The biofilm characteristics and management of skin flap infection following cochlear implantation: A prospective study from 2001 to 2021

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Abstract

Objective: To assess the clinical features and the management of skin flap infection (SFI) following cochlear implantation (CI) and to characterize the biofilm features by the scanning electron microscopy.Setting: The study was conducted at a tertiary care center.Participants: A total of 1,251 patients receiving CI in the First Affiliated Hospital of Fujian Medical University between August 2001 and March 2021 were enrolled. Scanning electron microscopy was utilized for characterizing the etiology of infection. Main outcome measures: A proposed stratification system was applied to optimize treatments for post-operation flap infection.Results: After CI, SFI was reported in 16 patients (1.28%) and patients under 18-year-old were more prone to flap infection. Staphylococcus Aureus was found to be the most common bacterial culprit for flap infection, with 6 cases explored in this group (6/16, 37.5%). Bacterial biofilm was observed within the jelly-like substance on the surface of CI equipment of SFI patients. A two-stage stratification was proposed for optimizing the treatment schemes. Conservative therapy was recommended for stage I cases while surgical treatment was the preferred method for stage II patients.Conclusions: Pediatric patients are more susceptible to SFI after CI. The formation of bacterial biofilm may be the vital cause of SFI. The proposed stratification can facilitate the management of SFI.

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Main outcome measures A proposed stratification system was applied to optimize treatments for post-operation flap infection.

Results After CI, SFI was reported in 16 patients (1.28%) and patients under 6-year-old were more prone to flap infection. Staphylococcus Aureus was found to be the most common bacterial culprit for flap infection, with 6 cases explored in this group (6/16, 37.5%). Bacterial biofilm was observed within the jelly-like substance on the surface of CI equipment of SFI patients. A two-stage stratification was proposed for optimizing the treatment schemes. Conservative therapy was recommended for stage I cases while surgical treatment was the preferred method for stage II patients.

Conclusions Pediatric patients are more susceptible to SFI after CI. The formation of bacterial biofilm may be the vital cause of SFI. The proposed stratification can facilitate the management of SFI.

Keywords Cochlear implant; biofilm; infection; scanning electron microscope; management

Key Points

· The study proposes a system to stratify the SFI treatments, which may optimize individual treatment strategies and reduce hospitalization and cost for all patients.

· Bacterial biofilm is found in the receiver-stimulator area of SFI after cochlear implantation.

· A treatment flow is conceived to address the SFI patients more accurately.

· The skin integrity of the infectious area indicates different regimens toward SFI after the implantation.

1.Introduction

Cochlear implantation (CI) is considered as a well-defined and safe surgical procedure allowing hearing rehabilitation of patients with severe or profound hearing loss[1,2] . With the advance and popularization of newborn hearing screening, bilateral severe or profound sensorineural hearing loss can be detected earlier. CI surgical technique has progressed strongly over the past decade, with operations increasing and postoperative complications decreasing. Postoperative skin flap infections, a recognized complication of cochlear implant procedure, may induce significant morbidity[2,3].

Generally, CI postoperative infections have been classified into the minor or major complications and also can be divided into early or delayed infections according to duration[4,5]. Skin flap infection (SFI) remains one of the most challenging and devastating modes of failure following cochlear implants, which is difficult for the otologists to predict and may ultimately lead to device removal, despite rigorous medical and surgical endeavors to eradicate the infections.

To date, however, few studies have compared the efficiency between conservative and surgical treatments. The current study focused on the bacterial biofilm formation-related infections of cochlear implantation. It aimed to investigate frequency and efficacy management of postoperative infections and to identify the potential causes of the refractory SFI.

2.Methods

Design

Each included patient gave their informed consent to participate in the study. The study protocol was approved by the ethics committee and institutional review board of the hospital.

All 16 SFI patients who developed postoperative infection received immediate conservative treatment or surgical intervention when the conservative treatment was proven ineffective.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon request.

Setting

The study was conducted at a tertiary care center.

