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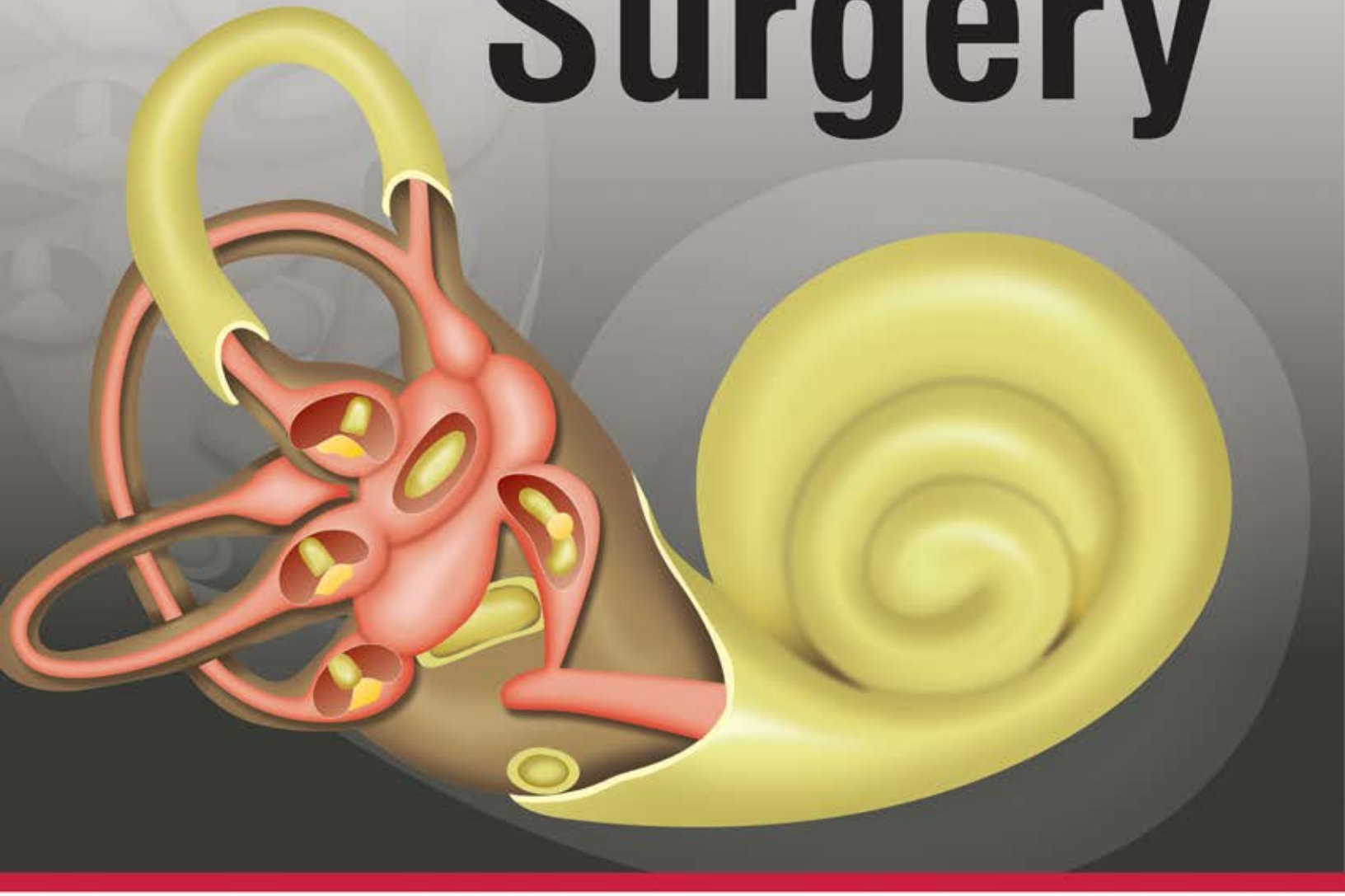

Asok Kumar Saha

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Otology and Middle Ear Surgery

