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Final Selective Paper
Dr. Bruce Browner preceptor
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Long-term outcome of treatment of chronic osteomyelitis with combined surgical and oral antibiotic therapy

Abstract:

OBJECTIVE: To conduct an observational study of the long-term outcome of people with chronic osteomyelitis treated with combined surgical and oral antibiotic therapy. **METHODS:** All patients included in the study were seen at the University of Connecticut Bone Infection Clinic from January 1992 to July 1999, had documented chronic osteomyelitis by intraoperative biopsy, and were treated with, but not limited to, combined surgical and oral antibiotic therapy. The charts of these patients were retrospectively reviewed specifically for the duration of postoperative parenteral antibiotic use. These patients were then sent a questionnaire concerning views about their health. This questionnaire included: (1) questions pertaining to the patient's background and treatment history; (2) a standardized Short Form-36 (SF-36) survey; and (3) the twelve "bother index" questions from the Short Musculoskeletal Function Assessment (SMFA). **RESULTS:** Retrospective chart review showed that the median duration of postoperative parenteral antibiotic use was 16 days. Outcome information was obtained from 44 of the 122 patients contacted after the first mailing. The data from these surveys reveal that patients suffering from chronic osteomyelitis view their overall health as "good" and are "moderately bothered" by functional problems associated with their disability. A majority of these patients (68%) say that their expectations of treatment have been met. **CONCLUSION:** At the University of Connecticut Bone Infection Clinic from 1992 to 1999, the median duration of postoperative intravenous antibiotic administration was well below the traditional 4-to-6 week course. Without a control group at this stage of the study, it is to be determined whether this shorter course of parenteral treatment has adversely affected patient outcome. Regardless, this survey can serve as a helpful point of reference for practitioners as they discuss quality of life issues with their chronic osteomyelitis patients.

Introduction:

Osteomyelitis that occurs at the site of trauma is, by definition, *chronic* from the outset because dead bone is already present. Therefore, therapy of any such infection must be focused upon elimination of all devitalized bone and soft tissue. The orthopaedic community is in full agreement that administering antibiotics without the complete excision of all necrotic tissue (sequestra, scars) is futile. Where there has been some controversy, however, is regarding the role of antibiotics in this group of patients. Traditionally, four to six weeks of postoperative

parenteral antibiotics has been the standard of care. Up until fairly recently, administering oral antibiotics during this time period was rarely considered as a viable option. However, because of the cost-effectiveness and non-invasiveness of substituting oral for intravenous medications, this issue has been the subject of several studies over the past fifteen years.

The purpose of this study is to review a group of patients with chronic osteomyelitis who have been treated with combined surgical debridement and a “substandard” duration of parenteral antibiotics (receiving oral antibiotics earlier on in their postoperative course). In addition to performing a chart review on this cohort, the ultimate goal will be to assess whether these patients are doing just as well as those treated with the traditional 4-to-6 week regimen.

Patients & Methodology:

All 140 patients selected for this study were seen at the University of Connecticut Bone Infection Clinic from January 1992 to July 1999, had documented chronic osteomyelitis by intraoperative biopsy, and were treated with, but not limited to, combined surgical and oral antibiotic therapy. The two aspects of this study consisted of a retrospective chart review and the administration of a survey regarding patients’ views about their current state of health. The questionnaire that was sent to the patients included: (1) questions pertaining to their background and treatment history; (2) a standardized Short Form-36 (SF-36) survey; and (3) the twelve “bother index” questions from the Short Musculoskeletal Function Assessment (SMFA). [The contents of these surveys are included in Appendices 1, 2 and 3 respectively].

The questions pertaining to the patient’s background and treatment history were designed by the research team specifically for this study. They have no historical precedent. In contrast, the two standardized questionnaires, the SF-36 and the SMFA, have been widely used and

reported upon in the literature over the past several years. It should be noted that neither of these surveys were created specifically for patients suffering from chronic osteomyelitis. In fact, no such assessment tools exist. The SF-36, instead, is a generic questionnaire of 36 questions designed for the assessment of functional outcomes in populations of patients with any type of disease. It was utilized in this study because of its proven reliability as an indicator of patients' perceptions about their health. The SMFA is a 46-item questionnaire abbreviated from the longer 101-question Musculoskeletal Function Assessment (MFA). Twelve of these questions are referred to as the "bother index," which are designed to assess how much patients are bothered by functional musculoskeletal problems. These questions, although originally intended for osteoarthritis patients, are broad enough to assess people with most musculoskeletal disabilities, such as those associated with chronic osteomyelitis.