Participants

Retrospectively reviewed were the medical records of 1,251 patients who underwent CI to treat profound hearing loss between August 2001 and March 2021.All patients suffered severe or very severe bilateral sensorineural hearing loss (HL, defined as hearing threshold $>$ 70 dB HL). Before the initial CI, assessments were conducted of acoustic impedance, auditory brainstem response, distortion product otoacoustic emissions, transient evoked otoacoustic emissions, auditory steady state response. Middle ear high-resolution CT (HRCT) and inner ear magnetic resonance hydrography were performed to rule out the deformity in middle and inner ears, middle ear mastoiditis, tympanic effusion, or other infections before operation. Brain MRI examination was conducted to reveal potential white matter lesions and CI was considered for those cases with mild and non-progressive white matter lesions.

Main outcome measures

Patients with postoperative infection were treated immediately with ceftriaxone sodium and subsequently with pathogen-specific antibiotics on the basis of the culture results. The pus was drained when the formation was localized in the subcutaneous tissue.

Patients irresponsive to conservative treatment received revision surgery or re-implantation surgery if the revision surgery failed. The former consisted of cleaning up granulation tissue in the bone groove, rinsing equipment with 3% hydrogen peroxide, normal saline, and 1% iodophor repeatedly, finally reverting suitable temporal muscle covering the groove. The latter involved explanting equipment but saving the electrode in cochlear, and implanting a new cochlear in the opposite side. Both surgical treatments were followed by a 3-day administration of ceftriaxone sodium.

The jelly-like biofilm on the surface of receiver/stimulator was rinsed with phosphate buffered saline (PBS) 3 times (1 minute per time), soaked in 1% osmic acid solution at < 4 for 2 h. Then, the samples were sequentially dehydrated in 30%, 50%, 70%, 85%, 95%, and 100% ethanol for 15 minutes per time, 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 20kv under a scanning electron microscope (SEM; American FEI company, model Quanta 450). Multiple bacterial biofilm SEM areas of each specimen were observed with multiple magnifications (50 10000 times).

The formation of bacterial biofilms was diagnosed when the images met the three criteria: dense

accumulation of bacterial cells, the presence of a polysaccharide matrix around bacterial cells, and firm surface binding[6].

All statistical tests were performed using SPSS software (version 26.0; SPSS Inc., Chicago, IL, USA). The differences of categorical variables were assessed using Fisher's test as appropriate including sex, age, implant side, different regimens and outcomes. P -values of less than 0.05 indicated statistical significance. All statistical tests were two-sided.

3 Results

A total of 1,251 CI cases (739 males, 59.05% and 512 females, 40.95%) were reviewed (Table 1), 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 old and a median age of 3.5 years old. All cases were operated by one surgeon in our institution between August 2001 and March 2021.

A total of 16 SFI patients were reported from the whole CI patient cohort (1.28%, 8 males and 8 females), who were all under 6 years old ($p < 0.05$), with a mean age of 3.09 years old (Table 2). 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 bilateral ear (6.25%). Gender were not significantly different. Laterality was significant difference ($p < 0.05$), but paired statistics revealed no significance ($p > 0.05$ for all three paired statistics).

Of the 16 children, three were cured by conservative methods (3/16, 18.75%) and thirteen by surgery (13/16, 81.25%). In the latter group, three patients were cured by revision surgery (3/13, 23.08%) and ten failed to be remedied by initial revision surgery but cured by subsequent re-implantation surgery (10/13, 76.92%) ($p< 0.05$).

In all infectious symptoms (Table 3), skin redness was reported in 2 patients (2/16, 12.5%), one cured by conservative method and the other by revision surgery; subcutaneous pus formation was found in 4 patients (4/16, 25%), two cured by conservative method and two by re-implantation surgery; punctured pus 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 indicated no significant differences in therapeutic efficacy between conservative and surgical treatments in skin redness or subcutaneous pus formation but noticeable significance for punctured pus when re-implantation was compared with either revision surgery or conservative treatment ($p < 0.05$, respectively). The revision surgery was not effective regardless of the clinical manifestations (Figure1).

On the images by scanning electron microscopy (Figure 2), microorganisms, consistent with *Staphylococcus* , and matrix were found over the surface of the stimulator-receiver, but not on the electrode. Large mesh can be seen in the middle of the grid.

Granulation tissue appeared in the bone groove and surrounding the cochlear equipment, foam-like tissue cells was visualized in the granulation tissue by the hematoxylin-eosin staining, which indicates that the symptoms of SFI cases are chronic inflammation reaction (Figure 2).

