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ORIGINAL STUDY

The outcome of patients with cultured pathogens at time of nonunion surgery

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The purpose of this study is to evaluate incidence, preoperative laboratory markers, and outcomes of patients who positively cultured pathogens (PCP) at time of surgery for long bone fracture nonunion.

Two-hundred and eighty-eight patients were enrolled in a trauma study on long bone nonunion. Two-hundred and sixteen of those 288 patients were cultured at the time of fracture nonunion surgery. Laboratory data were collected prior to intervention and infectious laboratory markers ordered on patients suspected for infection. Patients were followed for one year. Wound complications, antibiotic use, healing, function, and re-admission for further surgery were assessed.

Cultures returned positive on 59 patients (representing 20.5% of the 288 patient cohort or 27.3% of the 216 patients cultured in the operative suite). More PCP's (47.5%; 28 of 59) developed wound complications, with greater mean antibiotic duration and more frequent returns to the OR averaging 1.3 procedures per patient. Twelve-month follow-up was obtained on 249 of the 288 (86.5%) and PCPs reported globally worse function.

Patients who PCP at the time of operative management for long bone nonunion was a prognostic indicator of poorer long-term functional outcomes.

Key words: Nonunion, Outcomes, Infection, Culture Positive, Inflammatory Markers

INTRODUCTION

Delayed healing after fracture fixation occurs through several etiologic pathways and is associated with well documented risk factors. Frequently cited risk factors include initial open injuries, associated vascular lesions, sites with poor soft tissue coverage, complex fracture patterns with comminution or bone loss, inadequate fixation, development of infection, and patient-dependent characteristics including pre-existing medical co-morbidities (such as diabetes and peripheral vascular disease), as well as patient social habits (tobacco use).(*3,7,12,14,23*) Ultimately, the incidence of nonunion is approximately 5-10% after all fractures (*35*) and the complexity of the predisposing risk factors creates a challenging environment for even the most skilled surgeons.

In the context of remodeling soft and osseous tissues, wound infection and the development of

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osteomyelitis have been cited as predictors of poorer outcomes.(28) The significance of early detection of infection by clinical, radiographic, and laboratory evaluation is an important aspect of any patient presenting with a suspected fracture nonunion. Classic clinical findings for an acute infection include swelling, erythema, and wound drainage, with or without fever.(17) The standard laboratory workup includes a CBC plus inflammatory markers (ESR [erythrocyte sedimentation rate] and CRP [C-reactive protein]). However, the nature of elevated serologies in the absence of clinical signs is often difficult to interpret. Continued suspicion may warrant the use of other imaging modalities, including nuclear scanning or higher resolution MRI (Magnetic Resonance Imaging) for management and pre-operative planning.

While diagnostic tools have improved immensely, they still fail to be 100% sensitive for detecting microbial presence and intraoperative cultures remain the gold standard. Studies have reported positive culture rates in up to 29% of presumed aseptic diaphyseal nonunions at the time of nonunion surgery.(2) Given the multiplicity of risk factors and various potential etiologies predisposing to nonunion, we evaluated the incidence and significance of converting a positive culture in patients undergoing surgery for a long bone nonunion. The purpose of this study was to report on the ultimate outcome of a cohort of infected nonunions diagnosed by the gold standard, intraoperative cultures, with respect to achieving ultimate union, functional outcomes and need for secondary surgeries. A secondary aim of this study was to assess the utility of pre-operative inflammatory laboratory markers.

PATIENTS AND METHODS

Between 2004 and 2012, 288 consecutive skeletally mature patients (ages ranging 18 – 91 years) presented to our tertiary care University medical center with complaints of a non-healing fracture. Following diagnosis of a long bone fracture nonunion, patients were consented and enrolled in a prospective trauma research registry. The research protocol and all procedures followed were in accordance with the ethical standards determined by the Institutional Review Board and written informed consent was obtained from all participants. Trained research personnel recorded data and the patients were treated by one of four trauma fellowship trained orthopaedic surgeons with experience in the care of these injuries.