By using the SF-36 and the SMFA in concert, this observational study attempts to elucidate both: (1) the views patients with chronic osteomyelitis have about their overall state of health and (2) how much they are bothered by their disability in everyday life.

Results:

Of the 140 patients reviewed in this study, the vast majority suffer from chronic osteomyelitis secondary to open fractures from automobile and motorcycle accidents. The tibia is by far the most common site of involvement. They have all been treated with, but not limited to, a combined surgical and oral antibiotic approach.

Staphylococcus aureus (34.4% of patients) and coagulase-negative *Staphylococcus* (25.4%) were found to be the most common pathogens in these patients by way of intraoperative biopsy. [See Appendix 4 for a graphical distribution of bacterial isolates]. Retrospective chart

review showed that the median duration of postoperative parenteral antibiotic use was 16 days. Median duration is more reflective of the duration of postoperative parenteral antibiotics in this cohort because there were a few outliers kept on intravenous antibiotics for as long as a year who disproportionately elevate the mean.

Of the 140 patients who fulfilled criteria to receive the outcome questionnaire, 122 actually received it (87%) and, of that number, 46 (37.7%) returned it after the first mailing. Two people chose not to answer the questions, leaving 44 (36.0%) who were actual respondents to the questionnaire. The data from these surveys were entered into an Access database for analysis. [Mean results from the SF-36 and SMFA are depicted by shading in the closest corresponding answer box on the questionnaire forms in Appendices 5 and 6. Numbers are rounded for ease of viewing].

Of note from the SF-36 survey, an overwhelming majority of subjects (81%) say they are “limited a lot” in performing vigorous activities (question #3). On average, however, the subjects describe their current state of health as “good” (question #1). From the responses to the SMFA, it is apparent that these people are “moderately bothered” by their disability during most everyday activities, but rarely to the point of extreme pain and total dysfunction.

It is interesting to note that, before coming to the University of Connecticut Bone Infection Clinic, a majority of the respondents (54%) expected to have a “complete recovery” from their post-traumatic infection. 68% of respondents say their expectations of treatment have been met, 20% say they have not, and 12% say it is “too early to tell.”

Discussion:

Perhaps the most common terminology used to describe osteomyelitis is to label it as either *acute* or *chronic*. This division is not as elementary as it may seem. Stated simply, acute and chronic osteomyelitis are distinguished by the development of dead bone in the latter. Note that they are not defined by the duration of infection as their names might suggest. Acute osteomyelitis is most frequently hematogenous in origin, usually affecting prepubertal children, and has a good response to antibiotics. In acute hematogenous osteomyelitis, microorganisms (usually *S. aureus*) infiltrate vascularized bone and produce a vigorous inflammatory response. Since bone is a rigid tissue, this influx of phagocytes and other inflammatory cells into its canals has the unintended effect of raising intraosseous pressure and occluding its own blood supply. Without the intervention of antibiotics, bone death or osteonecrosis may result. What makes this natural history particularly troublesome is that these fragments of devitalized bone, also called sequestra, act like foreign bodies and perpetuate the problem by exposing sites to which pathogenic bacteria can bind. At the point in which bone death actually occurs, the infection can then be properly referred to as a chronic osteomyelitis. However, it is important to realize that this is rarely the manner in which chronic osteomyelitis develops. In fact, acute hematogenous osteomyelitis progresses to chronic osteomyelitis less than 5% of the time.

By far the most common etiology of chronic osteomyelitis is trauma, in which bone is devitalized from the outset. Because of its obvious association with motor vehicle accidents, chronic osteomyelitis occurs primarily in adults. In contrast to the cascade of events in acute hematogenous osteomyelitis whereby pathogenic bacteria seed previously alive bone, the role of bacteria in chronic osteomyelitis is solely an opportunistic one. In this case, bacteria take advantage of bone that is already injured and ischemic. Because necrotic bone is present from the

outset, therapy must be first and foremost focused upon the surgical elimination of all devitalized tissue. If not excised, this tissue would otherwise serve as a nidus for further infection by providing a sanctuary for virulent micro-organisms which are essentially “hidden” from the bloodstream. Once again, *S. aureus* is the most common culprit, but the possibility of co-infection with gram-negatives and anaerobes needs to be entertained in these cases of post-traumatic infection.