4 Discussion

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

In the current study, the integrity of local skin is a significant index that greatly influences the diagnosis and efficacy of treatments for post-CI infection. Before the skin ruptures, oral or intravenous antibiotic therapy was prescribed. Puncture and etiology-guided antibiotics were administered after abscess was formed. Once the integrity of the skin flap was breached, the majority of patients were cured by re-implantation. These findings suggest that for all SFI cases, the integrity of skin flap can serve as a facilitating index for stratifying the clinical manifestations (Figure 3):

Stage I: Complete skin with redness and swelling or subcutaneous pus formation that can be properly addressed by conservative treatment.

Stage II: Ruptured pus formation or exposed implant that can be remedied by re-implantation.

Of note, the revision surgery was attempted to prevent the cochlear equipment from explant, which proved to be ineffective at any stage in the current study. Thus, re-implantation plays an important role in the prognosis of patients at stage II.

This stratification system only targets the post-CI SFI, whose bacterial culture was a positive result. The 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 stratification system. The similar symptoms of infection, antenna pressure, and foreign body response may pose some confusion in choosing a correct system, which needs a more comprehensive study.

It is worth mentioning that in all cases of post-CI infection, no obvious malfunctions were reported in 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. But some studies have reported that the function of the device was affected after SFI[9,10], which is related to persistent infection and the hypersensitivity caused by the infection[9]. Therefore, such complications should also be considered.

The rate of postoperative infection in the current 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. Staphylococcus and pseudomonas are recognized as the most easily-colonized bacteria on the surface of implants in most studies[5,8]. But for all cases of infection in our center, conservative treatment, even guided by culture results, cannot eradicate SFI thoroughly, which may relapse in weeks or months.

We found a jelly-like substance on the flap-covered side, which concentrated in the center and scattered around, and observed a bacterial biofilm under the scanning electron microscope. We suspect that antibiotic-resistant bacterial infection may be one of the recurrent reasons, while the formation of biofilm has a greater impact on the recurrent SFI.

Biofilm is easily found on the surface of the device, and most distributed in the center of the device[9]. This may be due to the absence of a silicone package over the magnetic pole in the center of the equipment, which indicates that the design and material improvements are needed for the receiver-stimulators so as to reduce the probability of infection after CI. Tea tree oil (the essential oil of Melaleuca) was found to remove methicillin-resistant Staphylococcus aureus from the surface of the implants[13-15]. Bioactive glass particles can inhibit the mature bacterial biofilm on the surface of the cochlear equipment[16]. But the availability and safety of these materials await further exploration.

Bacterial biofilm is a complex ecosystem. Multi-microbial aggregates composed of a variety of bacteria are embedded in the exopolysaccharides (EPS), mainly composed of polysaccharides, protein-nucleic acids, and lipids[17]. Antibiotics only inhibit the planktonic bacteria released by the biofilm, but fail to eliminate the biofilm[18]. Bacteria are generally located in the middle layer of the membrane and are wrapped with the EPS[19], which makes it difficult for antibiotics to penetrate every layer of the biofilm and clean bacteria up. On the other hand, the implanted cochlear may provide acquired conditions for the biofilm to resist the environmental changes and the human immune system[20], which usually terminates when the antenna is removed from the body by procedure[18]. This complexity may explain the recurrent bacterial infection and the irresponsive antibiotic treatment.

In the revision surgery of SFI, the surface of the receiver-stimulator was covered with the jelly-like biofilm, which was similar to the substance found by Jiri et al[21]. On the electron microscopic images at 5000 times, a morphology of typical dense network can be observed in the bacterial biofilms, with pipe-shaped channels, which is in line with the morphology reported by Gi Jung Im et al[9].

How to eradicate biofilm is a challenging handicap. We managed to remove the granulation around the implant and soaked the receiver-stimulator of the implant with 1.5% hydrogen peroxide and the aqueous solution of betadine for 30 minutes as reported by Jiri Skrivan et al.[21], and covered with part of temporalis to protect the equipment, but the results were negative. Mohnish Grover et al. chose to re-grind a new bone groove which was located away from the original bone groove and infected area to place the receiver[3]. This is a method that can be used as a reference, but it will damage the skull of patients. The original place with a weak skull is vulnerable to intracranial trauma when hit by force.