At presentation, all patients were assessed with a standardized questionnaire including basic demographic data, details of baseline injury, medical history, previous surgeries, and a baseline assessment of functional status using the SMFA validated questionnaire (Short Musculoskeletal Functional Assessment).(30) Nonunion was defined as a fracture at least nine months after initial injury / index operative intervention with no progression of bony healing on serial radiographs. In cases where the diagnosis was unclear on plain films, a CT scan was obtained. Baseline radiographic evaluation was performed and included at least 2 orthogonal views of the affected site and other oblique views as needed in order to identify the nature of each patient's nonunion (atrophic versus hypertrophic). Nonunions were classified as atrophic or hypertrophic according to the system detailed by Weber and Cech.(32) Medical clearance was obtained prior to surgical intervention. Laboratory data, including white blood cell counts (WBC), were available for 267 patients (92.7%). Standard inflammatory markers, namely ESR and CRP, were ordered when previous infection was documented or when infectious etiology was suspected as the source of nonunion. Values of ESR and CRP were available on 104 (36.1%) and 106 (36.8%) of patients, respectively.

The type of surgical intervention chosen was left to the discretion of the treating surgeon. The general principles applied during the assessment of injuries and decision to perform surgery was similar for all surgeons. Patients without previous surgery underwent internal fixation; patients with previous surgery underwent revision internal fixation, and patients with suspected infection or those with limb deformity received dynamic external fixation. All patients who had undergone previous surgery either for their initial fracture fixation or previous nonunion treatment were cultured intra-operatively at the time of nonunion repair for aerobic, anaerobic and fungal pathogens. Length of hospital stay after surgery was recorded. When applicable, patients were re-cultured at follow-up debridement or revision surgery.

Post-operative protocol was standardized amongst all patients and included physical examination, radiographs, and follow-up questionnaire assessments at regular intervals (3, 6, 12 and 24 months). Follow-up assessment included length of antibiotic use, hospital re-admission, return to the operating room (either for debridement or revision), re-assessment with the SMFA and healing at the site of nonunion. In the setting of wound complications (with or without hospitalization), patients were seen more frequently than the stated interval and these complications were documented. The wound complications noted include wound drainage, sinus tract development, wound dehiscence, and wound breakdown. During the course of post-operative management, all patients with positive cultures were presumed to have an "infected nonunion" and were treated in consultation with an infectious disease specialist who prescribed culture sensitivity directed intravenous antibiotics.

Long bone healing at the time of follow-up was determined based on clinical findings and radiographic evaluation. Bony union was defined as the presence of healed bone identified on, at least, three of four cortices without change/failure in fixation construct, gross motion, nor tenderness at the nonunion site.(*7; 8; 13; 27*) CT scans were sometimes used for evaluation, otherwise, when two orthogonal x-rays views were inconclusive. Healing status was often determined in consultation with an attending radiologist.

Statistical Analysis

The main surgical outcomes analyzed are progression to bony healing, time to union, wound complications, duration of antibiotics prescribed, return to the operating room for debridement, subsequent surgical revision, ultimate amputation, and standardized functional assessment scores (SMFA). We compare the outcomes of patients who cultured positively (PCPSs) either at the time of nonunion surgery or during their course of post-operative care with others from the registry who were grouped negative culture and non-cultured patients (NCPs).

Comparisons of parametric continuous variables were analyzed using a Student's t-test and categorical comparisons were made using Chi-square analysis. Non-parametric continuous data (WBC/ESR/CRP) was statistically compared using an independent-samples Mann-Whitney U test. All statistical tests were performed using SPSS 20 (IMB, Chicago, IL) with a significance level of p=0.05.

RESULTS

No strict inclusion or exclusion selection criteria were applied to the trauma registry patients used within the statistical comparison. After enrollment of the 288 study participants, 10 patients did not comply with post-operative follow-up and thus healing status was available for 278 patients (96.5%). Two hundred and forty-nine patients (86.5%) achieved a minimum of one year follow up and were available for functional assessment.

Demographic characteristics were similar between groups (Table I). PCPs were significantly more likely to have had high-velocity, initial-open baseline injuries, which had been treated with a greater number of previous nonunion surgeries (Table I). There was a predominance of atrophic nonunions in the overall cohort, with no significant difference between the compositions of each group (Table II). There was a difference in the distribution of the anatomic sites composing each group (Table II, p<0.02) with the greatest difference being amongst tibial nonunions (PCP: 57.6% versus NCP: 35.7%). Overall, the culture positive tibial sub-group represented 11.9% of the nonunion cohort (n = 288).

