The treatment of osteomyelitis in patients with stage IV sacral pressure ulcers is controversial. We conducted a systematic literature review and did not find evidence of benefit of antibacterial therapy in this setting without concomitant surgical debridement and wound coverage. Furthermore, many patients with chronically exposed bone do not have evidence of osteomyelitis when biopsied, and magnetic resonance imaging may not accurately distinguish osteomyelitis from bone remodeling. The goal of therapy should be local wound care and assessment for the potential of wound closure. If the wound can be closed and osteomyelitis is present on bone biopsy, appropriate antibiotic therapy is reasonable. We find no data to support antibiotic durations of >6 weeks in this setting, and some authors recommend 2 weeks of therapy if the osteomyelitis is limited to cortical bone. If the wound will not be closed, we find no clear evidence supporting a role for antibiotic therapy.

Keywords. osteomyelitis; sacral pressure ulcer; antibiotic; debridement; wound flap.

A 79-year-old man with a history of spinal cord injury was referred for further evaluation of a sacral pressure ulcer. The ulcer developed several years earlier from local trauma related to a motorized wheelchair. Over the subsequent months, the ulcer progressed and tunneled to the level of the sacrum.

The patient was referred for infectious disease consultation due to an increase in wound discharge over the preceding month. Outpatient magnetic resonance imaging (MRI) indicated an increased size of the ulcer over the right ischial tuberosity with increased granulation tissue, reactive myositis, and mild marrow edema. The MRI did not reveal a drainable fluid collection or abscess.

The patient had normal vital signs. He appeared comfortable and had a deep penetrating ischial ulcer of approximately 6 cm × 3 cm, without significant purulence or erythema of the surrounding soft tissue. White blood cell count, creatinine, and a liver panel were unremarkable.

METHODS
Clinicians often struggle with the appropriate diagnostic and therapeutic management of patients who have chronic, sacral pressure ulcers. Establishing the diagnosis of osteomyelitis in this setting is challenging, and if present, whether it can be successfully treated without covering the wound is unclear. We hypothesized that eradication of osteomyelitis in the setting of exposed bone cannot be achieved without debridement and soft tissue coverage of the wound, and thus antibiotics to attempt to treat osteomyelitis are not indicated in this setting. We conducted a systematic review of the literature to determine if data are available to support or refute this hypothesis.

We searched for the keywords “pelvic osteomyelitis” or “decubitus AND osteomyelitis” or “sacral osteomyelitis” from 1975 to the present using PubMed, Google Scholar, and Web of Science search engines. We reviewed abstracts from all identified, peer-reviewed, published articles to determine if they included information on clinical outcomes or diagnostic accuracy, in which case we reviewed the full manuscripts. We also reviewed references from identified articles to identify other relevant studies.

RESULTS
We found a total of 30 manuscripts that met our search parameters. Of these, we excluded 5 as they did not specifically address pelvic/sacral osteomyelitis or focused on chronic osteomyelitis as a general entity. We excluded an additional 5 manuscripts that described the role of hemicorpectomy and hemipelvectomy for intractable pressure ulcers. The majority of published papers were case series or retrospective analyses. There were no available randomized controlled studies.

Histopathology of Exposed Bone in Sacral Pressure Ulcers
Contrary to the perception that exposed bone by definition must contain osteomyelitis, several case series in which bone biopsies were conducted described histological evidence of...
osteomyelitis (defined as leukocytic inflammatory influx into bone [1, 2]) in a minority of such patients. For example, Türk et al examined histologic autopsy specimens of 28 patients with advanced-grade pressure ulcers, specifically those with visible bone [3]. Based on the histopathologic findings, 4 distinct groups were identified. Group 1 (n = 7) had full thickness soft tissue disease but no inflammation of the bone, with the cortical layer of the sacrum intact. Group 2 (n = 7) had bone cortex involvement with increased osteoclast activity and reactive new bone formation. Group 3 (n = 1) had fibrotic/remodeling bony involvement without osteomyelitis changes, in the presence of suppurative soft tissue disease. Group 4 (n = 13) was subdivided into 6 patients with chronic osteomyelitis restricted to the superficial and subcortical aspects of the sacrum without involvement of the medullary cavity of bone, and 7 patients who had mild small confined foci of acute superimposed on chronic osteomyelitis changes without suppurative inflammation or wide destruction of bone. The highlight of these findings was that in more than half of cases (groups 1–3) osteomyelitis was not detectable histologically, whereas in cases with osteomyelitis, disease was generally more focal and superficial [3].