Editor

Asok K Saha

MS DNB D Ortho MSc MNAMS
Associate Professor
Department of ENT and Head & Neck Surgery
Medical College
Kolkata, West Bengal, India

Foreword

Naresh Panda

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Contents

1. **Anatomy of Ear** 1
   Asok K Saha
   - Inner Ear (Labyrinth) 15

2. **Physiology of Hearing** 25
   Asok K Saha

3. **Audiology** 36
   Asok K Saha, Indranil Chatterjee
   - Pure Tone Audiometry 36
   - The Audiometer 36
   - Speech Audiometry 39
   - Special Tests for Hearing 40
   - Impedance Audiometry 41
   - Evoked Response Audiometry 43

4. **Hearing Loss** 50
   Asok K Saha
   - Hearing Loss 50
   - Sensorineural Hearing Loss (SNHL) 53
   - Noise-induced Hearing Loss (NIHL) 55
   - Ototoxicity 57
   - Immune-mediated SNHL 59
   - Familial Hereditary Progressive Sensorineural Hearing Loss 60
   - Sudden Sensorineural Hearing Loss (SSNHL) 61
   - Nonorganic Hearing Loss (NOHL) 63

5. **Physiology of Balance and Its Disorders** 67
   Asok K Saha

6. **Vestibular Function Tests** 77
   Asok K Saha
   - Clinical Testing 77
   - Laboratory Tests (For Vestibular Function) 83

7. **Diseases of the External Ear** 93
   Asok K Saha

8. **Otitis Media** 124
   Asok K Saha
   - Definition and Classification of Otitis Media 124
   - Acute Otitis Media (AOM) 125
   - Otitis Media with Effusion 128
   - Chronic Otitis Media 136
   - Tubercular Otitis Media (TOM) 165

9. **Facial Nerve and its Disorders** 169
   Asok K Saha
   - Anatomy of Facial Nerve 169

10. **Otosclerosis** 187
    Asok K Saha
    - Definition 187
    - Tympanometry 191

11. **Meniere's Disease** 208
    Asok K Saha
    - Definition 208
    - Meniere's Syndrome 208
    - Watanabe's Classification of Stages of MD 212
    - Treatment of Meniere's Disease 215

12. **Acoustic Neuroma (Vestibular Schwannoma)** 225
    Asok K Saha
    - Pathology 225
    - Growth of Tumor 225
    - Classification of AN 226
    - Signs and Symptoms 226
    - Investigations 227
    - Treatment 228
    - Conservative Management 233

13. **Vertigo–Approach and Management** 234
    Asok K Saha
    - Incidence of Disease 234

JAYPEE BROTHERS

- Types of Vertigo 234
- Differential Diagnosis for Vertigo 234
- Approach to a Dizzy Patient 234
- Investigation 237
- Treatment 240

14. Deafness, Assessment of Deaf Child and Rehabilitative Measures 253

Asok K Saha

- Degree of Hearing Handicap 253
- Only One Ear Hearing 253
- Assessment of Deaf Child 254
- Etiology 254
- Prevention 257

15. Tinnitus 259

Asok K Saha

- Classification 259
- Causes 259
- Pathophysiology of Tinnitus 260
- Investigations in Tinnitus 262
- Clinical Examination 262
- Measurement of Tinnitus 262
- Management of Tinnitus 263
- Tinnitus Retraining Therapy (TRT) 264

16. Tumors of Temporal Bone 266

Jaimanti Bakshi, Abdul Wadood

- Classification 266
- Vascular Tumors 269
- Neural Tumors 272

17. Radiology of Ear 275

Chaturbhuj L Rajak

- External Ear 275
- Middle Ear 276
- Inner Ear 281

18. Cochlear Implant 290

KK Handa, Arpit Sharma

- History 290
- Components 290
- Preoperative Selection 291
- Importance of Neural Plasticity 291
- General Criteria for Cochlear Implant Surgery 292
- Preoperative Counseling 292
- Candidancy Categories 293
- Ideal Candidate for Cochlear Implant 293
- Surgical Technique 293
- Complications 298
- Postoperative Rehabilitation 299