Pre-operative laboratory markers were grossly elevated within the PCP group, as compared with NCPs (Table III). The elevation of PCPs ESR (p=0.001) and CRP (p=0.001) laboratory values reached greater levels of statistical significance than WBC (p=0.03). The percentage of PCP patients whose WBC levels exceeded 10,500(*11*) (abnormal at our institution) was 22.4% (versus 9.3% in the NCP group; p=0.007). There was

Table I. Baseline Demographics and Injury

	PCPs	NCPs	P-value
Patients n# (%)	59 (20.5)	229 (79.5)	n/a
Age (mean years, [SD])	44.7 (15.3)	48.7 (16.9)	0.10
Female Gender (%)	21 (35.6)	107 (47.1)	0.11
BMI (mean, [SD])	28.3 (4.7)	28.9 (5.8)	0.41
Tobacco (%)	14 (24.1)	45 (20.4)	0.53
Medical Comorbidities (mean sum, [SD])	1.0 (1.4)	1.2 (1.5)	0.21
Initial open injury (%)	29 (50.0)	55 (25.0)	**<0.001**
Mechanism: *Low Energy* (%)	18 (31.0)	113 (50.0)	**<0.01**
High Energy (%)	40 (69.0)	113 (50.0)	
Previous Nonunion Surgeries (mean, [SD])	2.1 (2.3)	1.1 (1.1)	**<0.001**

PCPs = Patients who Cultured Positive; NCPs = Negative/Non-Cultured Patients; BMI = Body Mass Index

