OTOLOGY

The biofilm characteristics and management of skin flap infection following cochlear implantation

Caratteristiche del biofilm e gestione dell'infezione da flap cutaneo dopo impianto cocleare

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SUMMARY

Objective. This study aims to assess the frequency, bacteriology, biofilm characteristics and management of skin flap infection (SFI) following cochlear implantation (CI).
Methods. The study enrolled 1,251 patients receiving CI in the First Affiliated Hospital of Fujian Medical University between August 2001 and March 2021. Scanning electron microscopy (SEM) was utilised to characterise the aetiology of infection. A proposed classification system was applied to optimise treatments for post-operative skin flap infection.
Results. After CI, SFI was reported in 16 patients (1.28%) and occurred more frequently in patients under 6 years of age. Of all SFI cases *Staphylococcus aureus* was the most common pathogen for flap infection, with 8 cases (50%) and bacterial biofilm was evident within the jelly-like substance on the surface of implanted devices in SFI patients. A two-stage classification was proposed to optimise the treatment schemes. Conservative therapy was recommended for stage I cases and surgical treatment for stage II patients.
Conclusions. Paediatric patients are more susceptible to SFI after CI, which may be attributed to the formation of bacterial biofilm. The proposed classification can facilitate the management of SFI.

KEY WORDS: cochlear implant, flap infection, biofilm, scanning electron microscope, management

RIASSUNTO

Obiettivo. Questo studio mira a valutare la frequenza, la batteriologia, le caratteristiche del biofilm e la gestione dell'infezione del lembo cutaneo di ricostruzione (SFI) dopo l'impianto cocleare (CI).
Metodi. Lo studio ha arruolato 1.251 pazienti che hanno ricevuto CI nel First Affiliated Hospital della Fujian Medical University tra Agosto 2001 e Marzo 2021. Questo studio ha utilizzato la microscopia elettronica a scansione (SEM) per caratterizzare l'eziologia dell'infezione. È stata proposta una classificazione allo scopo di ottimizzare la terapia dell'infezione post operatoria del lembo cutaneo.
Risultati. Dopo CI, SFI è stata segnalata in 16 pazienti (1,28%) e si è verificata più frequentemente in pazienti di età inferiore ai 6 anni. Lo studio ha rivelato che lo Staphylococcus aureus era l'agente patogeno più comune per l'infezione del lembo, con 8 casi registrati, equivalenti al 50% di tutti i casi di SFI. D'altra parte, il biofilm batterico era evidente all'interno della sostanza gelatinosa sulla superficie dei dispositivi impiantati nei pazienti con SFI. La classificazione proposta per ottimizzare gli schemi terapeutici prevede due stadi. La terapia conservativa è raccomandata per i casi di stadio I e il trattamento chirurgico per i pazienti di stadio II.
Conclusioni. I pazienti pediatrici sono più suscettibili a SFI dopo CI. La formazione di biofilm batterico può essere la causa di SFI. La classificazione proposta può facilitare la gestione degli SFI.

PAROLE CHIAVE: *impianto cocleare, infezione del lembo, biofilm, microscopio elettronico a scansione, gestione*

Introduction

For decades, cochlear implantation (CI) has been considered as best therapeutic method for hearing rehabilitation of patients with severe or profound sensorineural hearing loss [1,2]. Thanks to the advance and popularisation of newborn hearing screening and the revolutionary progress of CI surgical technique, bilateral severe or profound sensorineural hearing loss can be detected earlier, and postoperative complications have been significantly decreased. To date, CI surgery has been regarded as a safe procedure for auditory rehabilitation, but like any other procedure, complications still may arise. The procedure of implanting the internal device of the cochlear implant is not entirely risk-free and may result in complications that require corrective surgery. Among the recognised postoperative complications of the cochlear implant procedure is skin flap infection (SFI), which remains a substantial concern that may induce significant morbidity [2,3].

