Skull Base Osteomyelitis

Historical Perspective, Diagnosis and Management Update

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KEYWORDS

• Skull base osteomyelitis (SBO) • Malignant otitis externa (MOE) • Diabetes mellitus

KEY POINTS

- The hallmark presenting symptom of SBO is otalgia, typically described as a persistent and severe deep pain with nocturnal worsening.
- SBO is a chronic bone infection with high morbidity and mortality.
- Appropriate duration of medical treatment is crucial to avoid incomplete treatment that results in relapse and complications.

HISTORICAL PERSPECTIVE AND NOMENCLATURE

The clinical entity which is known to cause severe otalgia and otorrhea, with potential progression to cranial nerve palsies, intracranial complications, and ultimately death, in an elderly diabetic or immunocompromised population has been given a variety of names over the past 150 years, including temporal bone osteomyelitis,[1] diabetic ear,[2] necrotizing otitis externa,[3] malignant external otitis,[4] and finally skull base osteomyelitis.[5] Each "name" has merit and shortcomings. "Diabetic ear" does not allow for other

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causes of an immunocompromised state that can also lead to a severe otologic infection, including children and adults receiving chemotherapy, individuals with HIV, those on immunosuppressives, and the elderly. Chandler 1968 coined the term malignant external otitis to describe "a severe infection which tends to occur in elderly patients with diabetes … which may be responsible for multiple cranial nerve palsies, meningitis and death."[4] Necrotizing otitis externa (external otitis) was first coined by Kohut 1979 to confirm that the disease is not "malignant,"[6] It emphasizes the nature of the disease as a progressive cellulitis of the ear and skull base. Finally, skull base osteomyelitis by Nadol 1980 has been employed to describe the observed pathology, including active osteomyelitis along the sigmoid sulcus, posterior fossa surface of the temporal bone, and petrous apex.[5] As skull base osteomyelitis (SBO) most accurately describes this disease process, without the potential confusion with a "cancerous lesion," it will be used exclusively in this article with the exception of describing results from historical literature.

Toulmouche 1838 was the first to describe this ailment with intracranial complications in "Observations d'Otorrhee Cerebrale; Suivis des Reflexions,"[7] The organism responsible for this life-threatening infection was identified by Zaufal 1873 and called *Vibrio cyanagenus*; now referred to as *Pseudomonas aeruginosa*.[8] Chambers 1900 reported on 6 cases of severe otologic infections caused by *V cyanagenus*, three of which died of the infection.[9] Wakefield 1904 and Voss 1906 both described intracranial complications and death from pyocyaneus otologic infections.[10,11] The first animal models of otitis externa were reported in 1914 using guinea pig and in 1926 with a mouse model.[12,13] Both animal models demonstrated suppurative labyrinthitis following ear canal inoculation with *V cyanagenus*. The pathologic changes occurring in the temporal bone were likely first described by Brunner in 1942, which he termed "acute, protracted, progressive osteomyelitis." He also reported a characteristic leaping from focus to focus of osteomyelitis, which indicated a hematogenous spread, rather than direct extension through the pneumatized spaces.[1,14] A detailed description of the clinical course of disease with a pathologic correlate was not reported until 1959.[3] These authors chronicled a patient with "severe" diabetes who developed acute otitis externa with Pseudomonas, and despite aggressive medical and multiple radical surgical procedures (including 2 radical mastoidectomies, infratemporal fossa approach for removal of abscess cavity, TMJ and mandible, resection of both internal and external carotid) the patient died 8 months after initial diagnosis. They too demonstrated the spread of disease along vascular channels rather than through the pneumatized spaces of the mastoid and petrous apex, differentiating this disease process from acute or chronic mastoiditis.

Chandler coined the term malignant external otitis when reporting on 13 patients with "a particularly severe type of infection which tends to occur in the elderly diabetic patient.[4] It results in unremitting pain, purulent discharge, and tends to invade cartilage, bone, nerve, and the adjacent soft tissues." Not only did he define the classic history and physical examination findings, he also was the first to describe the route of spread via the fissures of Santorini to the parotid gland and soft tissues in the neck and skull base. In his series, 12/13 had diabetes, 13/13 were caused by pseudomonas, 3/13 were bilateral, 6/13 had facial paralysis and 6/13 died of disease. Chandler advocated for aggressive surgical resection, given the lack of adequate anti-pseudomonal antibiotics at the time.[4] Over the past 50 years it has been shown that any condition that leads to an immunocompromised state, in addition to diabetes, has the potential to lead to SBO. It can occur in both children and adults, although the outcome in children appears more optimistic.[15,16] Aggressive surgical procedures have been abandoned for the most part, given advances in antibiotics, and lack of demonstrable benefit.[17,18]