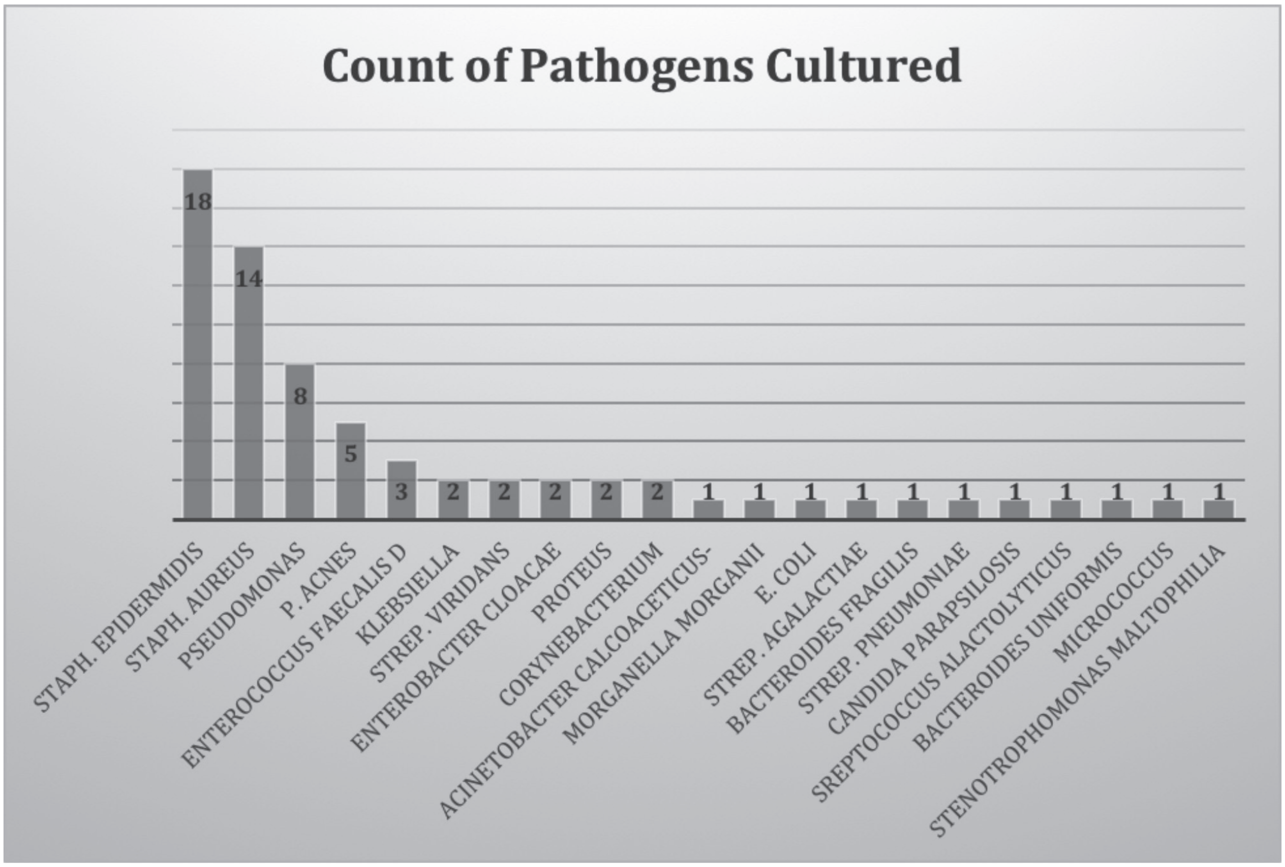

Fig. — 1. Pathogens cultured at primary surgical intervention.

little to no correlation between absolute WBC values and culturing pathogen positive (r=0.17, p<0.01). Although ESR and CRP values were strongly correlated with each other (r=0.60, p<0.01), their statistical correlations with patients culturing positively in the OR were both weak, but statistically significant (ESR: r=0.35, p<0.01; CRP: r=0.30, p<0.01). Elevated ESR values (>20 mm/hr) (*21*) associated with 69.6% sensitivity and 49.2% specificity for detecting PCP status. Elevated CRP values (>20 mg/L)(*20*) associated with 43.5% sensitivity and 87.5% specificity. When evaluating patients with elevations in ESR and CRP, sensitivity and specificity were 39.1% and 89.3%, respectively.

Cultures returned positive on 50 patients from samples taken in the operative suite during primary surgical intervention for their long bone nonunion. This represents 23.1% of the 216 patients sampled, or 17.4% of the entire 288 patient cohort. The pathogens cultured included a variety of common and uncommon pathogens, as shown in Figure 1. An additional 9 patients, who were initially culture negative, converted to PCP status during the course of follow-up and subsequently returned to the operating room. The final PCP group thus represented 59 patients which was 20.5% of the entire 288 patient cohort and 27.3% of the 216

Table II. Nonunion Type and Anatomic Site

	PCPs	NCPs	P-value
Atrophic (%)	80.4	81.4	0.86
Hypertrophic (%)	19.6	18.6	
Nonunion Site:			
Forearm (%)	3.4	7.0	**<0.02**
Clavicle (%)	1.7	5.7	
Femur (%)	28.8	26.9	
Humerus (%)	6.8	20.7	
Tibia (%)	57.6	35.7	
Foot/Ankle (%)	1.7	4.0	