Aseptic enhancement during the initial surgery can reduce the patients' pain and preserve the expensive devices via inhibiting the formation of biofilm. The CI surgery can only commence after the complete curation of inflammation in the ears[5]. Preoperative skin preparation in the operating room significantly reduces the postoperative infection rate[22,23], including waxing the patient's hair a few days before CI, lavaging the patients' external auditory canal with 70% alcohol daily with 0.5% chlorhexidine, and wiping the skin of the surgery area[5].

The position of CI incision also impacts the infectious 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 the short C-type incision behind the ear was compared with the long incision, the infection rate dropped from 2.43% (11/452) to 1.28% (8/624)[5]. In our cohorts, all cases were operated with short C-type incision behind the ear and the overall infectious rate was lower than in many institutions[11].

Ceftriaxone sodium injection is generally used as a preventive medication for 3 days after the initial surgery. Garcia Valdecasas et al. reported that ceramic-coated cochlear implants such as MED-EL implants and

Cochlear Nucleus and Advanced Bionics implants employ titanium silicon for the artificial coating, using ceftriaxone sodium before surgery and clarithromycin after surgery, in which the postoperative infection rate is significantly lower than that of ceftriaxone sodium alone[5]. This can be a different inspiration. Lisa Kirchhoff et al.[24] tried to utilize bioactive glass (BAG) of type S53P4 as a promising tool for the reduction of biofilm formation.

5. Conclusion

In summary, with the reviewed clinical data of the enrolled cohort patients, this study proposes a staging system to stratify the treatment of SFI, which may optimize individual treatment strategies and reduce hospitalization and cost for all patients. The bacterial etiological analysis reveals that the presence of bacterial biofilm contributes to the recurrent CI infections, which can be cured by re-implantation. Given the large cohort of CI patients and infectious risk factors analyzed, younger patients with CI surgery are at a high risk of refractory repeated infection, indicating that additional efficient follow-up strategies should be implemented for the underaged.

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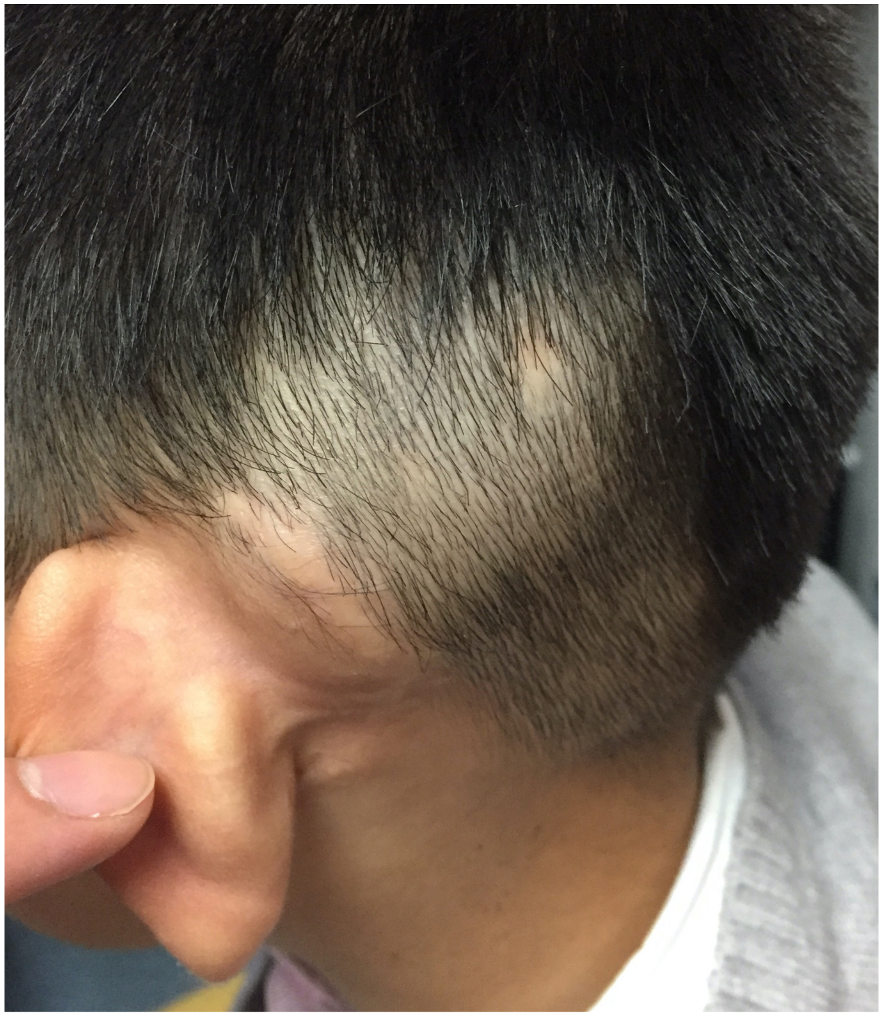