SBO must be differentiated from chronic otitis externa, in which the ear canal demonstrates variable thickening of the skin with a resultant narrowing of the lumen. Senturia was the first to describe this entity with its pathologic correlation.[19] The primary symptom is itching, and the physical examination reveals excessive, dry adherent, exfoliated debris; mucopurulent drainage may also be found, with papules and foul odor.[19] Culture results often demonstrate gram-negative bacilli, but they vary considerably due to the widespread use of topical antibiotics.[20] Treatment is directed toward frequent cleaning and the use of acidifying agents. Surgery is rarely indicated but useful if canal narrowing leads to further complications.

PATIENT FACTORS PREDISPOSING TO SKULL BASE OSTEOMYELITIS AND PROGRESSION

The most frequently described risk factor for developing SBO is diabetes mellitus which is reported in 80% to 90% of cases.[21,22] Patients with SBO and diabetes often have worse outcomes including prolonged hospitalization and greater disease-specific mortality in comparison to non-diabetics.[23,24] In diabetics, the ear canal can be affected by microangiopathy and neuropathy predisposing to soft tissue infection with contiguous extension to the cranial base and potential for vascular involvement with hematogenous seeding. In this setting, antibiotic activity is reduced due to compromised microvascular perfusion.[25] Additionally, impairment of chemotaxis and phagocytosis of leukocytes and a higher cerumen pH foster bacterial overgrowth.[22,23] Pseudomonas aeruginosa, commonly identified in SBO, is an opportunistic pathogen that infects damaged or unhealthy tissues in patients with diabetes and is associated with virulence factors and biofilm formation.[26] While the duration of diabetes and poor blood sugar control have not correlated with SBO severity in all series, chronic hyperglycemia is known to drive angiopathy; and elevated hemoglobin A1c is associated with risk for limb loss in diabetic foot infection, underscoring the importance of glycemic management in diabetes-related infections including SBO.[25,26]

Advanced age, immunosuppression from uncontrolled Human Immunodeficiency Virus (HIV), organ transplantation, hematologic disorders, chemotherapy, and co-morbidities affecting the vascularization and oxygenation of bone have also been associated with SBO.[22,27] Age greater than 65 years portends worse SBO outcomes in some series with a greater need for surgical intervention.[21,23,27] Co-morbid conditions are found more frequently in older patients, while aging is also associated with significant shifts in the distribution and function of immune cells leading to loss of adaptive immunity and susceptibility to infection. As in diabetes, aging also impairs microvascular circulation.[28] SBO in patients with HIV is associated with low CD4 T lymphocyte counts (<100 cells/mm3) with pathogens other than Pseudomonas reported including Aspergillus spp. arising from a middle ear or mastoid source.[29,30] SBO is also occasionally reported in patients without underlying diabetes or immunosuppressive conditions with more favorable outcomes, reinforcing the need to maintain a high index of suspicion for SBO in any patient with extended otologic symptoms.[22]

DISEASE PRESENTATION

The hallmark presenting symptom of SBO is otalgia, typically described as a persistent and severe deep pain with nocturnal worsening. Pain can often be out of proportion to the findings on physical exam. Purulent foul-smelling drainage is present in most cases. Conductive hearing loss can occur when the ear canal becomes

obstructed by drainage, edema, or granulation tissue.[27,31,32] On physical exam patients will commonly present with ear canal edema, purulent drainage, and characteristic granulation tissue at the bony cartilaginous junction of the ear canal. Tympanic membrane (TM) and middle ear are often uninvolved. However, the visualization of the TM is often obscured due to the ear canal edema[27,31,32].