19. Hearing Aids, Implants and Assistive Listening Devices 300

Indranil Chatterjee

- Components of Hearing Aid 300
- Types of Hearing Aids 300
- Electroacoustics Characteristics 303
- Hearing Aid Care 305
- Bone-anchored Hearing Aids 306
- Indications and Patient Selection Criteria 307
- Surgery 307
- Efficacy 307
- Middle Ear Vibrant Bridge 308
- Auditory Brainstem Implants 310
- Electric Acoustic Stimulation 311
- Assistive Listening Devices 313

20. Biofilms in Otology 316

Dev Roy

- Diagnosis 317
- Role in Otitis Media with Effusion 317
- Role in Cholesteatoma 318
- Cochlear Implant Infection 318
- Treatment 318

21. Anesthesia for Ear Surgery 320

Enakshi Saha

- Local Anesthesia 320
- General Anesthesia 321

22. Superior Canal Dehiscence Syndrome: Diagnosis and Management 324

Dev Roy, Anirvan Banerjee

23. Middle Ear Surgery 329

Asok K Saha

- Surgical Approaches to Middle Ear and Mastoid Diseases 329
- Tympanoplasty 333
- Ossiculoplasty 337
- Austin's Classification 338
- Mastoid Surgery 343
- Endoscopic Ear Surgery 353

Index *357*

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Chapter

20

Biofilms in Otology

Dev Roy

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INTRODUCTION

A biofilm is a structured community of bacteria embedded in a self-producing slime like extracellular matrix composed of proteins, polysaccharides, nucleic acids known as extracellular polymeric substances (EPS), which is attached to an inert or living surface.[1] Only 1% of bacteria exist in a free-floating or planktonic form while the remaining 99% exist as biofilms.[2] A mature biofilm undergoes through the following stages: 1. Seeding, 2. Attachment to inert or living surface, 3. Colonization, 4. Growth phase, 5. Seeding again, thus completing a cycle (Fig. 1). The unique feature of biofilms is shedding of isolated bacteria from its surface, which seeds infection to distant parts of the body similar to septic emboli. This planktonic shedding of bacteria is a continuous process, which appears to increase during conditions of physiological stress and starvation.[3] These bacteria then get attached to an inert or living structure. The bacterial community then secretes extracellular matrix in which colonization of the bacteria takes place. As more bacteria and other multicellular organisms like algae, parasites and protozoa get attached and colonize, the biofilms grows in size. This increase in growth results in formation of a matured biofilm. These matured biofilms then start shedding bacteria which seeds infection in distant parts, thus completing a life cycle.[4] Planktonic shedding and seeding of bacteria are key to biofilm survival (Fig. 2).

