Chronic Osteomyelitis in Sacral Pressure Ulcers Management Review in QA Format

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Key Points

- Most cases of reported osteomyelitis in stage 4 pressure ulcers are almost exclusively chronic and superficial (when depth is reported).
- Wound cultures or bone specimen cultures lack diagnostic sensitivity or specificity. Histopathological diagnosis is necessary to make an accurate diagnosis of osteomyelitis.
- Surgical debridement is the mainstay of treatment for chronic osteomyelitis. Duration of antibiotics in combination with surgical management is unclear but choice should consider bone and biofilm penetration.
- Shorter durations of antibiotics to treat the soft tissue infection should be considered in the absence of a concrete plan for wound coverage with primary closure or rotational flap.

Introduction

Osteomyelitis is, by definition, inflammation of the bone and the bone marrow that can be secondary to bacteria, mycobacteria, or fungi [1]. Defining, diagnosing, and managing chronic osteomyelitis continues to be a challenge for clinicians. Chronic osteomyelitis represents bone infection that is long standing although the exact duration of time before osteomyelitis is considered chronic is

unclear. Histological, rather than clinical or imaging based diagnosis is needed. While osteomyelitis can be from hematogenous spread or direct inoculation, in the setting of sacral pressure ulcers, it is commonly from local extension. The most common settings include spinal cord injury or cerebrovascular accident [2]. This is related to local, persistent compression of the area with secondary ischemia. As little as two to six hours of persistent ischemia can lead to cell necrosis and tissue sloughing [3].

Once this process starts, the stages progress in size and depth defined by the U.S. National Pressure Ulcer Advisory Panel as follows [4]:

- Stage 1: Injury confined to the dermis with lack of tissue necrosis. Once compression is removed the skin is hyperemic and non-blanchable.
- Stage 2: Injury confined to the dermis WITH tissue necrosis. May present as hyperemic area with superficial epidermolysis.
- Stage 3: Injury and necrosis present all the way to the deep fascial layer with lack of exposed muscle, tendon, or bone. May have eschar formation and undermining at wound edges.
- Stage 4: Injury and necrosis breaches deep fascial layers with exposed muscle, tendon, or bone.

With persistent pressure and ischemia, bone infection can progress to bone necrosis and sequestrum (fragments of dead bone) formation, thereby limiting access to the bodys immune response as well as antibiotics. Chronic pressure injury also leads to bone remodeling which can be difficult to differentiate from infection on various imaging techniques. Additionally, positive cultures may represent colonization of adjacent soft tissue.

Treatment should include a combination of surgical debridement with tissue coverage, urine and stool diversion, and systemic antibiotics (oral or intravenous). Ultimately, this is a challenging topic as data are limited, heterogeneous, and from small sample sizes with a lack of randomized controlled trials. Additionally, much of the data are decades old. Sacral pressure ulcers represent a complex problem which should be co-managed with multiple specialties including internal medicine, infectious disease, general and plastic surgery, social work, dietician, wound care, and nursing.

Pathogenesis

In order to develop an understanding of a treatment algorithm and a sound approach to management of sacral osteomyelitis, the pathophysiology of osteomyelitis must be understood.

What is the pathogenetic sequence of events in development of osteomyelitis?

- The pathogenetic sequence can be divided into three major phases. This includes initial microbial invasion, whether exogenously or via a hematogenous route, followed by biofilm proliferation. Biofilm is a matrix of extracellular polymeric substances which provides protection from host defense mechanisms and antibiotics. This is followed by a local immune response to the bacterial biofilm with immunoglobulins and complements leading to activation of polymorphonuclear neutrophils (PMN) as well as production of proinflammatory cytokines. Finally, the bacterial invasion can release virulence factors affecting cell apoptosis, decreased proliferation of osteoblasts, and promotion of osteoclastogenesis. This ultimately leads to destruction of bone tissue [5,6].

How does the bacterial metabolic state affect chronicity, management, and response to antibiotics?

- During early biofilm formation the microorganisms are mainly in an aerobic, planktonic state with a high metabolic activity. Once the biofilm is mature, organisms are mainly in an anaerobic state with significantly reduced metabolic activity [6]. They can also hide intracellularly, further limiting access. These properties define the chronicity of infection. Limited in vitro data exist regarding certain antibiotics with activity against bacteria in stationary phase and within biofilms [7].

How do bacterial virulence factors influence development of osteomyelitis?