Early presentation of SBO has significant overlap with acute or chronic otitis externa. Therefore, making the SBO diagnosis requires a high index of clinical suspicion in patient with known risk factors. Although some patients initially present with signs and symptoms to prompt further SBO workup, others are diagnosed when there is a lack of or incomplete response to otitis externa treatment.[32] In later stages, patients can develop additional symptoms indicating the spread of infection outside the confines of the ear canal in multiple directions through adjacent bone, soft tissue, or vascular extension.[33] Temporomandibular joint pain, swelling, and trismus occur with anterior spread through the fissures of Santorini. Facial nerve paralysis can develop with spread to the stylomastoid foramen, which can happen relatively early in the disease course compared to other cranial neuropathies.[34] Dysfunction of cranial nerves IX, X, XI can result from medial spread to the Jugular foramen resulting in dysphagia, dysphonia, aspiration, palatal and shoulder weakness.[35] More rarely, further spread to the petrous apex can result in deficits of cranial nerves II, III, V, VI resulting in vison changes, facial numbness, and double vison.[35,36] Contralateral symptoms can occur as infection spreads along the skull base.[33] Due to potential cranial nerve involvement, complete cranial nerve exam is important when SBO is suspected. Flexible laryngoscopy should be performed in patients with a concern of CN X dysfunction to aid in prompt diagnosis and treatment of aspiration.

Intracranial spread can result in cerebral venous thrombosis, meningitis, intracranial abscess.[33] Patients with intracranial complications may present with nausea, vomiting, headaches, and mental status change. Patients can present with areas of fluctuance indicating abscess formation in the surrounding extracranial soft tissues (neck, parotid, infratemporal fossa).[27,32] Importantly, SBO can also present without ear canal involvement. For this entity, the typical presentation consists of headaches that progress to cranial neuropathies when the infection is centered on the sphenoid or occipital bone.[37]

LABORATORY WORK-UP

Labs can be helpful in making the diagnosis of SBO and as markers of treatment response. Diabetes mellitus-related tests (blood glucose, hemoglobin A1C) should be obtained to determine glucose control in patients with the established diagnosis of diabetes or to check for new diagnoses.[38–40] Complete Blood Count (CBC) will typically be normal to slightly elevated.[27] Inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-Reactive Protein (CRP) are typically elevated and can be used to monitor treatment response.[40,41]

Culture from ear drainage or tissue should be performed to guide treatment. *Pseudomonas aeruginosa* is found in the majority of patients.[27,42] *Aspergillus fumigatus* and *Candida spp* are the most common fungal organisms found with fungal infections being more common with immunosuppression.[27,43]

Tissue biopsy should be obtained to rule out malignancy given a significant overlap between the clinical and imaging characteristics of the two. Re-culture may also be necessary if the initial culture is negative or with poor response to antibiotic treatment.[44] Differential diagnosis to consider and differentiating factors are listed in **Table 1**.

Table 1
Differential diagnosis and differentiating factor

Differential Diagnosis	Differentiating Factors
Otitis Externa without osteomyelitis	• Lack of imaging findings supporting SBO • Resolution of symptoms with the short treatment of antibiotic/antifungal
Malignant Lesion of External Ear Canal or Nasopharynx	• Biopsy should be performed in all cases due to overall in clinical/imaging characteristics • Biopsy shows evidence of malignant disease
Cholesteatoma w/wo secondary infection	• Prior history of chronic ear disease • Clinical findings of cholesteatoma (retraction pocket, keratin debris, white middle ear mass, conductive hearing loss, and so forth). • Imaging features on CT (scutal erosion, ossicular involvement), MRI (restricted-diffusion on non-echo planar DWI)
Granulomatous disease	• Biopsy findings • Other sites of involvement

IMAGING

Diagnosis of SBO is challenging both clinically and on imaging, thus requiring a high degree of suspicion.[45] Imaging plays a central role not only in establishing accurate diagnosis, but also in evaluating for complications and guiding management. The imaging techniques commonly employed to diagnose SBO include noncontrast and contrast-enhanced CT, contrast-enhanced MRI, and nuclear imaging.[45–48]

CT is almost always performed as the first-line imaging method. High-resolution thin-section CT using a bone algorithm can easily be reformatted in multiple planes and is excellent to detect cortical bone erosions or trabecular bone destruction that accompany SBO.[45,47] It identifies the opacification of temporal bone structures, mucosal disease, and air-fluid levels in the paranasal sinuses and mastoid air cells.[45,47] Contrast-enhanced CT in soft tissue algorithm is useful to assess for cellulitis and soft-tissue infiltration, phlegmonous changes underneath the skull base, in the infratemporal region and rim enhancing abscess in the pre-clival soft tissues or along the mastoid tip. CT angiography or venography is employed to evaluate for vascular complications such as dural sinus or cavernous sinus thrombosis and neurovascular complications which are more common in aggressive fungal SBO.[45,47–49]