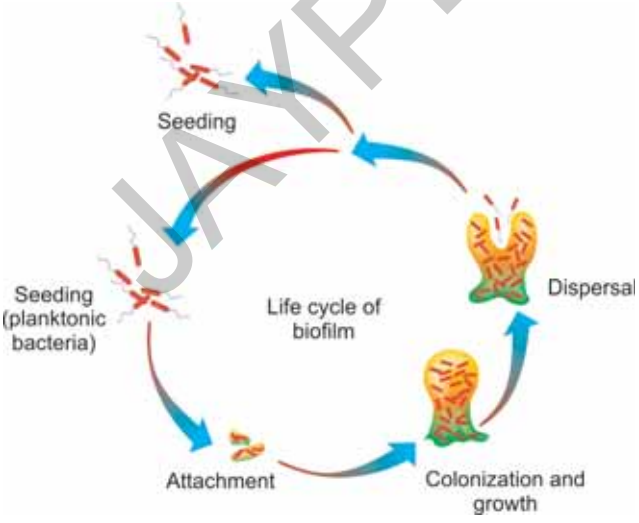

Fig. 1: Life cycle of Biofilm

Most of the bacteria are susceptible to antimicrobials. But when the bacteria are enclosed in a biofilm, their behaviour is different and complex and has a unique feature of resistance to antimicrobials.[5] There is variety of defense mechanisms against immune system of the host, which results in resistance against the antimicrobials. The free floating bacteria are susceptible to antimicrobials, but once they are in a biofilm, the behavior changes and they exhibit a spectacular defense mechanism against the immune system of their host and antimicrobial agents. The bacterial colonies show a highly organized growth involving complicated intercellular communicating systems, which help them to protect themselves against the host and the hostile environment. [6]There is also a division of work among bacteria of different species as well as with fungi, algae and protozoa. There is an organized handling of wastes and nutrients in such a manner that when antimicrobial agents are added, they are depleted to suboptimal levels in the bulk fluid before they reach the biofilm. The colony of bacteria responds to changing environment by intercellular signaling between individual members within the biofilm. Through the process of quorum sensing, pathogenic bacteria can coordinate their virulence to evade immune capture and successfully infect their host.[6,7]

The unique feature of biofilms is resistance to antibiotics. Bacteria in a biofilm are up to 1000 times more resistant to action of antibiotics than their planktonic counterparts.[8] The causes of antibiotic resistance are as follows:

- Poor antimicrobial penetration
- Decreased oxygen and nutrient requirements
- Increased expression of resistance genes (e.g., beta-lactamase)
- Reduced permeability to topical and intravenous antibiotics
- Slower growth rate
- Oxygen depleted microenvironment
- Quorum sensing involves intercellular transmission of molecules and genetic information which permits coordinated behavior and reaction to local environment.[6-8]

DIAGNOSIS

Various animal models have been used to culture biofilms. The most common culture is using Chinchilla animal. In Chinchilla, *S. pneumonia* can be inoculated into the middle ear, giving rise to otitis media. The advantage of using chinchilla model is bacteria can be inoculated in the middle ear and induce otitis media; it does not spread outside the middle ear and is easily accessible for culture.[9,10] The bacterial biofilms can be identified by scanning electron microscopy (SEM) and confocal laser microscopy (CFLM). There are newer and more sophisticated methods like fluorescent in situ hybridization (FISH), lectin-binding and immunohistochemical techniques.[11-14] In vivo studies of middle ear biofilms in humans are difficult since adequate samples from the middle ear are needed to carry out the tests. Moreover, study of adenoid biofilms is only possible after adenoidectomy. Hence, to carry out in vivo studies animal model of chinchilla is used. In the quest for noninvasive in vivo detection of middle ear biofilms, there is a new tool called Optical coherence tomography (OCT). This is based on ultrasound like near infrared laser waves, which produce 3D images. It can be used in children, causes no tissue injury and there is no radiation exposure. The OCT has recently been used to detect in vivo biofilm in patients with otitis media.[15] In a follow-up study, in similar adult population acoustic parameters of the tympanic membrane from the ear have been evaluated. These in vivo studies have limited application since the sample size is small. But still, OCT remains a highly promising noninvasive method of detecting biofilms which may play a major role in biofilm related diseases in middle ear. Despite new technology, the prohibitive costs of the above tests limit their practical role in routine clinical situations for identifications of biofilms.

ROLE IN OTITIS MEDIA WITH EFFUSION

In otitis media with effusion (OME), it is difficult to culture bacteria. The recent discovery of mRNA and DNA in the culture media suggests that OME may be a biofilm disease.[12,14,16] There are various explanations for development of recurrent otitis media. Initially, there is exposure of nasopharynx to known middle ear infection followed by colonization and subsequent formation of biofilm by these bacteria. Eustachian tube dysfunction creates a negative pressure and allows planktonically shed bacteria from nasopharynx to enter the middle ear cavity. It is followed by colonization and subsequent biofilm formation in the middle ear, which results in development of recurrent acute otitis media.[8] With antibiotic treatment, there is a good response, leading to sterile middle ear effusion. Initially, there is a partial response to antibiotic treatment; however this treatment may result in chronicity. The adenoid in the nasopharynx contains biofilm; they shed planktonic bacteria to reinfect the middle ear, resulting in recurrence of the middle ear infection.[17] Based on the above evidence, the practice of "watchful waiting" may promote biofilm formation. Treatment by insertion of grommets helps in draining the middle ear fluid and has a drying effect. Grommets alter middle ear flora by providing ventilation and increased oxygen tension.[13,18] Some patients after grommet insertion develop chronic otorrhea. As a foreign body, grommets may promote biofilm growth.[19] Biofilms have been cultured from grommets removed from affected children. Thus, biofilm has been implicated as a cause of chronic postgrommet insertion otorrhea.