These results are consistent with studies by Darouiche et al [4] and Sugarman et al [5], who also found that on bone biopsy only 6 of 36 (17%) and 6 of 14 (43%) of patients with stage IV sacral pressure ulcers (mean extension of ulcer to exposed bone) had histological evidence of osteomyelitis. Furthermore, in the latter study the investigators found no correlation between duration of ulcer and findings of osteomyelitis by histopathology; even ulcers that had been present for months to years were found to have no evidence of osteomyelitis in bone. However, pressure-induced reactive fibrosis, medullary edema, and reactive bone formation occurred in all cases, even those with intact cortical bone. Thus, histopathology was necessary to distinguish noninfectious fibrotic/inflammatory changes in bone from inflammation consistent with osteomyelitis. When osteomyelitis was present it was generally restricted to the superficial layers of cortical bone.

Other investigators evaluating patients with deep pressure ulcers due to spinal cord injury also found no correlation between histologic findings of osteomyelitis on bone biopsy and the presence of fever, leukocytosis, or increased erythrocyte sedimentation rate [6]. The authors postulated that the extent of soft tissue infection was more likely the cause of systemic symptoms.

In summary, available retrospective data indicate that osteomyelitis is not an inevitable—and may even be a rare—complication of a chronic sacral pressure ulcer.

Microbiology of Osteomyelitis in Sacral Pressure Ulcers
Multiple case series have described microbial flora identified from various culture and sampling methodologies. Anaerobic cultures were not always utilized, likely causing underrepresentation of anaerobic pathogens in published studies. Furthermore, antibiotic therapy administered prior to bone biopsy may have affected culture results, and it is difficult to discern this effect from published studies.

Bodavula et al conducted a retrospective cohort study of 270 patients with stage IV pressure ulcers and a concurrent clinical diagnosis of pelvic osteomyelitis [7]. One hundred thirteen (51%) patients had microbiologic cultures taken, of which 20% were bone biopsies, 23% deep tissue cultures, and the remaining 57% drainage swab cultures. The most frequent organisms encountered included Staphylococcus (18%) and Streptococcus (8%) species. In 30% of patients, multiple organisms were identified. In some specimens, mixed flora was also described but not identified further.

In a retrospective analysis of 179 patients with surgically treated sacral pressure ulcers, Larson et al described the results of operative bone cultures in 67% of patients, and of these only 52% grew pathogens [8]. They found no association between culture positivity from bone biopsy and 2-year ulcer recurrence. Of note, the patients who did not undergo a bone biopsy had a 2.78-fold higher odds ratio of complications (including wound dehiscence, wound infection, or flap failure) at 1 year of follow-up compared to patients with a negative bone culture.

In 4 other case series totaling 150 patients, the majority of cultures grew multiple organisms, with Staphylococcus aureus as the predominant pathogen, and Enterobacteriaceae commonly encountered, followed by Peptostreptococcus and Bacteroides species [5, 9–11]. Unusual organisms including Nocardia or Fusobacterium were also occasionally encountered [12, 13].

Diagnostic Testing
Larson et al compared the results of bone biopsy to imaging results for 44 patients with stage IV sacral pressure ulcers who underwent surgical debridement [14]. Using bone biopsy as the reference standard, they found a sensitivity and specificity of only 61% and 69%, respectively, for a combination of radiographs and computed tomographic (CT) scans to identify histologically confirmed osteomyelitis [14]. In another study, CT scans performed even worse, achieving a sensitivity of only 11% for detecting osteomyelitis compared to histopathology in 61 patients with spinal cord injury and sacral pressure ulcers [15]. Additionally, due to the variable extent of bone involvement in chronic pressure ulcers, radionucleotide indium scan has been reported to have variable sensitivity and low specificities [14, 16], so these tests are not of apparent utility either.

The role of MRI in diagnosing sacral osteomyelitis is unsettled. One study reported better sensitivity (98%) and specificity (89%) of MRI for diagnosis of osteomyelitis when compared to clinical diagnostic criteria [17]. However, as mentioned above, clinical diagnostic criteria cannot distinguish histopathological evidence of bone remodeling/fibrosis from osteomyelitis. Thus, when Brunel et al compared MRI to bone histology as
the reference standard, the sensitivity of MRI was high (94%), but the specificity was very poor (22%) [10]. This poor specificity is consistent with the fact that histology often demonstrates fibrotic inflammatory changes that are noninfectious, but likely appear consistent with typical infectious marrow edema on MRI.