MRI is superior to CT for determining the complete extent of the disease process and is better in assessing bone marrow involvement and extraosseous soft tissue structures (**Fig. 1**A, B, D). A dedicated skull base MRI protocol (**Box 1**) is necessary for complete evaluation, including DWI, fat suppression, and thin section contrast-enhanced images. Early findings of SBO include nonspecific soft tissue thickening and enhancement in the EAC, with erosion at the petrotympanic fissure, obliteration of the retrocondylar fat pad, and with marked edema and inflammation of the periauricular soft tissues.[49] With progression, the soft tissue infection can spread via fascial planes to surrounding soft tissues and osseous structures and may extend to the skull base foramina to involve the cranial nerves and the intracranial compartment.[49] With advanced cases of SBO, bone marrow may become necrotic and form an abscess,

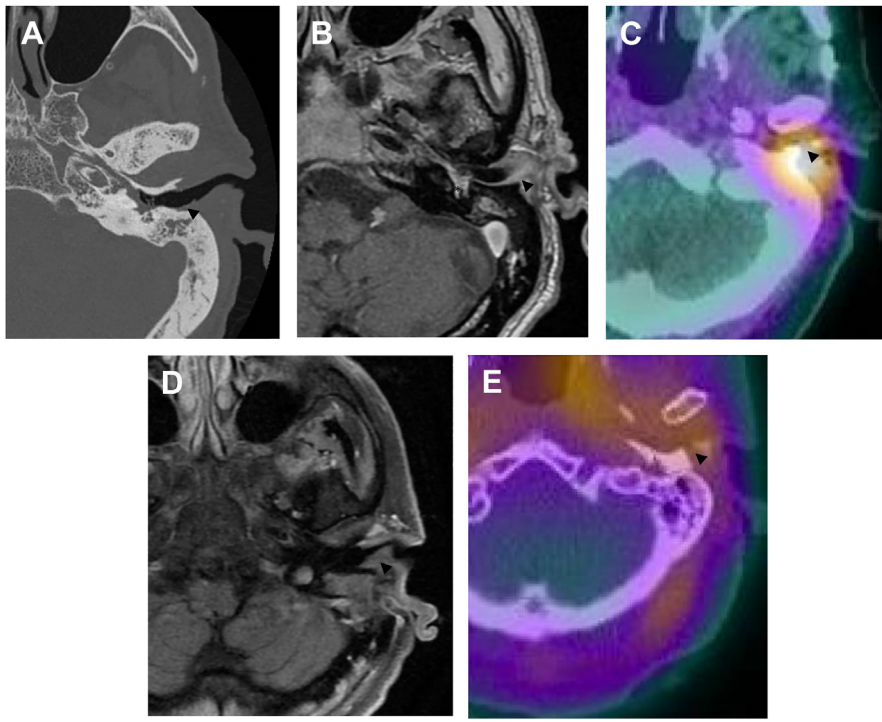

Fig. 1. Comparison of different imaging modalities. (*A*) CT temporal bone: demonstrating increased soft tissue and edema of left EAC, middle ear/mastoid opacification (*B*) MRI axial T1 w Gadolinium contrast with soft tissue enhancement along left EAC (*arrow*) (*C*) Follow-up Nuclear Medicine Gallium Fused SPECT CT scan shows marked tracer accumulation in left EAC (*arrow*) (*D*) MRI T1 w Gadolinium contrast shows the resolution of enhancement. (*E*) Nuclear Medicine Gallium Fused SPECT CT scan shows resolution of previously seen tracer accumulation (*arrow*).

with peripheral rim enhancement and central diffusion restriction. The soft-tissue abnormality in the nasopharynx may be the most prominent finding and therefore these cases are often misdiagnosed as infiltrative neoplasm, especially nasopharyngeal carcinoma.[50,51] Diffusion imaging also allows distinction between SBO and other

Box 1
MRI protocol for SBO

MRI PROTOCOL FOR SUSPECTED SKULL BASE OSTEOMYELITIS
- 3-plane localizer
- Sagittal T1 3D
- Axial DWI (preferably readout-segmented echo-planar diffusion - rs-DWI)
- Axial T2 fat saturated 3 mm (preferably whole brain)
- Coronal STIR 3 mm
- Axial T1 3 mm
- Coronal T1 3 mm
- Postcontrast axial T1 3 mm with fat saturation
- Postcontrast coronal T1 3 mm with fat saturation
- Optional: MR Angiography or MR Venography (as necessary)

neoplastic mimics. Apparent diffusion coefficient (ADC) values in bacterial SBO are generally higher than those in nasopharyngeal carcinoma or lymphoma.[45,47,50] The soft-tissue invasion and neurovascular complications can occur before or without frank bone destruction, especially in early or aggressive diseases such as fungal SBO.[45]