Because the injured bone in chronic osteomyelitis is, by definition, lacking adequate blood supply, antibiotics (whether they be delivered parenterally or orally) are useless without surgical debridement. The purpose of antibiotics then is not to heal the dead tissues per se, but rather to kill any bacteria in the periphery that would otherwise prevent adequate blood supply to the “transition zone” around the sequestrum. In this light, it is easy to understand why the route of administration of the antibiotic should theoretically not affect patient outcome so long as it is in the bloodstream at bacteriocidal levels.

If both parenteral and oral antibiotics can attain such levels, oral delivery would naturally be favored as it is clearly more comfortable for the patient, decreases the chance of line infections, and is more cost-efficient. There are a few contraindications to oral delivery which should be mentioned. These include: insensitivity of the microbe to oral treatments (i.e., MRSA), a patient who cannot tolerate oral medication or is noncompliant, and lastly, a patient who is acutely ill (thus altering GI absorption).

Conclusion:

At the University of Connecticut Bone Infection Clinic from 1992 to 1999, the median duration of postoperative intravenous antibiotic administration (=16 days) was well below the

traditional 4-to-6 week course. Undoubtedly, this result stems from a belief that antibiotics are simply an adjunct to complete surgical debridement. Their success in maintaining bacteria-free soft tissue around the devascularized focus of infection, it is theorized, depends not on their route of administration but rather on their bacteriocidal properties. While this makes sense, it has not been proven in the literature that decreasing the duration of postoperative intravenous antibiotics is harmless. This study is an attempt to prove just that.

Has our study proven this? The answer is no, at least not yet. While we do have a cohort of patients who have received less parenteral antibiotics than is standard and we do have standardized ways to assess their outcomes (i.e., via the SF-36 and the “bother index” from the SMFA), this observational study falls short on two accounts. Firstly, there are a number of variables in the therapies of these patients. Some patients utilized electric stimulation devices to facilitate bone growth at the site of injury. Others were tried on trials of hyperbaric oxygen. Still others had antibiotic beads placed during surgery to fill dead space or required muscle flaps to help revascularize areas of low perfusion. Indeed, while each of the 44 respondents were treated with combined surgical debridement and oral antibiotics, these were far from their only therapeutic interventions. Therefore, it is difficult to conclude that the outcome of these patients is directly linked to the route of postoperative antibiotic administration and not, for instance, some other treatment modality which happens to be more frequently employed at the University of Connecticut Health Center than at other institutions. Second, without any control groups at this stage of the study, it is difficult to say what “normal” SF-36 or SMFA answers may be for people suffering from chronic osteomyelitis. It would be extremely informative in the future to include patients treated at other centers with more traditional postoperative regimens and send them the same outcome questionnaires by way of comparison. If incorporating another bone

infection center proves to be problematic, perhaps a control group could be achieved by randomizing patients at the University of Connecticut Health Center into two different treatment groups.

At this stage of the study therefore, it is impossible to make any conclusions regarding the efficacy of a combined surgical and oral antibiotic approach to patients with chronic osteomyelitis. If, after a control group is added, outcomes are shown to be similar to those achieved with more traditional regimens, the following treatment algorithm utilized by the University of Connecticut Bone Infection Clinic may be considered by other centers:

- (1) Obtain the patient's history and perform a physical exam in the office. If clinical suspicion of chronic osteomyelitis is high, order appropriate radiologic tests, lab work, and cultures of exposed sinus tracts, pus, and fistulae.
- (2) If the patient is diagnosed with chronic osteomyelitis, surgery (i.e., complete excision of all devitalized tissue) remains the cornerstone of treatment. If the patient is going to surgery without any cultures and sensitivities, it is best to cover presumptively for the most commonly involved pathogen, *S. aureus* (with parenteral cefazolin, a first-generation cephalosporin). If the lower extremity is involved, as in a punctured foot wound, or the patient has Diabetes Mellitus, also cover for *Pseudomonas aeruginosa* (with parenteral ceftazadime, a third-generation cephalosporin).
- (3) If the cultures and sensitivities are back prior to surgery, cover with the appropriate parenteral antibiotic.
- (4) Switch to oral antibiotics around post-operative day #2, guided by intraoperative cultures and sensitivities. Do not switch to oral medication if the patient has one of the contraindications described previously.