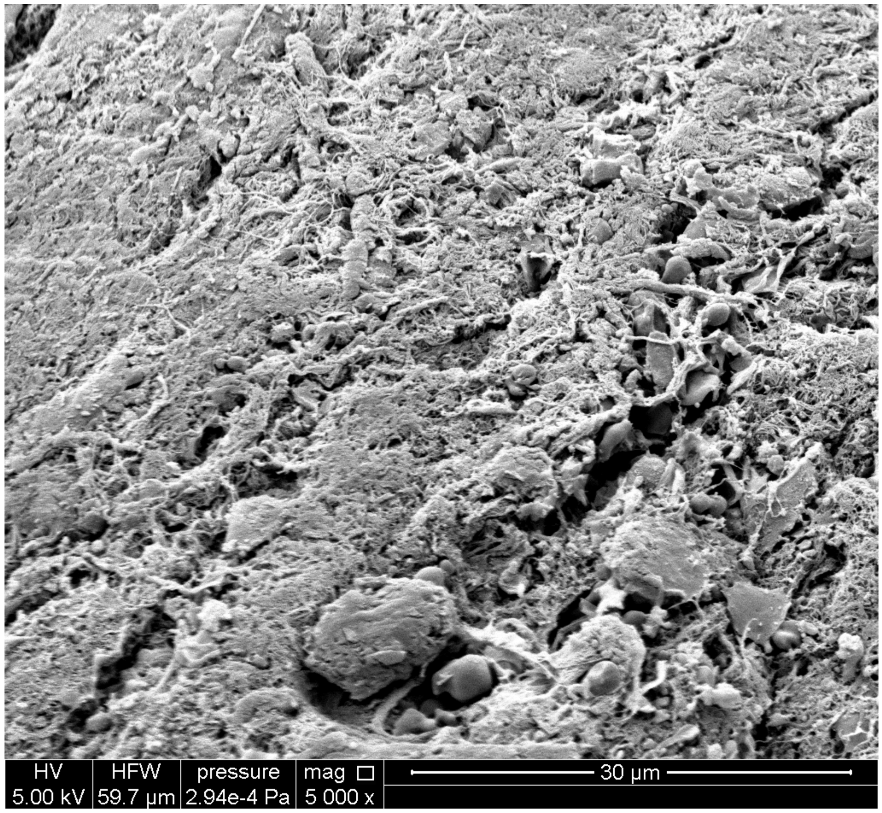
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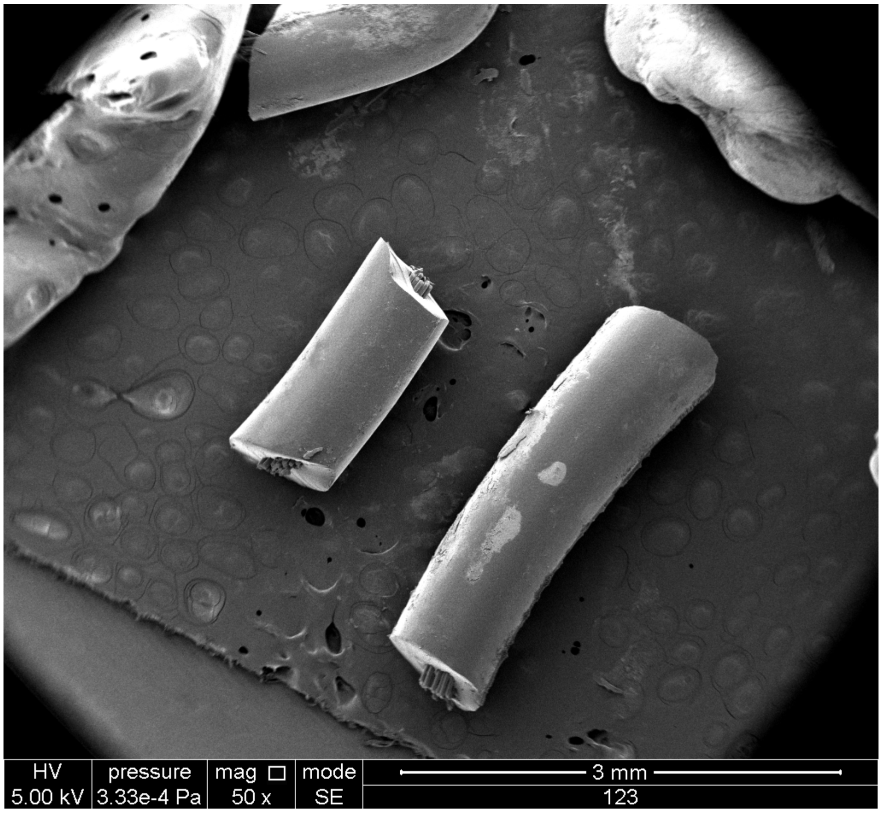
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