PCPs = Patients who Cultured Positive;
NCPs = Negative/Non-Cultured Patients

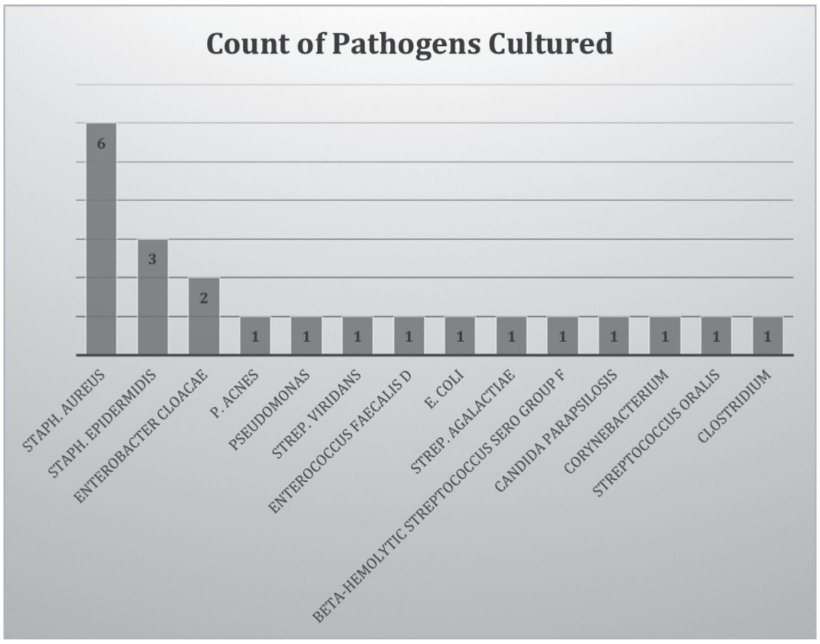

Fig. — 2. Secondary OR intervention positive culture pathogens

Table III. Laboratory Markers and Outcome

Measures	PCPs	NCPs	P-value
Pre-Operative WBC (mean, [SD])	8.7 (3.1)	7.5 (2.3)	**0.03**
Pre-Operative ESR (mean, [SD])	47.3 (34.2)	26.5 (21.2)	**0.001**
Pre-Operative CRP (mean, [SD])	35.5 (51.4)	13.2 (15.3)	**0.001**
Length of Hospital Stay (days, [SD])	7.2 (7.5)	3.5 (2.3)	**<0.001**
Achieved Union (%)	93.2	95.7	0.43
Time to union (mean months, [SD])	9.8 (10.5)	6.3 (4.2)	**<0.01**
Wound Complications (%)	47.5	8.8	**<0.001**
Antibiotics (mean days, [SD])	95 (162)	3 (15)	**<0.001**
Irrigation and Debridement (mean, [SD])	1.3 (1.4)	0.3 (1.0)	**<0.001**
Removal of Implant (%)	44.1	4.9	**<0.001**
Re-operation (%)	39.0	15.0	**<0.001**
Amputation (%)	3.4	0.4	**<0.05**
SMFA at 12-months (mean, [SD])			
Function	29.6 (21.5)	19.3 (17.7)	**0.001**
Bothersome	32.5 (28.5)	21.7 (23.1)	**<0.01**
Activity	39.2 (28.1)	25.4 (23.4)	**0.001**
Emotion	33.4 (25.0)	23.1 (22.1)	**<0.01**
Arm & Hand	8.5 (18.1)	5.7 (12.9)	0.23
Mobility	34.8 (26.4)	21.8 (22.3)	**0.001**

PCPs = Patients who Cultured Positive; NCPs = Negative/Non-Cultured Patients

patients sampled during primary or secondary operative intervention.

Many of the Staphylococcus aureus [SA] patients remained positive at the time of secondary culture (Figure 2 shows positive cultures at the time of secondary sampling in the operative suite). History of osteomyelitis was documented in 25.4% of PCPs, whereas NCPs had significant history in 2.2% of cases (p<0.001). Positive history weakly correlated with culturing positive at the time of surgery (r=0.37, p<0.01).

With only two exceptions, (A) achieving ultimate union and (B) the Arm & Hand function index of the SMFA, PCPs experienced globally worse outcomes than NCPs (Table III). Although PCPs achieved bony union at similar rates (93.2% versus 95.7%), they did so at the mean expense of 105 additional days of healing time (p<0.01). The main clinical complications that developed among the 47.5% of PCPs with wound problems were superficial infections (32.1%), wound drainage (28.6%) and deep wound infections (17.9%). Overall, 39% of the PCPs returned to the OR for debridement, removal of implant, or revision. This percentage was significantly greater than the 15% who returned to the OR in the NCP group (p<0.001).

A sub-group analysis was performed to evaluate those PCPs who developed wound complications during post-operative management. When wound complications were present, PCP's achieved ultimate union in 89.3% of cases, versus 96.8% in PCPs who remained post-operatively wound complication free (p=0.25). Although these patients with wound complications required secondary procedures, their mean time to union did not statistically differ from PCPs without wound complications (11.4 ±14.5 months versus 8.7 ±5.8 months; p=0.36), however, this sub-group analysis is limited in power.

Twelve-month functional assessment scores revealed significant differences within the overall function, bothersome, activity, emotion, and mobility indices between the two groups (Table III). Mean final length of follow up amongst PCPs was 21.8 [±14.6] months and 18.4 [±12.3] months for NCPs. At final follow up, SMFA scores were still significantly worse in the same five domains: function (p=0.001), bothersome (p<0.01), activity (p=0.001), emotion (p=0.002), and mobility (p=0.002). Overall poorer outcomes were seen in the patients who initially cultured negative, but converted to positive after their initial surgical intervention. This group of 9 patients achieved healing in 100% of cases, but in a mean time of 14.3 (±22.6) months. Failure to achieve union after multiple attempts at revision occurred in 3.4% of PCPs, versus 0.4% amongst NCPs, and led to decisions for amputation (p<0.05).