As the other treatment modalities of the subjects are controlled for, the sample size of the study increases, and a control group is added, we will be better able to determine whether the current standard of postoperative care in chronic osteomyelitis should be replaced with a less-invasive and less-costly alternative. Nonetheless, even at this early stage, this observational study

has important value. As there are currently no standardized outcome studies in the chronic osteomyelitis literature, these data will prove to be helpful to orthopaedists and general practitioners by providing them with some general prognostic information regarding the quality of life patients suffering from this indolent disease can expect after surgery. Undoubtedly, it will be of some comfort to the recently infected polytrauma patient to know that there is a study out there which clearly demonstrates that most chronic osteomyelitis patients, even after all of their debridements and hardship, view their overall health as “good” and are able to continue with their lives usually without extreme dysfunction.

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Selective Addendum
Dr. Bruce Browner preceptor
28 April 2000

My selective in chronic osteomyelitis

This year my selective project turned out to be more of a *chronic osteomyelitis tour-de-force* than working on just a specific study. Although my survey on the “Long-term outcome of treatment of chronic osteomyelitis with combined surgical and oral antibiotic therapy” was a major part of my year, I wanted to give you an outline of how my selective months were spent on a few other projects.

JULY: The first thing I had to do was expand upon the database set-up by Lance Baldo (Uconn School of Medicine 1998) and enter all the patients seen by Drs. Browner and Pesanti over the past 7 years into it. I entered not just the patients’ postoperative antibiotic usage, but also a plethora of other factors. This was a very time-consuming process, requiring extensive chart review (looking for each patient’s trauma history, past medical history, social history, intraoperative bacteriology, radiologic tests, surgical reports, etc.). In the end, I successfully entered data on all 140 patients into an Access database.

During this time I also was helping Dr. Browner put together a lecture he was giving on grand rounds concerning treatment of chronic osteomyelitis. Dr. Browner gave me a lot of freedom with this task and, by the end of July, I had made about half of the power-point slides for his lecture. In these slides, I incorporated the new data from my chart review (regarding duration of parenteral antibiotics, bacteriology, and comorbidities of his clinic’s patients), as well as revising his outdated slides on the role of nuclear medicine testing in diagnosis.

After completing this assignment, I then searched the literature for which questionnaires would be most suitable to send out to the 140 patients in the database. Ms. Rose Maljanian at the Hartford Hospital Institute for Outcomes Research and Evaluation was particularly helpful in helping me decide which questionnaires to use.

DECEMBER-FEBRUARY: During this time, I developed a questionnaire regarding the patients’ background and treatment history, drafted a letter to the 140 people in the database (see Appendices 1 and 7 respectively), and transformed all three surveys into “scannable” forms which facilitated data entry. This last task could not have been done without the help of Myron Yousman also at the Hartford Hospital Institute for Outcomes Research and Evaluation. The questionnaires were sent out to the 140 subjects in mid-February.

MARCH: In the middle part of March, the questionnaires started to come back. Of the 140 people in my initial database, 122 were contacted, and 46 responded. I then scanned these data into the database. While I was getting back surveys, Dr. Browner asked me if I would like to be the lead-author of the new chapter on osteomyelitis in the 3rd edition of his textbook, **Skeletal Trauma**. Naturally, this was an exciting opportunity and I am currently busy working on it with Drs. Salvana, Browner, and Pesanti as my “senior editors.”

APRIL AND BEYOND: As I am staying here at UConn for residency in orthopaedic surgery, I plan on continuing all of the following projects over the next several months and into the upcoming academic year:

- (1) Expanding the database of the Bone Infection Clinic's patients.
- (2) Continuing with my outcome analysis (hopefully adding a control group by making it a multi-center study or by randomizing the postoperative treatment of our own patients).

****Please note that my study is currently just an observational one. It has not been rigorously statistically analyzed. I will be able to do this (and acquire p-values) once I add a control group to which I can compare my data.****

- (3) And, last but not least, writing my chapter. The date the latest edition of **Skeletal Trauma** goes to press is December of 2000. Currently, I am focusing most of my time on trying to get a rough draft to Dr. Browner.
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Finally, I'd like to say thanks because my selective project this year has truly been a great opportunity for me to learn about orthopaedics, the topic of osteomyelitis, and to immerse myself in several projects pertaining to it.

Sincerely,

Craig Rodner