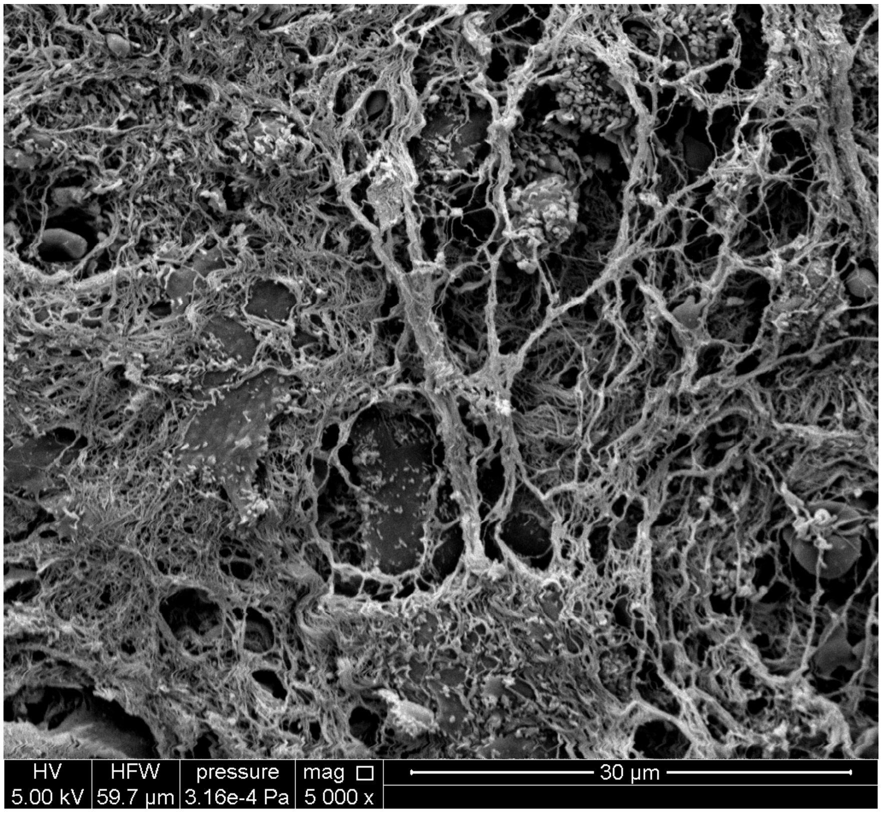
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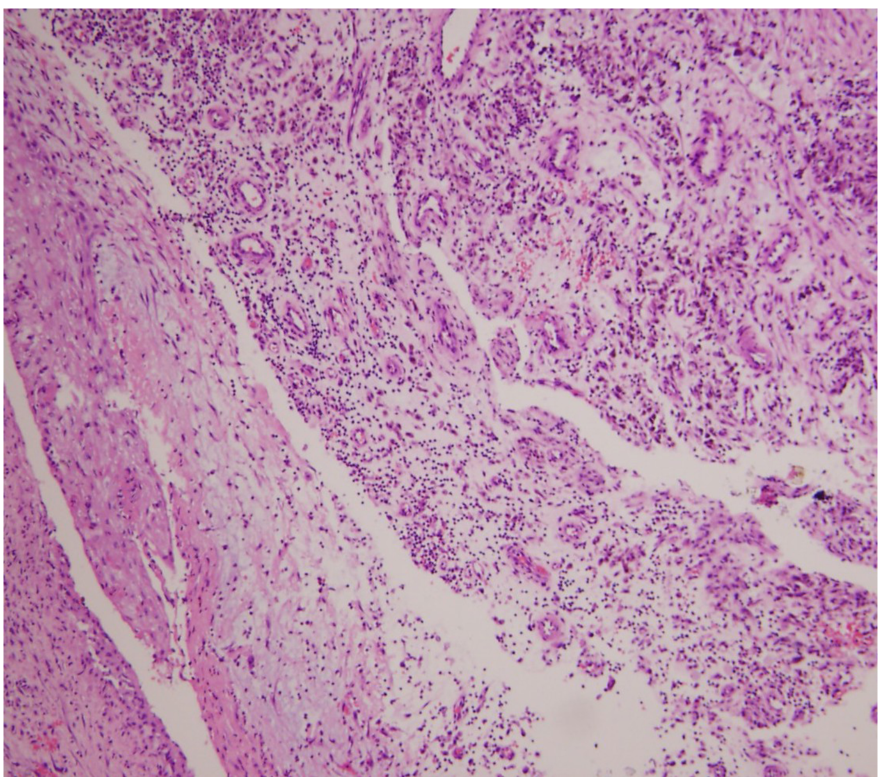