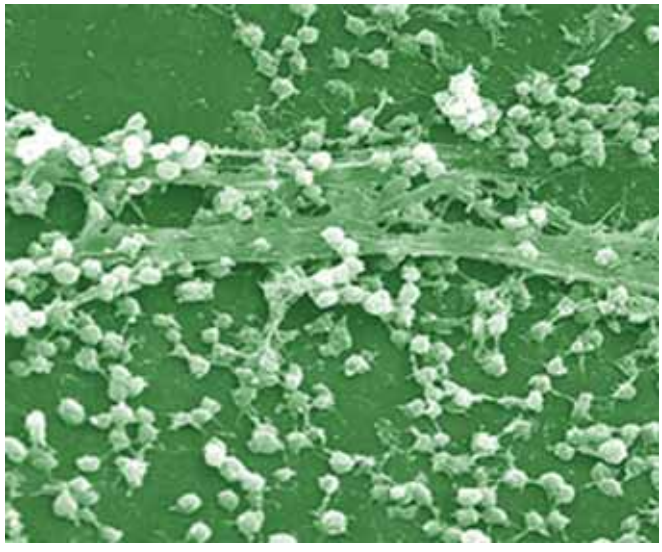

Fig. 2: Mature Biofilms showing *Staph aureus*

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A number of studies have been carried out to identify surface adherence properties of grommets and have shown a reduction to biofilm formation. There are several studies that show protective effect of coated grommets. MRSA is inhibited by vancomycin-coated tubes, *P. aeruginosa* biofilms are inhibited by polyvinylpyrrolidone (PVP) and piperacillin–tazobactam coated tubes.[20,21] In cases of chronic otorrhea or recurrent and persistent otorrhea, removal of grommets and treatment with antimicrobials are effective. In addition to grommet insertion, removal of the adenoids by curettage or diathermy results in better resolution of middle ear effusion, possibly due to removal of biofilms from the nasopharynx.[17]

ROLE IN CHOLESTEATOMA

Cholesteatoma is a chronic disease with resistance to medical therapy. The culture of cholesteatoma has shown colonies of *pseudomonas aeruginosa* and *staphylococcus aureus*. These form biofilms and have a role in the pathogenesis of this condition. Matrix samples of cholesteatoma were induced in gerbils. The cholesteatoma produced contain gram-positive, gram-negative bacteria and acellular polysaccharide matrix similar to biofilms. Based on this finding, recurrent infection in cholesteatoma may be related to biofilm formation.[22] Recurrent active otorrhea is due to release of planktonic bacteria, which respond to antimicrobial treatment, since planktonic bacteria are more susceptible to antibiotic therapy as compared to bacteria in biofilms. Unfortunately, the resistant biofilm remains within the cholesteatoma and releases further bacteria and thus ensures the chronicity of the condition. Bacterial endotoxins release and binding of sessile bacteria to epithelial cells are thought to lead to regulation of signals that contribute to increased epithelial turnover and keratin production. The definitive treatment of cholesteatoma includes mastoid surgery with microsurgical removal of the cholesteatoma matrix and associated biofilm. It is important to remove the hypertrophic granulation tissue from the normal tissue. There are many reasons for failure after the operation. If the tissue with the potential to harbor biofilms, such as granulation tissue, cannot be removed, residual biofilm may be one reason for surgical failure.[23]

In presence of cholesteatoma, the use of patient's own ossicles for reconstruction after removal of the cholesteatoma matrix is not appropriate. One can argue that there is a risk of cholesteatoma matrix remaining on the ossicles. But studies have show that presence of biofilms is significantly higher in middle ear as compared to mastoid and ossicles. In addition, biofilm formation is less on the ossicles, probably because they remain suspended in the middle ear.[24]