- *S. aureus* biofilms secrete soluble molecules which directly impact osteoblasts by decreasing viability and osteogenic potential. *S. aureus* also secretes protein A (SpA) which is capable of binding to osteoblasts and inhibiting the proliferation and mineralization process. It also induces apoptosis in osteoblasts in vitro [6].

What role do beta-defensins play in development of chronic osteomyelitis?

- Human beta-defensins are typically expressed in epithelial and bone tissue that play a key role as antimicrobial peptides and are part of the innate immunity. They are cationic peptides that interact with the anionic membrane of bacteria and encapsulated viral and fungal pathogens, leading to destruction of the cellular membrane and interference with intracellular functions. In extrapolating data from jaw osteomyelitis, Benedicta et al. determined osteomyelitis of the jaw to be a fairly rare event considering it is in a setting of exposed bone after tooth extraction that is exposed to a milieu of oral bacteria. There may be some genetic predisposition or immunosuppressive drug contribution leading to an insufficient immune response. This may lead to an insufficient production of certain beta-defensins. Thus, people on immunosuppressive therapy or with certain genetic predisposition may be more prone to developing chronic osteomyelitis [8].

What local anatomical factors contribute to sacral osteomyelitis development and progression?

- Both blood flow and neurological status are key local factors in determining progression to osteomyelitis. Local perfusion arterial networks provide nutrients and oxygen. This can be compromised by direct compression or shear forces that disrupt blood distribution. This combined with neurological insults that would normally allow for change in position to relieve the local pressure in a sensate patient leads to tissue ischemia and focal thrombosis [3].

In addition to local pressure injury, what else leads to local bone destruction?

- Local immune response to pathogens leads to infiltration by leukocytes which release enzymes and pro-inflammatory mediators to destroy the pathogens. This also leads to bone cells and matrix destruction as well as disruption of local blood flow. This results in an avascular area of necrotic, infected bone (sequestrum) and reactive, surrounding formation of new bound involucrum [3].

What is the clinical significance of a sequestrum?

- Sequestrum is osseous tissue that lacks blood supply and therefore no longer has access to nutrients, to the immune system, or to system antibiotics. This acts essentially as a foreign body and a potential carrier for bacteria and biofilm. Surgical debridement is the only method for eradication [3].

Microbiology

Culture result data from sacral pressure ulcers are challenging to interpret as various methods have been utilized for specimen collection, inconsistent collection of anaerobic cultures, and antibiotic administration prior to culture collection. Additionally, cultures have been obtained from superficial swabs, deep swabs, and bone samples.

What are the most common pathogens for empiric coverage?

- The most common organisms are Staphylococcus aureus, including MRSA, *Staphylococcus epidermidis*, *Streptococcus*, *Pseudomonas*, and enterobacteria as well as anaerobes [3]. Up

to 30% of cultures can be polymicrobial [3]. However, even with limited data, most studies have found no association between treatment failure and culture positivity, so the utility of culture directed therapy in the setting of chronic osteomyelitis is unclear. Most of the failures were attributable to patient characteristics, wound management, and lack of source control [5,9,10].

Does presence of bacteria on exposed bone lead to osteomyelitis?

- No, it is expected for bone exposed to the external environment to be colonized with bacteria and a wound swab, superficial or deep, is not sufficient to make a diagnosis of osteomyelitis [3].

Do positive culture results from a bone specimen by definition indicate osteomyelitis?

- No, cultures of bone specimens are frequently contaminated with organisms residing in adjacent soft tissue [2].

What is the usefulness of sacral wound swab for culture?

- It is expected for exposed bone to be colonized with bacteria. For this reason, a simple bedside wound swab of a chronic ulcer is not helpful to diagnose the presence of osteomyelitis. Osteomyelitis is an infectious condition characterized by both pathogenic organisms and a corresponding inflammatory or immune response within the bone [3]. When cultures were positive, quantitative bone cultures yielded a similar number of bacterial isolates and a comparable range of bacterial concentration in patients with osteomyelitis vs. those without osteomyelitis [2].

Clinical Findings

Most of the data support a histologic diagnosis of osteomyelitis. In some cases, it may not be feasible to obtain a biopsy specimen for histology and culture. Again, the data is limited on the ability of clinical findings to make an accurate diagnosis but fairly consistent.

Does duration of exposed bone assist in diagnosis of osteomyelitis?