In summary, the role of imaging to diagnose osteomyelitis related to sacral pressure ulcers is poorly defined and is limited by variable specificity. Some authors have suggested that MRI may have better utility in assessment for the depth of associated soft tissue changes and guidance of surgical management [17, 18]. Furthermore, diagnostic imaging can only be helpful if therapeutic intervention is planned based on the diagnostic results. If antibiotic therapy is not clinically effective (discussed further below), identifying the osteomyelitis to treat with antibiotics would not be a rational strategy, and MRI imaging would be irrational even if accurate.

**Therapeutic Management**

Data regarding therapeutic management for osteomyelitis in sacral pressure ulcers are limited to case series. Acknowledging the limitations of the data, multiple authors have indicated superior long-term cure rates with a combined medical and surgical approach, in particular with wound coverage [9, 19, 20]. For example, investigators conducted a retrospective analysis of 157 patients with sacral pressure ulcers [20]. They used deep bone shavings to ensure adequacy of debridement (ie, negative histopathology), enabling closure of the wound with muscle or myocutaneous flaps. Patients with acute, neutrophilic-predominant osteomyelitis on histology were treated with a full 6-week antibiotic course. In contrast, patients with chronic inflammatory infiltrate into bone or histological findings negative for osteomyelitis were treated with 5–7 days of intravenous antibiotics. For patients treated with shorter antibiotic courses, there was no difference in duration of postoperative hospitalization, rate of ulcer recurrence, or rate of subsequent wound breakdown when comparing the patients with chronic osteomyelitis and the negative osteomyelitis group [20]. However, the acute osteomyelitis group that had received the 6-week antibiotic treatment had a longer hospitalization duration and higher complication rate (ie, wound breakdown and ulcer recurrence) [20]. Of note, as the authors did not match patients for disease severity or comorbidities, the higher complication rate may have been driven by patients with more severe illness being treated with the longer course of therapy.

Bodavula et al described a large cohort study of patients with sacral osteomyelitis, 105 (39%) of whom received antibiotic therapy alone, 55 (25%) of whom received both antibiotics and surgical debridement, and 7 (13%) of whom received a myocutaneous flap [7]. Patients treated with a combined medical and surgical approach were significantly less likely to be rehospitalized in the successive 12 months.

Similarly, Jugun et al reported on 70 episodes of infected sacral pressure ulcers that occurred in 31 patients [11]. All of the patients underwent surgical debridement and received antibiotic therapy, and 54 of the episodes were found to have active osteomyelitis based on bone biopsy. The only factor associated with clinical recurrence of the infection (biopsy proven by histopathology and culture) was age; by both bivariate and multivariate analyses, inflammatory markers, proportion of patients that received >6 or <6 weeks of antibiotics, proportion of patients receiving at least 2 weeks of intravenous antibiotics, and the presence or absence of osteomyelitis did not predict recurrence. Furthermore, evaluating the duration of antibiotic therapy as a continuous variable failed to define any correlation with antibiotic duration and risk of recurrence, and failed to identify any specific threshold of minimum days of antibiotics that diminished recurrence.

Firriolo et al described 24 patients with 30 sacral pressure ulcers (5 stage III, 25 stage IV), all of whom underwent flap coverage [21]. Fifteen of the ulcers had bone biopsy–proven osteomyelitis, 6 had radiographic features suggesting osteomyelitis on MRI, and 9 did not have evidence of osteomyelitis. Half of the patients experienced recurrence of the ulcer after flap coverage. Ulcer recurrence was associated with failure to comply with nonoperative management (eg, pressure off-loading), but was not associated with the presence or absence of osteomyelitis. Similarly, the presence of osteomyelitis was not associated with ulcer recurrence in 48 patients with spinal cord injury and sacral pressure ulcers described by Goodman et al [22].

Finally, Sugarman et al found no relationship between antibiotic therapy and permanent healing of stage IV sacral pressure ulcers [5]. Four of 6 patients without osteomyelitis treated with only local wound care and no antibiotics had complete healing, and the remaining 2 had partial healing. Five of the 8 patients with osteomyelitis experienced complete healing of the wound with surgery and antibiotics, but 3 of the 5 required “amputation” to affect healing.

In summary, numerous case series conducted by a variety of investigators across a variety of patient populations have failed to identify a relationship between healing of stage IV sacral pressure ulcers and whether antibiotics were administered or not, whether antibiotics were administered intravenously or orally, or the duration of antibiotic administration.

