if *S. pneumoniae* reaches the inner ear from the middle ear. Therefore, any direct communication between the middle ear and the inner ear should be surgically corrected [10, 37].

In a study involving 120 cochlear implant recipients (age, 5–27 years), the mean titer of pneumococcal antibodies before PPV23 vaccination was less than the protective threshold value [38]. However, serum antibody levels to all vaccine-specific serotypes increased significantly after immunization with PPV23 [38]. Interestingly, in a comparison of the older implant recipients, the immune response to PPV23 was weaker in patients with implants who were aged 5–8 years [38], with a particularly weak response to serotypes 6B, 14, and 23F. On the other hand, PVC7 induced higher levels of antibodies than PPV23 in 38 children with implants who were aged 2–5 years [39]. Even receipt of 1 dose of PVC7 can induce a protective level of antibodies in children with implants who are aged < 2 years [39].

Although, to our knowledge, there have been no published clinical studies of the efficacy of pneumococcal immunization against meningitis in implant recipients, pneumococcal meningitis was reported in 3 children with implants who had received PCV7 and 1 child with an implant who had received PPV23 [2]; all 4 children were < 6 years of age. The serotypes of the bacteria that caused the disease were unknown for 3 of these children; in the fourth child, meningitis was caused by serotype 10A, which is not covered by PCV7. Two other children who acquired meningitis after receiving PCV7 vaccine may have had serum antibody levels that were less than the threshold, because they had received insufficient doses of the vaccine. One child with an implant developed pneumococcal meningitis 6 days after vaccination with PPV23. The immune system in this child might not have the sufficient maturity or time to respond to the vaccine. Although some serotypes contained in PCV7 may evoke a cross-reactive response to pneumococci of

the same serogroup not contained in the vaccine [40], children with implants are still vulnerable to infection with many other serotypes not covered by the vaccine. Similarly, although PPV23 covers a broader spectrum of pneumococcal serotypes, there are almost 70 other serotypes not covered by the vaccine. In addition, although PPV23 covers 85%–90% of the serotypes responsible for invasive infection in the United States [41], there are large variations in the relative frequency of serotypes of *S. pneumoniae* in different geographic areas and in specific regions over time [42]. Although pneumococcal vaccination does not necessarily prevent all cases of pneumococcal meningitis associated with a cochlear implant, there is still considerable benefit to be gained from immunizing all current and future implant recipients.

THE USE OF LOCAL ANTIMICROBIAL AGENTS TO PREVENT POSTIMPLANTATION MENINGITIS

The use of local antimicrobial agents to prevent infection due to foreign bodies may be another alternative option to combat postimplantation meningitis [43]. Current clinical data indicate that one-third of cases of implant-related meningitis occur during the first 4 weeks after cochlear implantation [1, 2]. A recent animal study that involved the use of ciprofloxacin to coat the surface of the implant reduced the risk of pneumococcal meningitis after subsequent pneumococcal bacteremia 4 weeks after surgery [43]. Although there was evidence to suggest that an electrode array coated with antimicrobial agents may reduce the risk of subsequent pneumococcal meningitis, additional research should be performed before the concept is applied to clinical practice. The major concern is the development of drug-resistant strains of *S. pneumoniae*.

CLINICAL RECOMMENDATIONS BASED ON THE CURRENT RESEARCH FINDINGS

Several clinical implications and recommendations follow from this review. First, subjects who have implants should be considered to have an increased likelihood of developing pneumococcal meningitis irrespective of the route of inoculation, whether via otitis media or a systemic infection. Because of the threshold reduction effect of a cochlear implant, patients who develop symptoms of acute otitis media or bacteremia should be assessed and treated urgently by their physicians, to reduce the risk of the infection reaching the threshold for meningitis. This is particularly paramount in cochlear implant recipients who have other preexisting risk factors. A number of clinicians have advocated the early detection and treatment of acute otitis media in cochlear implant recipients [4, 10, 44]. The use of perioperative and postoperative antibiotic prophylaxis has been recommended by the FDA [1] and implant surgeons [4, 11] to reduce meningitis in the immediate postimplantation period.

The insertion of tympanostomy tubes (grommets) and/or the use of prophylactic antibiotics in children who have received implants and who are prone to otitis media have been recommended as ways to avoid potential CNS complication until the children outgrow their susceptibility to otitis media [45–47]. Second, all cochlear implant recipients should be immunized against invasive strains of *S. pneumoniae*. Immunization should protect against otitis media and bloodborne infection but would be less effective against direct inoculation of bacteria into the cochlea. Third, minimal trauma or atraumatic surgical technique and implant designs should be implemented in clinical practice to reduce the risk of meningitis. Manufacturers have been recommended to avoid using potentially traumatic electrode arrays [48]. Biological safety testing of the meningitis risk for cochlear implants should consider all potential routes of infection, including the middle ear and hematogenous spread. Fourth, using the techniques described in the current literature, it may now be possible to quantify the risk of meningitis associated with new implant designs or novel implant materials before their release. The current FDA recommendation is to vaccinate children with implants who are aged <5 years with a series of PCV7 [1]. For children aged <6 months, 3 doses of PCV7 should be given 2 months apart, as well as an additional dose given at 12–15 months of age. For children aged 7–11 months, 2 doses of PCV7 should be given 2 months apart, as well as an additional dose given at 12–15 months of age. For children aged 12–59 months, 2 doses of PCV7 should be given 2 months apart. One dose of PPV23 is recommended for implant recipients aged >2 years.

CONTINUED DATA COLLECTION AND EPIDEMIOLOGIC STUDY

Because meningitis is associated with high morbidity and mortality, ongoing monitoring of the safety of the cochlear implant should be implemented. All cases of meningitis in implanted patients should be reported to the manufacturers and to the appropriate public authorities in each country [48, 49]. In every case of postimplantation meningitis, bacteria should be isolated from the CSF specimens and middle ear specimens, if a middle ear effusion is present [50]. Serotyping of *S. pneumoniae* cultured from implant recipients should be performed. These data are very important for understanding the frequency and distribution of different serotypes in the implanted population. The data are also useful for examining the effect of vaccination on the prevalence of postimplantation meningitis due to non-vaccine serotypes and for helping in the development of new vaccines to cover the serotypes that most frequently cause meningitis in implant recipients. In the event of a patient death due to meningitis, a postmortem examination, including examination of the temporal bones, should also be performed, to continue assessing the etiology and pathogenesis [50].

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