SBO is generally categorized according to an anterior, posterior, medial, or an intracranial spreading pattern or a combination of these. In an *anterior* spreading pattern, the temporomandibular joint (TMJ), masticator space, parotid gland, or surrounding fat planes are involved. The *posterior* spreading pattern affects the mastoid process, and the *medial* spreading pattern affects the sphenoid, clivus, nasopharyngeal or pharyngeal muscles/fat, and cranial nerves IX, X, and XI. The *intracranial* pattern shows the involvement of the jugular fossa, jugular vein, sigmoid sinus, and meninges.[52] The spread of SBO from the external ear canal to the anterior pattern is thought to occur via the fissures of Santorini (which are not seen on imaging), by extending through osseocartilaginous junctions of the external ear canal, spreading through fascial planes and blood vessels to surrounding compartments. Some patients with SBO have a variant anatomic structure called a *persistent foramen of Huschke* aka, "foramen tympanicum," which is a dehiscence antero-inferiorly in the osseous external auditory canal (EAC) posterior-medial to the temporomandibular joint (TMJ). Its prevalence is higher in women and on the left side, and ranges from 4.6% to 20%. This anatomic pathway puts the TMJ, masticator space, and parotid gland at risk.

While CT and MRI are critical in the initial diagnosis of SBO, they are not necessarily helpful in determining real-time disease resolution as imaging findings generally lag clinical improvement. There can be improvement in soft-tissue findings which is likely the best imaging marker for improvement and response to treatment; but abnormalities of bone may persist for weeks to months despite adequate clinical response.[45] A variety of nuclear medicine studies are very sensitive in providing functional and metabolic information, and can help to confirm and localize infection to the skull base. These nuclear medicine studies are complementary to CT and MRI studies in monitoring treatment response. Technetium methylene diphosphonate (Tc99m MDP) bone scan, gallium-67 citrate (Ga-67) scan, and technetium-labeled white blood cell scan have all been used in patients with SBO but generally, the literature has variable data regarding the overall diagnostic value of these nuclear medicine tests with poor specificity. We, therefore, *advise against the routine use of these studies* in diagnosis or even follow-up of patients with SBO.[53] However, these examinations can serve as adjuncts in complicated patients with an unclear diagnosis and disease course (**Fig. 1**C, E). (18F) Fluorodeoxyglucose (FDG)-positron emission tomography (PET) CT has advantages over other nuclear studies with much wider availability, shorter imaging time, and higher spatial resolution and can be complementary to determine the extent of infection in confirmed cases of SBO and for the evaluation of treatment response.[54] Hybrid PET-MRI scanners offer exquisite soft-tissue detail and metabolic information in a single study. The summary of imaging teaching points is listed in **Box 2**.

SURGICAL MANAGEMENT

Tissue biopsy is required to confirm the diagnosis, to eliminate other possibilities such as cancer, and to determine the causative organisms. In the chronic draining ear, biopsy of any abnormal tissue in the ear canal is easily performed in the outpatient clinic under the operative microscope using cup forceps. Ear polyps can be removed and

Box 2
Imaging pearls

- Enhancement and fullness without destruction of fascial planes and absence of a discrete soft tissue mass may support a diagnosis of SBO over tumor.
- early changes of SBO are subtle and easily missed. One of the earliest findings is infiltration of the retrocondylar fat pad.
- Soft-tissue infiltration of the retroantral fat and pterygopalatine fossa with obliteration of normal fat in these regions is typical of SBO associated with invasive sinusitis.
- knowledge of persistent foramen of Huschke is important to identify patients with early SBO and its patterns of extension, thus aiding in improved diagnosis and outcomes.

sent for culture. These types of biopsies do not always reveal the causative organism. Deeper biopsy material can be obtained through either image-guided biopsy or surgery. CT-guided biopsy can often be performed and is a less invasive procedure than open biopsy.[55] For infections that originate in the central skull base, endoscopic endonasal approach can be used to obtain appropriate biopsy and culture material.[56] For infections that arise from the middle ear and mastoid, mastoidectomy can yield appropriate tissue. Indications for mastoidectomy are listed in **Box 3**.