Thus, data are not available demonstrating that prolonged courses (ie, >6 weeks) of antibiotics are more effective to treat sacral osteomyelitis. Nor do data to support a duration of antibiotic therapy beyond 4–6 weeks for chronic osteomyelitis in general [23, 24]. Furthermore, for osteomyelitis limited to cortical bone, some authors have advocated for a 2-week course of antibiotic therapy [25, 26]. Longer antibiotic courses may lead to more complications without evidence of benefit.
DISCUSSION

Our review of available literature suggests that osteomyelitis may be relatively uncommon in patients with stage IV sacral pressure ulcers, even if the ulcers are chronic. Unfortunately, no diagnostic study (whether inflammatory marker or radiographic study) other than bone biopsy appears to be accurate to rule in osteomyelitis. Furthermore, the available data do not support the concept that osteomyelitis affects the risk of recurrence after wound coverage. Nor are data available supporting the practice of administrating antibiotics to treat osteomyelitis for >6 weeks, or to support intravenous rather than oral antibiotic administration [24, 27].

At first blush, the absence of reliable diagnostic testing, absence of compelling evidence for nonsurgical therapeutic options, and relatively high recurrence rates even with a multimodal medical–surgical approach, combined with a paucity of data and a total absence of controlled investigations, can leave the clinician in a frustrating quandary. However, patients affected by this syndrome have complex psychosocial issues aside from medical comorbidities. The focus diagnostically and therapeutically may be better targeted toward the underlying factors that created the conditions of the stage IV sacral pressure ulcer in the first place. Achieving complete healing is unlikely absent mitigation of these underlying drivers no matter what other medical or surgical interventions are applied.

From this perspective, whether or not to administer antibiotics, and for how long and by what route, are actually peripheral considerations, the answers of which do not appear to drive outcome. They are tempting to focus on because physicians have historically viewed antibiotic administration as a definitive, curative intervention. But for this disease they appear to be neither, and focusing on these considerations distracts from far more meaningful psychosocial and clinical interventions. When it comes to antibiotics for treating sacral osteomyelitis, less may be more.

In summary, given the cumulative nature of the suboptimal data, we draw several conclusions:

1. Clinicians should not assume osteomyelitis is present in a chronic sacral pressure ulcer; biopsy after debridement appears to be necessary to establish the diagnosis.
2. When osteomyelitis is present, we do not find data supporting antibiotic therapy in the absence of a plan to cover the wound. Lacking wound coverage, antibiotic therapy may offer only a transient response.
3. Short-term (eg, ≤1 week) antibiotics may be administered to treat an acute soft tissue infection extending from the ulcer (eg, in the presence of rubor, tumor, calor, and dolor in soft tissues, with purulent drainage). Longer courses of therapy should be avoided for this purpose as there is no evidence of benefit, and harm will accrue due to side effects, superinfections, and selection for resistant pathogens.
4. If assessment of the patient’s medical and psychosocial factors results in a belief that debridement and wound coverage can be feasibly completed, the plan should include to obtain a bone biopsy (not a surface swab) after debriding away surface contaminated material to guide antibiotic therapy. Empiric antibiotics should be held, if possible (eg, the patient does not have sepsis or another indication for urgent empiric therapy), until the bone biopsy is completed. Once the biopsy is completed, a rational empiric regimen may be started that covers gram-positive and gram-negative aerobic and anaerobic pathogens. Initial empiric therapy should be modified based on findings from the culture of biopsied bone.
5. The duration of antibiotic therapy may be chosen to be 2 weeks for osteomyelitis found to be restricted to superficial bony cortex (the majority of cases based on literature), or 4–6 weeks if medullary bone is affected—it is not rational or evidence-based to extend antibiotic therapy beyond 6 weeks.
6. Antibiotic therapy may be administered orally or intravenously.
7. Randomized controlled trials are critically needed in this space to improve evidence-based decision making, including around the impact of biopsy on diagnosis and treatment decisions, and the breadth and duration of antimicrobial therapy.
8. While the above recommendations are supported by the limited available literature, clinically we must be prepared to adjust our approach as new data become available in the future.

Applying these principles to the initial case, our patient had minimal signs of soft tissue disease and no systemic symptoms. After discussion with family members, the decision was to defer any invasive surgical procedure. Therefore, the patient continued local wound care measures as well as regular pressure offloading, and no antibiotics were administered. At 1 year of follow-up, he continued to have minimal intermittent drainage, but otherwise, he remained afebrile without significant decline in clinical status.

Note

Potential conflicts of interest. In the last 12 months, B. S. has received consulting fees from Bayer, Forge, Shionogi, Alexion, Synthetic Biologics, Paratek, and Ovagene, and owned equity in Motif, BioAIM, Synthetic Biologics, Mycomed, and ExBaq. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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