Generally, postoperative CI infections have been classified into minor or major categories and divided into early or delayed infections according to duration [4,5]. Skin flap infection (SFI), despite rigorous medical and surgical endeavours, remains one of the most challenging and devastating modes of failure following cochlear implants, which is difficult for otologists to predict and which may lead to the removal of the implanted device. Although SFI has been considered as a common complication following cochlear implantation, only a few studies have compared the efficacy of conservative and surgical treatments of SFI to date. The current study focused on bacterial biofilm formation-related infections in cochlear implantation, aiming to investigate the frequency and efficacy of management for postoperative infections and to identify the potential causes of the refractory SFI. Moreover, this study proposed a system for SFI classification that can serve as a framework in determining the most adequate type of treatment for patients.

Materials and methods

This study retrospectively reviewed the medical records of 1,251 patients who underwent CI to treat profound hearing loss at the First Affiliated Hospital of Fujian Medical University between August 2001 and March 2021.

All patients suffered from severe or profound bilateral sensorineural hearing loss (HL, defined as hearing threshold > 70 dB). Before the initial CI, assessments were conducted for acoustic impedance, auditory brainstem response, distortion product otoacoustic emissions, transient evoked otoacoustic emissions and steady-state auditory response was conducted. Middle ear high-resolution CT and inner ear MRI were performed to rule out deformity in middle and inner ears, middle ear mastoiditis, tympanic effusion, or other infections before operation. A brain MRI was conducted to reveal potential white matter lesions, and CI was considered for cases with mild and non-progressive white matter lesions. In this study, 72-hour intravenous ceftriaxone was administered for prophylactic anti-infection to both children and adults during the first and revision surgery. Meanwhile, intravenous clindamycin was used as alternative antibiotic prophylaxis for patients with penicillin allergy. Lastly, the researchers routinely administered amoxicillin-clavulanate or cefaclor orally in outpatients to control infection for seven days. For patients who suffered from severe swelling and pain, intravenous antibiotics were prescribed for one week, if the patient responded well to the antibiotic treatment.

Patients who developed postoperative infection received immediate conservative treatment or surgical intervention when the conservative treatment was ineffective. The conservative treatment was considered ineffective in the following conditions: (1) post-CI patients with SFI still manifested symptoms such as redness, swelling and pus in the exact location, and accompanied with severe pain, along with elevated white blood count, C-reactive protein (CRP) and procalcitonin (PCT), even after receiving treatment; (2) post-CI patients with SFI suffered from refractory implant extrusion, thus requiring further surgical treatment; and (3) exposed implant with skin necrosis.

Conservative treatments

The researchers routinely administered amoxicillin-clavulanate or cefaclor for outpatients to control infection for seven days. However, if the patient suffered from severe swelling and pain, intravenous antibiotics were prescribed for one week. Patients with postoperative infection were treated immediately with ceftriaxone sodium, which can penetrate the blood-brain barrier and achieve concentrations in the central neural system adequate for the potential infecting pathogen. If the patient suffered from SFI by methicillin-resistant *Staphylococcus aureus* (MRSA), the the anti-infection protocol was adjusted according to the results of pathogen culture and sensitivity analysis results for one week after revision CI. The pus was drained by needle aspiration when the formation was localised in subcutaneous tissue and sent to pathogen culture for precise antibiotic adjustment. A mastoid pressure bandage was applied for one week after the needle aspiration.

Surgical treatments

Patients unresponsive to conservative treatment received revision surgery or re-implantation surgery if the revision surgery failed. The former consisted of wound debridement,

cleaning up granulation tissue in the bone groove, rinsing devices with 3% hydrogen peroxide, normal saline and 1% iodophor repeatedly, before covering the groove with suitable anterosuperior temporal muscle. The latter involved explanting receiver/stimulator but saving the electrode in cochlear to avoid fibrosis and cochlear ossification, and implanting a new implant in the contralateral side. A 3-day administration of ceftriaxone followed both surgical treatments.

Scanning electron microscopy

The jelly-like biofilm on the surface of the receiver/stimulator was rinsed with phosphate-buffered saline (PBS) 3 times (1 minute per time), and soaked in 1% osmic acid solution at $< 4°C$ for two hours. Next, samples were sequentially dehydrated in 30, 50, 70, 85, 95 and 100% ethanol for 15 minutes each, respectively. After the CO_2 critical dry-point and correcting the position and orientation, samples were placed on the platform for sputter-coated with gold in a vacuum condition and examined in a high vacuum of 20 kv under a scanning electron microscope (SEM; American FEI company, model Quanta 450). Multiple bacterial biofilms in the SEM areas of each specimen were observed by multiple magnifications (50-10,000 times).