Chronic suppurative otitis media, infected mastoid cavity and chronic otitis externa—in these conditions, the moist, warm environment of the middle ear, Eustachian tube and mastoid cavity provides a safe haven for chronic infection, fungal overgrowth and suspected biofilm formation. Control of discharge is a problem. The use of aural toilet, saline irrigations and adjunctive use of topical antibiotics helps in these conditions. The topical regimen that involves the physical agitation, disruption or removal of the biofilms by active irrigation or debridement with microdrill might improve the efficacy of treatment.[24]

COCHLEAR IMPLANT INFECTION

A cochlear implant was removed from a pediatric patient due to chronic otorrhea despite antibiotic treatment. Scanning EM revealed presence of fungal candida biofilm in the cochlear implant receiver and the electrode array. The child received 6-week course of liposomal amphotericin. Cochlear replantation was done in the same ear, 8 months after the first implant was removed.[25] Whenever there is recurrent and chronic infection not responding to antibiotics, removal of the implant with the embedded biofilm on its surface will help in greater antibiotic penetration and faster resolution of the infection.

TREATMENT

Cases of chronic infection apparently resistant to antibiotic treatment, particularly in the presence of implantable devices or foreign body must raise concern of biofilms. The most important step in treating biofilm infection is first to have a high index of suspicion. The mainstay of treatment includes antiseptic techniques, removal of infected foreign bodies, and provision of meticulous debridement. However, with the understanding of the biofilms and how bacteria interact to form biofilms newer methods can be developed in the future. Specific enzymes are known to be capable of digesting the biofilms' protective mucoid extracellular polysaccharide (EPS) coat. With pseudomonas, the EPS is alginate, which can be treated with alginase and simultaneous antibiotic treatment. The alginase dissolves the biofilm intercellular matrix and allows greater penetration of the antibiotic and has higher curative rates.[26] Some chemicals like N-acyl homoserine lactone group are involved in bacterial intercellular signaling; furanones are similar to N-acyl homoserine. These furanones can be used to disrupt intercellular signaling and making the biofilms more susceptible to antimicrobials. In case of tracheoesophageal valve colonization, probiotic biofilms are developed to combat pathogenic biofilms.[27] Some bacteria produce biosurfactants which release bacteria

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from the biofilms, damage the biofilm matrix and make them susceptible to host immune system and antimicrobial agents.[28]

CONCLUSION

A biofilm is a complex matrix of multicellular colonies, which have the capability to exploit the environment and protect themselves from the host and antimicrobial treatment. Standard tests are unreliable in identifying biofilms and conclusive tests are expensive. Conventional antibiotic sensitivity may be misleading, since they test sensitivity of free-floating bacteria and not the bacteria embedded in the biofilms. An index of suspicion of the presence of biofilms is important in chronic and resistant diseases. The mainstay of treatment remains manual irrigation, removal of the implanted foreign body and debridement. Understanding the biofilms will enable us to develop novel therapeutics in the treatment of biofilms.

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Asok Kumar Saha MS DNB D Ortho MSc MNAMS is Associate Professor, Department of ENT and Head and Neck Surgery, Medical College, Kolkata, West Bengal, India. He did his MBBS and postgraduate diploma with Orthopedics from Calcutta University, MS (ENT) from PGIMER, Chandigarh. He is an eminent and distinguished postgraduate and undergraduate teacher and examiner. He has been a member of National Academy of Medical Sciences (India) and was awarded with Prof PK Khasnobish award for the best article in Journal of Otolaryngology and Head and Neck Surgery (WB), June 2007. He is the author of more than 25 peer-reviewed articles in different national and international journals. His clinical interest in otology includes chronic ear discharge, facial nerve injury and skull base surgery. His field of interest also includes surgical oncology of head and neck cancers and facial trauma. He conducted the first facial trauma course on 19th January 2014 at Apollo Hospital, Kolkata. His research is also being focused on molecular genetics for treatment of hearing disorder.



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