- No, duration of exposed bone does not by default assist in diagnosis of osteomyelitis and bone that is exposed over a longer period of time is not necessarily more likely to have osteomyelitis [3, 11]. See discussion below.

What is the clinical usefulness of probe to bone?

- Traditionally, it was thought that exposed bone defined osteomyelitis but as discussed above both pathogen and histologic examinations are required for the diagnosis [3]. This is important when assessing various studies as the study definition of osteomyelitis impacts the prevalence of osteomyelitis in its patient population.
- Turk et al. [12] used four distinct categories in autopsy patients with stage 4 sacral pressure ulcers.
    - Full-thickness soft-tissue disease without osseous involvement (seven patients);
    - Increased osteoclastic activity and reactive bone formation with inflammatory cells (seven patients);
    - Fibrotic osseous involvement without evidence of osteomyelitis (one patient);
    - Osteomyelitis (13 patients).
- Even in patients defined as having osteomyelitis, only half had cortical involvement with chronic osteomyelitis and the rest with small foci of acute on chronic osteomyelitis without extensive bone destruction. If the cases of superficial chronic osteomyelitis are excluded, then even fewer cases remain and the location of osteomyelitis in those cases were focal and are not diffuse or extensive.

- Other authors looking at this found similarly low rates of osteomyelitis when defined by histology [2,3,11]. While other authors have reported higher rates of osteomyelitis, the data is unclear regarding location of disease including whether it was focal or diffuse [3].
- Thus, chronically exposed sacral bone by itself does not define active osteomyelitis.

Lab Findings

Most patients being managed for chronic osteomyelitis in the inpatient or outpatient setting at one time or another have received typical blood tests, including inflammatory markers to assist in the diagnosis of osteomyelitis. Even though most data suggest poor correlation of many of these tests with chronic osteomyelitis, they are still frequently ordered.

What are the most common blood tests used for assessing chronic osteomyelitis and are they accurate?

- The most common tests include erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and alpha-1 acid glycoprotein [5]. They are usually elevated but have low sensitivity and specificity. They may be helpful to assist in early diagnosis of postoperative bone infection and to assess the effectiveness of antibiotics during the course of antibiotic therapy [5].

What are the typical histological findings of chronic osteomyelitis?

- Most of the studies have shown histologically confirmed chronic osteomyelitis as typically being superficial or focal without deep or diffuse involvement [3]. On histology mild infiltrates of lymphocytes and plasma cells were seen involving mostly the superficial bone. Acute inflammatory cells were not observed in bone and tissue stains did not show any bacteria. Osteomyelitis was always associated with pressure-related changes, including the presence of encasing fibrotic tissue with some degree of chronic inflammation and reactive bone formation [2].

Imaging

There has been much discussion regarding the role of imaging in the diagnosis of osteomyelitis including radiographs, computed tomography (CT), magnetic resonance imaging (MRI), and scintigraphy. The challenge is differentiating via imaging the reactive bony changes from true infection.

Are CT scans or radiographs sensitive and specific for diagnosing osteomyelitis?

- Many studies reference Larson et al. [13], who showed a combined sensitivity of plain film and CT to be only 61% and specificity of 69%. However, osteomyelitis was defined based on positive bone culture rather than histopathology. Additionally, radiologic studies up to 1 year prior to surgery were included. However, Lewis et al. [14] showed, among 52 patients, the sensitivity and specificity of plain films and CT was 18% and 100% and 11% and 90%, respectively, compared to bone biopsy at surgical debridement. Histopathologic osteomyelitis was defined as both osteonecrosis and inflammatory infiltration of the bone.

Does an MRI add additional benefit to diagnosis of osteomyelitis?

- It can be difficult to distinguish chronic osteomyelitis from reactive bone formation or healed osteomyelitis [3]. Brunel et al., with 44 pressure ulcers, found that MRI scans when compared to bone biopsy and histology as the reference were highly sensitive (94.3%) but poorly specific (22%) [15].

What about bone scans?

- Sugarman et al. found bone scans to be highly sensitive but poorly specific for osteomyelitis [11]. However, this study evaluated only 28 pressure ulcers. Lewis et al. also did not recommend bone scanning to diagnose osteomyelitis associated with pressure ulcers [14].

Is a pre-operative MRI helpful for surgical planning including debridement and flap converge?

- Daniali et al. compared 26 patients with MRI diagnosed osteomyelitis to 21 patients with osteomyelitis diagnosed by intraoperative bone culture positivity. Osteomyelitis diagnosed via MRI compared to culture growth from an intraoperative specimen found no difference in surgical technique, perioperative management, or patient outcomes [16].