The formation of bacterial biofilms was diagnosed when images met three criteria: (1) dense accumulation of bacterial cells; (2) he presence of a polysaccharide matrix around bacterial cells; and (3) firm surface binding [6].

Statistical analysis

The two-sided statistical analyses in this study were performed using SPSS software (version 26.0; SPSS Inc., Chicago, IL, USA). Differences among categorical variables were assessed by Fisher's test as appropriate, including sex, age, implant side, different regimens and outcomes. P-values of less than 0.05 indicated statistical significance. Lastly, this study employed a 95% confidence interval.

Results

Demographic and clinical characteristics of patients receiving cochlear implantations

A total of 1,251 CI cases (739 males, 59.05% and 512 females, 40.95%) were enrolled (Tab. I), with CI performed on 898 right ears (71.79%), 337 left ears (26.90%), and 16 bilateral ears (1.28%); surgery age ranged from 10 months to 63 years old, with a mean age of 7.3 years and a median age of 3.5 years. All cases were operated by the same senior surgeon between August 2001 and March 2021.

A total of 16 SFI patients were reported in the entire CI patient cohort (1.28%, 8 males and 8 females), who were all under 6 years of age ($p < 0.05$), with a mean age of 3.09 years (Tab. II). The onset of SFI symptoms ranged from 20 days to 3 years after the implantation, affecting 14 right ears (87.5%), 1 left ear (6.25%) and 1 bilaterally (6.25%). Gender was not significantly different ($p > 0.05$). Laterality showed a significant difference ($p < 0.05$), but paired statistics revealed no significance ($p > 0.05$ for all three paired statistics). Three post-CI children (3/16) encountered mild skin injury after the first CI, and two patients reported sensitivity to cicatricial diathesis.

Clinical management

Among the 16 children, 3 were cured by conservative methods (3/16, 18.75%) and 13 by surgery (13/16, 81.25%). In the surgery group, 3 patients were cured by revision surgery (3/13, 23.08%) ($p > 0.05$) and 10 received re-implantation surgery after initial revision surgery (10/13, 76.92%) ($p < 0.05$). Among all infectious symptoms (Tab. III), skin redness was reported in 2 patients (2/16, 12.5%), in which 1 was cured by conservative methods and the other by revision surgery. Subcutaneous pus formation was found in 4 patients (4/16, 25%), in which two were cured by conservative methods and two by re-implantation surgery. Pus was managed by needle aspiration in 7 patients (7/16, 43.75%), one by revision surgery (1/7, 14.3%) and 6 by re-implantation surgery (6/7, 85.7%). The implant was exposed in 3 patients and rescued by re-implantation surgery (100%).

The results showed no significant differences in therapeutic efficacy between conservative and surgical treatments ($p > 0.05$) in skin redness or subcutaneous pus formation, but a noticeable significance was seen for punctured pus when re-implantation was compared with either revision surgery or conservative treatment ($p < 0.05$, respectively). The effectiveness of revision surgery was not statistically different in any symptom groups ($p > 0.05$) (Fig. 1). All patients received long-term follow-up, the mean duration of which was 5.1 ± 3.4 years after final treatment.

Scanning electron microscopy

On the images by scanning electron microscopy (Fig. 2), microorganisms consistent with *Staphylococcus aureus* or *Staphylococcus epidermidis* and exopolymeric matrix were found over the surface of the stimulator-receiver, but not on the electrode array. A large mesh was observed in the middle of the grid.

Histopathological examination

Granulation tissue appeared in the bone groove, and foam-like tissue cells surrounding the receiver/stimulator were visualised in granulation tissue by haematoxylin-eosin staining, indicating that the symptoms of SFI cases can be attributed to a chronic inflammatory reaction (Fig. 2).

Table I. Demographic and clinical characteristics of the 1,251 patients with cochlear implants.