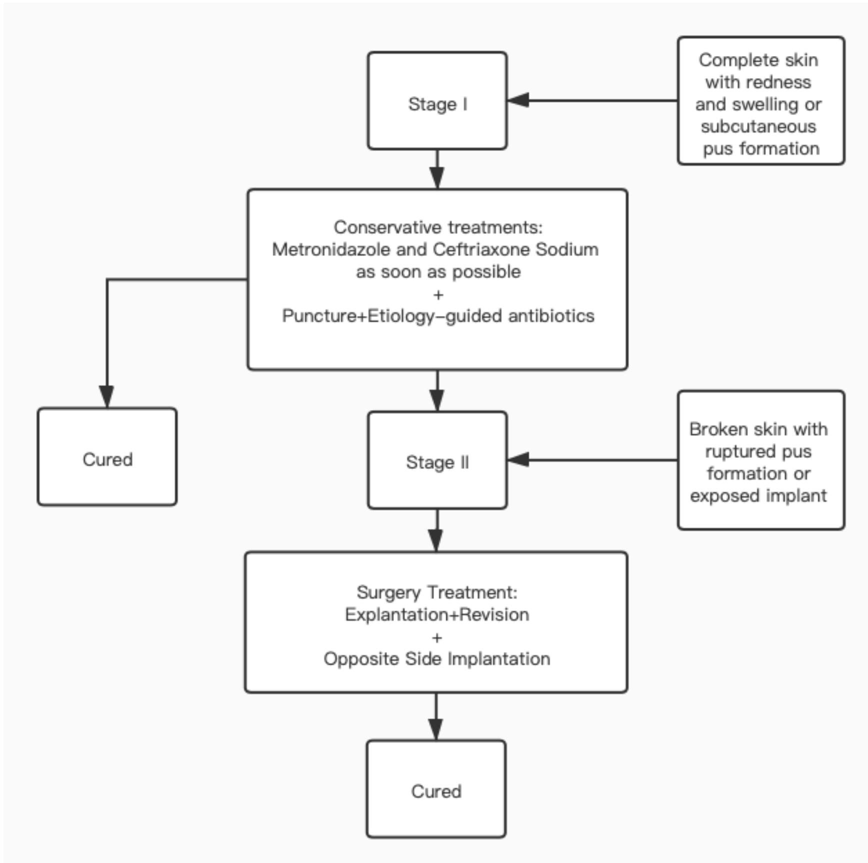

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