What is a cost effective approach to imaging to diagnose osteomyelitis?

- Most of the data regarding true sensitivity and specificity of imaging techniques are poor with small sample sizes and comparison to bone culture rather than histopathology. There does not seem to be a clear or proven benefit to obtaining any radiographs strictly for the diagnosis of chronic osteomyelitis in a sacral pressure ulcer. Logically, even if an imaging test revealed true osteomyelitis, antibiotics would not be initiated simply based on this result. Surgical management would have to be pursued including debridement, revascularization, and wound coverage at which time a reliable diagnosis can be made via bone biopsy and histopathology [3,13,16].

Management

Management of chronic osteomyelitis has been a challenge for decades related to accurate diagnosis, sufficient debridement, and proper revascularization with removal of dead space and coverage. Even when all this has been achieved, there exists issues related to nutritional status, BMI, smoking status, and insufficient offloading. Antibiotics have a role in management in conjunction with above and not as an isolated therapy.

Antibiotics

What is the recommended duration of treatment for chronic osteomyelitis?

- The traditional recommendation of 4–6 weeks of parenteral antibiotics is based on data from the 1970s and the idea that it takes 3–4 weeks for infected bone to revascularize [17]. Otherwise, data on this topic are very limited and most studies do not show clear benefits between duration of antibiotic treatment and impact on risk of ulcer recurrence [3]. There is no clear indication for antibiotic treatment without plans for definitive wound coverage [3].

Is there proven benefit of oral vs. intravenous antibiotics for treatment of chronic osteomyelitis?

- A Cochrane study published in 2013 that included pooled results from 150 participants did not show any difference in terms of the number of people who did not have symptoms at the end of treatment. Additionally, it did not show any difference in the number of people who had negative side effects or had a superinfection. These data suggest that the route of antibiotic administration does not impact disease remission if the bacteria causing the infection are sensitive to the antibiotic used. However, many of these trials are greater than twenty years old and the prevalence of resistant bacteria is greater now [1].

Which oral antibiotics have the highest bone to serum concentration ratio?

- Fluoroquinolones, sulfamides, cyclines, macrolides, rifamycins, and oxazolidinones [17,18]. These classes of antibiotics also have the highest bioavailability. A table of pathogen specific antibiotics including route of administration, dose, and frequency can be found in the work of Fantoni et al. [18].

What is the optimal duration of therapy and do all chronic osteomyelitis patients need prolonged therapy?

- There is insufficient data regarding optimal duration of therapy or best antibiotic choice. However, after sufficient surgical debridement to remove any necrotic bone and flap closure to restore sufficient vascular supply and remove dead space, the antibiotics can be tailored based on the bone cultures obtained at the time of surgery [3].
- Marriott et al. discussed patients that received the above therapy with pathology negative for acute osteomyelitis; they were treated for 5–7 days with intravenous antibiotics [10]. Patients treated with this shorter duration of antibiotics showed no difference in duration of postoperative hospitalization, rate of ulcer recurrence, or rate of subsequent wound breakdown when comparing patients with chronic osteomyelitis and the negative osteomyelitis group.
- Wong et al. [5] reviewed multiple additional studies which found no significant difference in infection recurrence and duration of antibiotics.

What can be done for better antibiotic penetration into a biofilm?

- Since biofilms can allow for relapses of chronic osteomyelitis, some experts suggest the use of an antibiotic (e.g., rifampin) with activity against microorganisms in biofilm as a combination drug in both parenteral and oral regimens [5]. Other agents include lipoglycopeptides, which kill *S. aureus* in the stationary phase and within biofilms [7,19]. These agents have allowed us to stop the combination treatment with rifampin and use only monotherapy.

What antibiotic choice should you use empirically to treat chronic osteomyelitis?

- In general, there is no role for empiric antibiotics without definitive plans for debridement and wound coverage. Parenteral beta lactams, however, have always been one of the mainstays of therapies as they provide high serum concentrations along with adequate bone and tissue penetration into the site of infection. Other options include the once-weekly lipo-glycopeptides which carry the added benefit of additional biofilm penetration. These are only to be used empirically in combination with a Gram-negative therapy agent until cultures have been obtained. It is good to remember though that two-thirds of all chronic osteomyelitis cases are caused by Staphylococcus aureus [7].

Surgical

Does presence of osteomyelitis prior to flap coverage lead to higher complication rates?