	Infection n = 16	P-value (95% CI)	No infection n = 1235	Total n = 1251
Gender		0.457 (0.257, 1.849)		
Male	8 (0.64%)		731	739(59.1%)
Female	8 (0.64%)		504	512 (40.9%)
Age		0.017* (0.975, 0.991)		
≤ 6	16 (1.28%)		930	946 (75.6%)
> 6	0		305	305 (24.4%)
Side implanted		0.038*		
Right	14		884	898 (71.78%)
Left	1		336	337 (26.93%)
Bilateral	1		15	16 (1.28%)
Pathogen				
MSSA	5 (31.25%)			
MRSA	3 (18.75%)			
MSSE	2 (12.5%)			
MRSE	2 (12.5%)			
P. aeruginosa	1 (6.25%)			
S. hominis	1 (6.25%)			
None detected	2 (12.5%)			
Treatment for last time				
Conservation	3 (18.75%)		-	
Surgical treatments				
Revision surgery	3 (18.75%)		-	
Re-implant surgery	10 (62.5%)		-	

MSSA: methicillin-sensitive Staphylococcus aureus; MRSA: methicillin-resistant Staphylococcus aureus; MRSE: methicillin-resistant Staphylococcus epidermidis; MSSE: methicillin-sensitive Staphylococcus epidermidis; P. aeruginosa: Pseudomonas aeruginosa; S. hominis: Staphylococcus hominis; 95% CI: 95% Confidence Interval. * P < 0.05.

Discussion

Postoperative infection is one of the most common complications [5,7], following cochlear implantation, and conservative treatments are suggested to be primary and first-line treatment. For post-CI infection, a routine procedure may sequentially involve antibiotic treatments, pus puncture, revision surgery and re-implantation [8], which does not take into account the specific clinical postoperative manifestations of CI and may cause refractory SFI. Therefore, a more accurate and efficient staging system is needed.

In the current study, the integrity of local skin was an index that significantly influenced the diagnosis and efficacy of treatments for post-CI infection. Before the skin ruptures, oral or intravenous antibiotic therapy was prescribed. Puncture and aetiology-guided antibiotics were administered after abscess formation. Once the integrity of the skin flap was breached, most patients needed to be cured by re-implantation. These findings suggest that the integrity of skin flap can serve as a facilitating index to stratify clinical manifestations (Fig. 3):
- **Stage I**. Complete skin with redness and swelling or subcutaneous pus formation that can be adequately address by conservative treatment
- **Stage II**. A skin defect or flap rupture with implant device extrusion that can be remedied by re-implantation.

Of note, in the current study, revision surgery was attempted to prevent the receiver/stimulator from explant, which proved to be ineffective at Stage II. Thus, re-implantation plays a vital role in the prognosis of patients at Stage II.

This classification system is proposed to address post-operative infection. It can promote the accuracy and effectiveness of a specific treatment, relieving pain and reducing hospitalisation and costs. However, due to a lack of adequate samples, the effectiveness of conservative treatments for Stage I was statistically insignificant, which needs further research.

In addition, this classification system was only applied for

Table II. Clinical data of the 16 patients with skin flap infection after cochlear implantation.

NO	Gender	Age (y/o)	Hospitalisation (days)	Side of infection	Post-op (days)	Clinical manifestations	Pathogen	Prognosis
1	F	2.75	2	Left	20	Ulcer and purulent	MRSA	Revision Surgery + Cured
2	M	5	2	Left	1095	Skin redness	MSSA	Revision Surgery + Cured
3	F	1	4	Right	300	Partial prolapse	MRSE	Explant + right implant
4	F	2.75	2	Right	210	Ulcer and purulent	MRSE	Explant + left implant
5	F	5	4	Right	912	Ear discharge	*P. aeruginosa*	Explant + left implant
6	M	1.83	3	Right	365	Ulcer and purulent	MSSE	Explant + left implant
7	M	4	3	Right	150	Ulcer and purulent	MSSE	Explant + left implant
8	M	2.75	3	Right	60	Completely out	MSSA	Explant
9	F	1.08	2	Right	30	Abscess formation	MSSA	Puncture + Cured
10	F	4	5	Right	365	Ulcer and purulent	*S. hominis*	Explant + left implant
11	M	2	3	Right	730	Abscess formation	ND	Explant + left implant
12	F	1.33	3	Right	45	Ulcer and purulent	MSSA	Explant + left implant
13	M	4	0	Right	365	Skin redness	MRSA	Puncture + Cured
14	M	6	0	Right	730	Abscess formation	MRSA	Puncture + Cured
15	M	3	3	Right	60	Partial prolapse	MSSA	Explant + left implant
16	M	3	2	Right	300	Skin redness and purulent	Nil	Revision Surgery + Cured