Since the infection is diffuse, mastoidectomy is not curative for this illness.[18] The goal of mastoidectomy is limited to obtaining appropriate tissue for culture and pathologic examination, and not the restoration of hearing (see **Box 3**).[17,42] Myringotomy and tube can be considered to allow drainage of the middle ear. Mastoidectomy is generally limited to abscess drainage, but sigmoid sinus thrombectomy can be performed when signs of Lemierre's syndrome are present.[57]

For central SBO, where the infection is in the clivus and petrous apex, a targeted approach via an extended nasopharyngeal biopsy can be helpful to obtain tissue to pathologic diagnosis and microbiology culture.[56] Any purulent material can be gathered on swabs for culture. Thickened mucosa and granulation tissue should be sent for pathologic examination and culture. Since the underlying infection is bony, sending bone specimens obtained with curettes or rongeurs can be helpful at identifying the offending organism.

In a systematic review of surgery for SBO, Mahdyoun and colleagues identified 21 publications covering 439 patients, and the majority of authors described limited surgery to remove bone sequestrate from the EAC or to obtain histologic and

Box 3
Surgery indications

Mastoidectomy Indications
- Clinical Evidence of Middle Ear/Mastoid Cavity disease
- Lack of Confirmed Diagnosis
- Lack of Causative Micro-organism
- Radiographic Evidence of Mastoid Involvement
- Inappropriateness or Unavailability of Less Invasive Technique for biopsy or diagnosis (ie, image-guided biopsy)
- Lack of Response to Medical Therapy
- Drainage of Abscess
- Debridement of Necrotic Tissue
- Possibly Facial Nerve Decompression for Facial Paralysis

microbiologic samples.[58] Stevens and colleagues performed a systematic review of the literature to determine criteria for separating malignant otitis externa (MOE) into severe cases, where surgery might be necessary, and nonsevere cases, where no surgery is required.[59] They identified four clinical variables (facial nerve palsy, disease relapse, required surgery, positive fungal culture) and 5 radiologic variables (TMJ, Infratemporal fossa, or tegmen erosion, and nasopharyngeal or intracranial involvement). In their article, severe cases demonstrated at least one of the following characteristics: (1) facial palsy, (2) two or more clinical variables other than facial palsy,[60] two or more radiographic variables, (4) one or more clinical variables and one or more radiographic variable. Although 12 out of 28 patients met their criteria for severe disease, only 2 patients underwent surgery.

Peled and colleagues described a relatively large series of 20 patients who underwent surgery out of a series of 83 patients with necrotizing otitis externa.[61] Their series consisted of local debridement (n = 7), canal wall up mastoidectomy (CWU) (n = 4), canal wall down (CWD) mastoidectomy (n = 7) and CWD with facial nerve decompression (n = 2). The primary indication for surgery was a lack of response to prolonged antibiotic therapy, and this indication covered 90% of their surgical patients. Lack of response was determined based on pain control, general condition, and physical findings after 2 weeks of antibiotic therapy. All surgical patients had evidence of extensive temporal bone involvement on high-resolution temporal bone CT. Their previous work indicated that elderly patients (average age 77 years) were at higher risk for conservative treatment failure and more likely to require surgery.[21] Others have used a 3-week,[62,63] 4-week,[64,65] or 6-week[23] treatment duration without improvement to consider the case refractory. Shavit and colleagues reported on 88 patients with SBO, of which 20 (23%) had a surgical procedure.[66] They performed external canal debridement in 12 and mastoidectomy in 8 (CWU in 4, CWD in 4).

A special consideration is made for patients with progressive facial weakness in the setting of SBO. Unlike the lower cranial nerves (CN IX-XII), facial paralysis in the setting of SBO generally does not improve with medical management alone.[35] Unlike Bell's palsy, where the facial nerve is compromised at the labyrinthine segment due to viral-induced swelling, facial nerve paralysis in SBO might be diffuse and related to granulation tissue and toxins along its course causing impaired axonal conduction.[35] Freeman and colleagues reported on 14 patients with facial paralysis and SBO and compared the facial nerve outcomes between patients who underwent surgical decompression versus those that were observed.[67] None of the patients treated with medical management had any significant improvement in facial function. Of the patients treated with mastoidectomy and facial nerve decompression, 3 of 5 patients had significant improvement (defined as a decrease of at least 2 points on House-Brackmann facial nerve scale.[68] In the mastoidectomy only group, 2 of 5 patients experienced a significant improvement on the HB scale. However, statistical analysis demonstrated no significant difference across the three cohorts, given the small numbers in the study. Patients who experienced the greatest improvement in facial function had facial nerve decompression <14 days from the onset of paralysis, a finding very similar to what is seen in Bell's palsy patients.[69] The goal of facial nerve decompression within 14 days can be difficult to achieve in a disease that can take weeks to manifest and be diagnosed.