- No, Goodman et al. studied 48 veterans with spinal cord injuries and although this group had a high rate of complications and rate of ulcer recurrence or new ulcer development, no correlation was found between poor outcomes and osteomyelitis [3,20].

Are bone biopsies necessary for improved outcomes?

- No, positive bone culture from a biopsy was not correlated with increased recurrence or complications. It would be reasonable to proceed with surgery for debridement and flap coverage without first delaying treatment with antibiotics. If cultures are positive, then appropriate antibiotics can be used for treatment in combination with surgical treatment [9].

- Larson et al. concluded that placing a patient on a prolonged course of antibiotics empirically, or guided by a diagnostic culture, without providing coverage over that bone is illogical and a waste of resources, as the bone is still open and susceptible to recurrent infection [9].

Is stool and urinary diversion necessary?

- Bejany et al. discussed four patients with paraplegia and pressure ulcers who had failed previous attempts at ulcer healing with muscular flaps and a suprapubic catheter. After undergoing a diverting colostomy for stool and a Miami pouch for urinary diversion, all four patients achieved ulcer healing [21]. Additionally, de la Fuente compared colostomy vs. non-colostomy with the majority of colostomies performed laparoscopically. The findings showed lower ulcer recurrent rate in colostomy group as well as a shorter healing time [22].

Recurrence and Complications

Recurrence seems to be a frequent problem reported at >50% in multiple studies [20,23], so understanding risk factors that can lead to an increased rate of recurrence would help in optimizing management and cost savings.

What risk factors increase recurrence or complications?

- In the data of Bamba et al., looking at 276 patients the risk factors associated with recurrence included: BMI < 18.5 kg/m^2, active smoking, low preoperative albumin [3,24]. Additionally, persistence of initial patient characteristics that led to the ulcer formation, including inability to offload pressure.

Are recurrences related to a new problem or continuation of the previous infection?

- Based on limited data of Jugun et al., most of the cases of recurrences were with a different bacteria compared to the original infection, suggesting a new problem rather than a failure of the initial management [23].

Does positive bone culture increase recurrence or risk of complications?

- Based on a retrospective study by Larson et al. looking at 101 patients with 179 pressure ulcers, there was no association found between positive bone cultures and recurrence or complications [9].

Summary

Based on the review of available data, it is clear that more research on this topic is necessary, especially randomized controlled trials. Additionally, much of the data are decades old with a limited sample size and variable definitions of osteomyelitis. What seems clear, however, is a single pronged strategy based on administration of prolonged antibiotics is likely to lead to treatment failure. A multipronged approach including treating the underlying cause of the pressure ulcer is most likely to be successful.

It would seem reasonable that the first step to managing a chronic sacral pressure ulcer should be debridement of all necrotic tissue down to healthy, vascular, viable tissue. During the debridement and after osteotomy, a bone biopsy should be obtained for histopathological diagnosis of osteomyelitis. Immediate reconstruction with tissue coverage should be performed.

After surgery, empiric antibiotics can be initiated pending final culture results and pathology. If there are no signs of sepsis, then a cephalosporin with coverage for *Staphylococcus aureus*, *Streptococcus*, and enterobacteria would be reasonable. This can be further adjusted based on culture and sensitivities, although most studies do not show a failure related to insufficient

antimicrobial coverage. Thus, overly broad-spectrum antibiotics are likely unnecessary. If pathology does not reveal osteomyelitis, then a short 5–7-day period of postoperative antibiotics should be considered. If osteomyelitis is present then as short as a 2-week course of antibiotics can be considered, assuming sufficient debridement, removal of dead space, and tissue coverage.

Next, steps should be taken to minimize failure and recurrence. This includes proper wound care without exposing the wound to damaging cleansers such as Betadine and peroxide. Wound contamination from stool and urine should be addressed through diversion. Additionally, an air circulating mattress can help minimize pressure points along with consistent management by a wound care team whether at a nursing facility or as an outpatient. Finally, a nutritionist should be involved to optimize calorie intake.

What is clear is that clinical evaluation of sacral osteomyelitis is poor and initial imaging likely unnecessary. Similarly, a prolonged course of parenteral or oral antibiotics without a sound plan in place is futile. Optimal management requires a dedicated team including multiple members with a proper protocol in place [2,3,9,13].

Conflicts of Interest: Vishal K Didwania is on the speakers bureau for Abbvie and Gilead.

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