MSSA: methicillin-sensitive Staphylococcus aureus; MRSA: methicillin-resistant Staphylococcus aureus; MSSE: methicillin-sensitive Staphylococcus epidermidis; MRSE: methicillin-resistant Staphylococcus epidermidis; P. aeruginosa: Pseudomonas aeruginosa; S.hominis: Staphylococcus hominis; ND: not detected.

Table III. The prognosis of optional treatments for skin flap infections.

	Feature	Conservative treatment		Surgical treatment		*P*-value (95% CI)
		Antibiotics or/and Puncture	Revision surgery	Re-implant surgery	*P*-value (95% CI)	
Stage I	Skin redness	1	1	0	0.99 (0.3,1.484)	0.464 (0.225,1.113)
	Skin complete with pus formation	2	1	1		
Stage II	A skin defect with purulent infection	0	1	6	0.00012* (0.016,0.642)	0.00001* (0.000,0.0898)
	Partial out	0	0	2		
	Completely out	0	0	1		
Total	-	3	3	10		

*95% CI, 95% Confidence Interval. * P < 0.05.*

post-CI SFI patients with positive bacterial culture results. Skin injury, from antenna pressure stratified by the National Pressure Ulcer Advisory Panel [5] and foreign body response including knot and device, is not involved in the current classification system. Similar symptoms from infection, antenna pressure and foreign body response may battle the decision on a correct system, which needs more comprehensive study.

It is worth mentioning that no apparent malfunctions were reported after cochlear implants, which suggests that post-CI infection only affects the bone groove and skin flap where the receiver/stimulator is located while the cochlear electrodes are safe. However, some studies have report-

ed that the device's function can be affected after SFI [9,10], which is related to persistent infection and hypersensitivity caused by the infection [9]. Therefore, such complications should also be considered.

The postoperative infection rate in this study is similar to that of several previous studies, within the range of 1.6~8.2% [11]. The incidence of complications has remained stable for many decades [5,12], no matter how experienced the surgeon is with cochlear implantation. This study revealed that all patients with SFI were under the age of 6 years, which may be attributed to malnutrition and potential trauma to the implanted site from daily activities, resulting in skin reactions and thinning of the flap. *Staphylococcus au-*

Figure 1. Local symptoms of different classifications on the stimulator/receiver sites. (**A-B**) the pus formed under the skin, with the skin integrity preserved. Features such as (A) and (B) were designated as stage I, in which conservative treatment was the preferred treatment; (**C**) implant was partly exposed; (**D**) implant was completely exposed. Features such as (C) and (D) were designated as stage II, in which the re-implant surgery was the preferred treatment.

reus, *Staphylococcus epidermidis* and *Pseudomonas aeruginosa* are recognised as the most easily-colonised bacteria on the surface of implants in most studies [2,5,8]. However, for most SFI cases in the research centre, conservative treatment, even guided by culture results, cannot thoroughly eradicate SFI, which may relapse in weeks or months.

A jelly-like substance on the flap-covered side of the receiver-stimulator concentrated in the centre and scattered around it, which turned out to be a bacterial biofilm by SEM. It can be suspected that biofilm formation has a more significant impact on the recurrent SFI than antibiotic resistant strains.