Peleg and colleagues reported 18 patients with SBO, of which 5 had severe disease.[64] These 5 patients underwent extensive operations, including any combination of radical mastoidectomy, temporomandibular joint (TMJ) excision, parotidectomy, partial removal of the zygomatic arch, and bony/soft tissue debridement of the infratemporal fossa and skull base; however, they did not report any outcomes. Omran and

colleagues performed similar extensive surgery (radical mastoidectomy, TMJ excision, partial removal of the zygomatic arch and debridement of the occipital bone and skull base).[70] Out of 10 patients with recurrent disease, 2 patients died, and 2 patients deteriorated during follow-up. Yigider and colleagues performed surgery in 9 out of 26 patients with SBO.[71] Five patients had radical mastoidectomy and 4 had subtotal petrosectomy. Two patients who underwent surgical intervention died of disease. Visosky and colleagues described a circumferential petrosectomy for patients that fail to improve with medical management or patients with impending complications.[72] These patients presented with complex CN deficits, such as Tolosa-Hunt syndrome or Gradenigo syndrome, and substantial inflammation around the petrous and cavernous carotid artery. In their procedure, most of the temporal bone was removed via combined retrolabyrinthine-apical petrosectomy and fallopian bridge technique. Middle fossa craniotomy is performed for petrosectomy. Their report describes 5 cases with disease resolution in all patients. Some authors have used tympanomastoid surgery after 6 months of treatment for removing the inflammatory lesion as much as possible.[73]

MICROBIOLOGY AND MEDICAL TREATMENT

Once the diagnosis of SBO is established, baseline cultures should be obtained whenever possible prior to initiating antimicrobial treatment. The culture data can be valuable when treatment fails or drug toxicities emerge. While *Pseudomonas aeruginosa* remains the most common organism seen in SBO,[21] other organisms such as *Staphylococcus aureus* (either methicillin sensitive or resistant) and other Gram-negative rods can also cause SBO. This fact further supports the importance of obtaining cultures prior to initiating empiric anti-Pseudomonal therapy.

Culture results should be examined critically in particular when they yield organisms which are unlikely to be pathogenic and may be colonizing the ear canal superficially such as coagulase-negative Staphylococci or Enterococci. Moreover, topical antimicrobial and antiseptic therapies that patients have received prior to evaluation and diagnosis may decrease the yield of true pathogen growth in culture.[74] Decisions on whether to treat potentially non-pathogenic organisms (ie, coagulase-negative Staphylococci or Enterococci) when they are the only organisms that grow in culture can be challenging. The decision to treat non-pathogenic organisms, in addition to empirically treating Pseudomonas (and other Gram-negative rods), is individualized depending on the patient's degree of immunocompromise and severity of disease. Since Pseudomonas is the most common SBO pathogen, treatment regimen that includes anti-Pseudomonal therapy is reasonable when no other pathogenic organism is found. It is critical to monitor these patients closely with close surveillance and ongoing consideration of alternative pathogens such as fungi in refractory cases.

The quinolones (ciprofloxacin and levofloxacin) are the only oral anti-Pseudomonal agents available to treat systemic infection. Due to their high oral bioavailability and bone penetration, these drugs are first-line treatment options for presumed or confirmed susceptible Pseudomonal infections. High "anti-Pseudomonal" dosing is appropriate (750 mg po BID for ciprofloxacin and 750 mg po daily for levofloxacin) with dose adjustment for renal insufficiency. When a Pseudomonal isolate is grown that is quinolone resistant or when the patient cannot tolerate quinolones, intravenous anti-Pseudomonal options include cephalosporins (cefepime or ceftazidime) or beta-lactam/beta-lactamase inhibitor piperacillin-tazobactam. These medications are favored over carbapenems (imipenem and meropenem) when possible, because Pseudomonas spp have the ability to develop resistance to carbapenems quickly

when a high organism burden is present, and because they can be used as monotherapy without an additional agent. In severe cases, carbapenems can be given in combination with a quinolone. In cases where a highly resistant Pseudomonas is cultured, the use of newer generation cephalosporins (eg, cefiderocol) or treating with combinations of agents may be necessary. While aminoglycosides are active against Pseudomonas, given their potential nephrotoxicity and ototoxicity with prolonged use, they are not ideal first-line therapy for SBO.