It was possible to remove the granulation tissue around the implant and soak the receiver-stimulator of the implant with 1.5% hydrogen peroxide and aqueous solution of betadine for 30 minutes as reported by Skrivan et al. [13] The implants were subsequently covered with part of temporalis for protection, but the results were negative. Grover et al. chose to re-grind a new bone groove located away from the original bone groove and infected area to place the receiver [3].
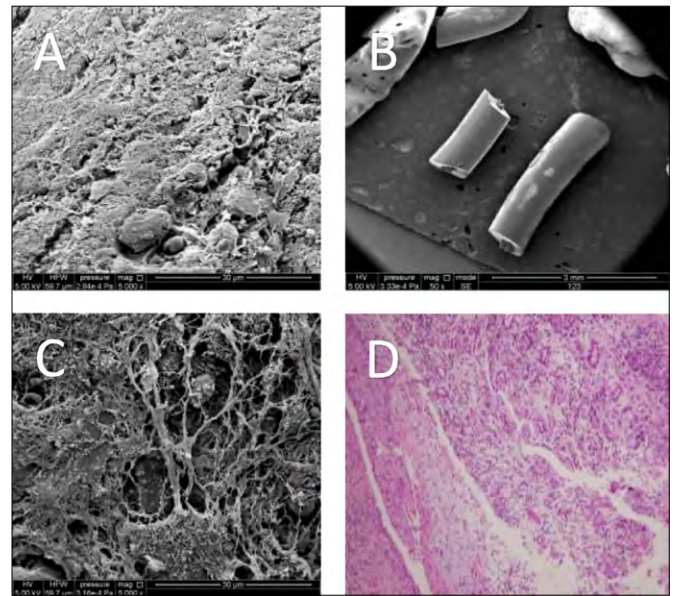

Figure 2. Scanning electron microscopic images of implants and histopathological images of bacteria-suspected material due to severe skin flap necrosis with the stimulator-receiver exposure. (**A**) Cocci were imbedded in exopolymeric matrix over the receiver/stimulator (5000×); (**B**) the electrode array was clear (50×); (**C**) Cocci were embedded in exopolymeric matrix over the receiver/stimulator. Large mesh was observed in the middle of the grid (5000×); (**D**) histopathological findings showed chronic inflammation, with epithelium in the foci absent, granulation tissue formed and foam-like tissue cells aggregated in the tissue section of granulation in the bottom of bone groove.
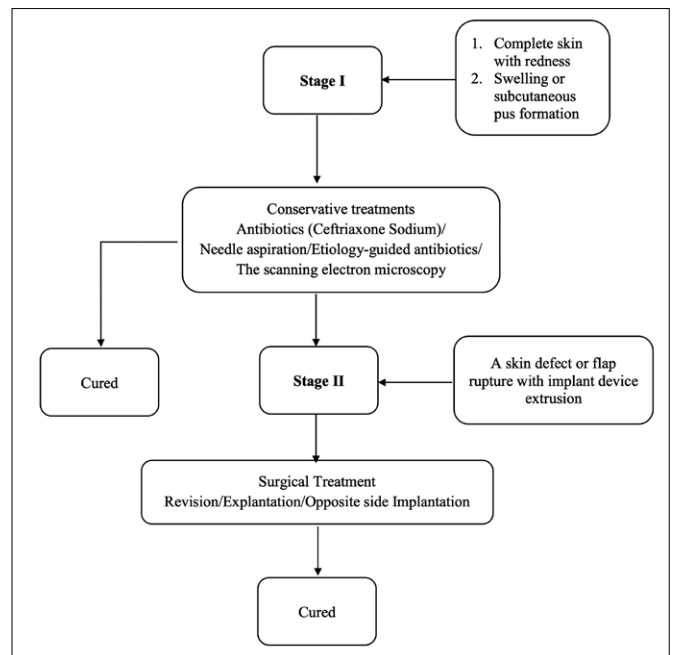

Figure 3. The flow chart of the management of SFI. If initial symptoms are classified as Stage I, conservative treatments and/or pus drainage and etiology-guided antibiotics are preferred. If initial symptoms are classified as Stage II or Stage I patients are irresponsive to the prescribed treatments, the surgical treatments, especially re-implantation is necessary.

This method can be used as a reference, but may potentially damage the skull of patients, making them vulnerable to intracranial trauma when hit by force.

Biofilm is easily found on the surface of the device and mostly distributed in the centre of the device [9]. This may be due to the absence of a silicone package over the magnetic pole in the centre of the receiver/stimulator, which indicates the need for design and material improvements of receiver-stimulators to reduce the possibility of post-CI infection. Tea tree oil (the essential oil of Melaleuca) has been demonstrated to remove methicillin-resistant *Staphylococcus aureus* from the surface of implants [14-16]. Bioactive glass such as S53P4, as a promising tool containing sodium oxide, phosphorus pentoxide, silicon dioxide and calcium oxide, can successfully inhibit the mature bacterial biofilm on the surface of the implanted receiver/stimulator [17-19]. Using polymer composite sponges with inherent antibacterial, haemostatic, inflammation-modulating in surgery may prevent biofilm dispersal [20]. However, the availability and safety of these materials await further exploration.

Bacterial biofilm is a complex ecosystem. Multi-microbial aggregates composed of various bacteria are embedded in exopolysaccharides (EPS), mainly composed of polysaccharides, protein-nucleic acids and lipids [21]. Antibiotics only inhibit the planktonic bacteria released by the biofilm, but fail to eliminate the biofilm [22]. Bacteria are generally located in the middle layer of the membrane and are wrapped with the EPS [23], making it difficult for antibiotics to penetrate all biofilm layers and eliminate the bacteria. On the other hand, the implanted cochlear may provide acquired conditions for the biofilm to resist the environmental changes and the human immune system [24], which usually terminates when the antenna is removed from the body through a procedure [22]. This complexity may explain the recurrent bacterial infection and the irresponsive antibiotic treatment.

We presume that implant rejection may occur in some cases instead of the biofilm-related infection, which can explain repeated infection after revision surgery. However, they can be cured by re-implantation surgery, and bacteria can be present in pus around the receiver/stimulator. Thus, rejection may not be the direct and primary cause of the flap infection.

Aseptic enhancement during the initial surgery can alleviate the suffering of patients and preserve the expensive devices by inhibiting the biofilm formation. CI surgery can only commence after the complete resolution of inflammation in the ears [5]. Preoperative skin preparation significantly reduces the postoperative infection rate [25], including waxing the patient's hair a few days before CI, cleansing the patients' external auditory canal with 70% alcohol daily with 0.5% chlorhexidine, and wiping the surgical skin area [5].

The position of CI incision also impacts the infection rate. Kabelka et al. found that the postoperative SFI rate of the incision behind the ear was about 15 times lower than that of the incision in the ear [5]. Gawecki et al. found that when a short C-type incision behind the ear was compared with a long incision, the infection rate decreased from 2.43% (11/452) to 1.28% (8/624) [5]. In this study, all cases were operated with a short C-type incision behind the ear, and the overall infection rate was lower than in many institutions [11]. Ceftriaxone injection is generally used as a preventive medication for 3 days after the initial surgery. Valdecasas et al. [5] reported that the postoperative infection rate was significantly reduced when patients with titanium-silicon-coated implants received 6 weeks of clarithromycin post-operative instead of only a preoperative dose (relative risk reduction of 8:1). They hypothesised that the presence of biofilms on these specific implant surfaces plays a primary role and that clarithromycin has potential bacteriostatic and bacteriocidal properties at low and high doses, respectively.

However, this study has some limitations given its retrospective nature. The number of patients who suffered from SFI was limited, and the results of this study should be confirmed in well-controlled, prospective, randomised controlled studies of clinical cases.

Conclusions

In summary, we propose a staging system to classify the treatment of SFI, which may optimise individual treatment strategies and reduce hospitalisations and costs for patients. Bacterial aetiological analysis reveals that bacterial biofilm contributes to recurrent CI infections, which can be cured by re-implantation. Younger patients with CI surgery are at a high risk of refractory repeated infection, indicating a need of efficient follow-up strategies for this patient population.

Author contributions

XC and YC contributed equally to this work as first author. XC and CL conceived and designed the study. XC and YC analysed the data, generated the figures and wrote the manuscript. ZL and SN collected the data. RZ and SY provided critical revision. All authors read and approved the article.

Ethical consideration

The Ethics Committee of the First Affiliated Hospital of Fujian Medical University approved the study (2016-138). The procedures and protocols implemented in the conduct of this study strictly adhered to the requirements established by the ethics committee and institutional review board of the First Affiliated Hospital of Fujian Medical University and followed the requirements of the World Medical Association's Declaration of Helsinki.

All participants included in the study signed informed consent.

Availability of data and material

The raw data are available on request.

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