Fungal pathogens which are more common in diabetics and other immunocompromised hosts, can plan a role in SBO, potentially being a culprit in "culture negative" cases potentially due to the difficulty in culturing fungi from clinical samples.[63] Aspergillus is the fungus most commonly seen in progressive SBO though other mold have been described rarely.[75] When Aspergillus is suspected based on exam concerning for mold or angioinvasion, or there is ongoing disease progression despite being on broad antibacterial therapy, antifungal therapy is appropriate with tissue debridement as needed. Voriconazole has high oral bioavailability and would generally be first-line anti-fungal therapy for Aspergillus. If drug interactions or intolerability preclude its use, other options now include oral isovuconazole or posaconazole, intravenous echinocandins and intravenous liposomal amphotericin B. Summary of treatment paradigm is shown in **Fig. 2**.

The specific duration of antimicrobial therapy in SBO cannot be predetermined dogmatically. As is the case for most infections involving bone, at least 6 weeks of systemic antimicrobials are indicated with ongoing close clinical follow up to determine if disease progression has halted, stabilized, and then improved. At times with extensive disease, treatment response can be slow and extended antibiotic regimens may be appropriate. Ongoing monitoring for patient adherence, drug tolerability, and toxicity should also continue concomitantly. When inflammatory markers such as ESR and CRP are highly elevated at the time of diagnosis, periodic monitoring of these markers while on therapy (eg, every 2–3 weeks) can be an adjunct measure in determining treatment duration. However, these lab results are notoriously non-specific and can

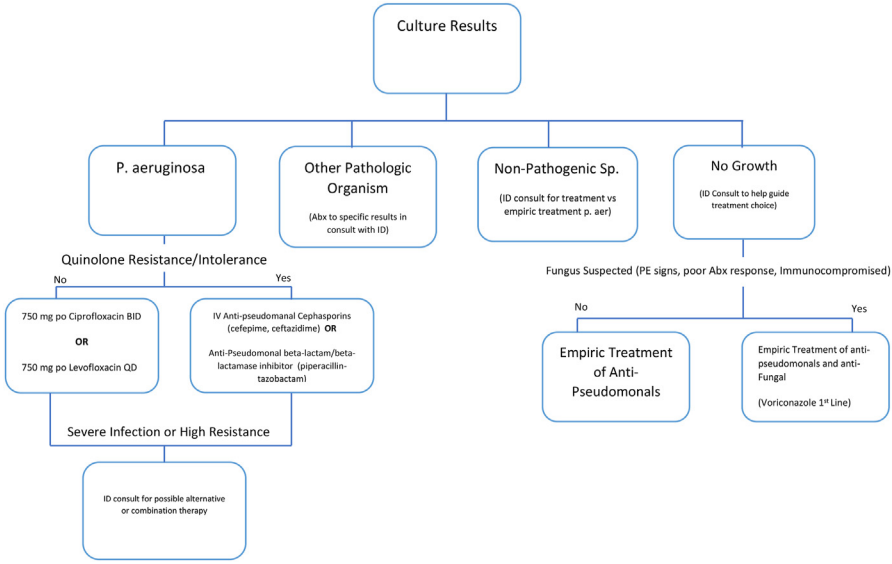

Fig. 2. Medical treatment algorithm.

at times be unhelpful. If the patient has improved on antimicrobials, the decision to stop treatment should be team-based approached, using interval clinical course and imaging studies. Follow-up for relapse should be continued in the year following discontinuation.

SUMMARY

SBO is a life-threatening disease that requires a high index of suspicion based on these patients complex underlying medical co-morbidities and clinician's acumen. Once a diagnosis is made, is it critical to communicate and work closely with other multidisciplinary teams (neuroradiology for appropriate choice of imaging study and interpretation; infectious disease for appropriate medical treatment and duration; internist to properly manage their underlying medical co-morbidities). Though this disease has been around for centuries with many different names, SBO is a chronic bone infection with high morbidity and mortality. Despite advances in imaging, the diagnosis is first made based on clinical judgment, appropriate culture, and tissue biopsy. Appropriate duration of medical treatment is crucial to avoid incomplete treatment that result in relapse and complications.

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