DISCUSSION

In a cohort of 288 patients presenting with nonunion after long bone fracture, there was a marked association between positive culture and poorer patient outcomes. While there was no statistically detectable difference in the rate at which PCPs achieved ultimate union (93.2% healed, versus 95.7% in the remaining cohort), there were significant differences detected within nearly every other outcome measured by this study. In particular, PCPs required significantly more healing time (approximately 105 days). On standardized validated measures of function, these pathogen positive patients continued to demonstrate subjectively worse outcomes out to nearly two years follow-up. Amongst this group of predominantly lower extremity nonunion patients, functional differences remained significant on all indices of the SMFA, with exception of upper extremity function.

The most universally used laboratory indicators of infection are leukocyte count, ESR(*10*) and CRP(*18; 19; 26*). When applied to the field of orthopaedic surgery, much of the research on the usefulness of these markers has been in the septic joint(*1; 4; 24*) and acute hematogenous osteomyelitis(*6*) literature. In those areas, studies have shown sensitivities of ESR and CRP for the detection of early infections to be as great as 94% and 95%, respectively.(*16*) In the setting of sub-acute and quiescent infection, as may be the case in long bone nonunion, the sensitivities of these tests likely diminish.(*22*) With regards to the utility of pre-operative laboratory markers to detect infection in our group, we did identify significant difference between the PCP and NCP groups. These differences, however, do not seem readily expandable as diagnostic guides for a treating physician seeking an infectious "red flag" indicator. Ultimately, the elevation of WBC that we identified bordered on statistical significance and, in fact, only 22.4% of PCPs achieved a laboratory marker level which would be deemed beyond normal limits. Overall, mean ESR and CRP elevations exceeded that of WBC, but these values also faltered in terms of correlating strongly with positive cultures at the time of surgery. We can conclude then that ESR and CRP values were diagnostically better indicators of indolent infection, when compared with leukocyte count. Considering the limited sensitivity of ESR and CRP (69.6% and 43.5%, respectively), we caution regarding their usefulness to detect and "rule-out" PCPs. However, these findings do support a role for the guided use of dual ESR and CRP values as a "rule-in" diagnostic tool, associated with an 89.3% specificity.

In a 2010 presentation on the preoperative diagnosis of infected nonunions, Stucken et al. detailed the sensitivity of laboratory work-up when detecting infection amongst a cohort of 93 patients. (*29*) His group found that WBC was 22% sensitive while ESR and CRP were 58% and 61% sensitive, respectively. Their conclusion was similar to ours in that the accuracy and utility of these markers to detect the presence of infection was controvertible. (*9*)

While our management strategies have evolved significantly to now include an array of culture directed antimicrobial medications, new technology implants employed in multi-staged internal fixation approaches as well as modern external fixation devices, the challenge to improve long-term outcomes amongst infected and positive culture patients remains very much the same. A review by Strujis and colleagues (2007) evaluated a broad range of high-level studies employing single-stage and two-stage strategies for managing infected long bone nonunion.(*28*) Strujis' group ultimately summarized what is a vast array of outcomes documented within the literature on objective outcomes after management of infected nonunion. In his review, he identified published rates of union ranging from 70 to 100% while rates of persistent infection ranged from 0 to 60%. The best outcomes, however, were seen amongst patients who underwent debridement with anti-biotic bead placement and subsequently planned secondary stage revision (union achieved in 93–100% of patients, persistent infection rates of 0–18%).

During the assessment and planning stages of presumed infection associated nonunion, early detection and prompt medical management are crucial. For some physicians, however, they are not afforded an opportunity to stage a pre-emptive pathogen attack. Infectious etiology of nonunion may lie indolent without obviating systemic complaints.(*34*) Rates of surprise positive OR pathogen cultures have been reported in up to 29% of fracture nonunion cases.(*2*) The significance of these surprise cultures has not been thoroughly studied. Two presentations regarding these cases (Tornetta et al., 2010 and Sachs et al., 2012) reveal varying degrees of success during management. (*25; 31*) Sachs reported a small case-series which had 40% successful outcomes (required no revision, removal of implant, nor debridement). Tornetta reported a larger series of patients (94 of whom cultured positive), and identified generally successful outcomes in 92% of patients, although 12 patients required removal of implants during their course of care.

In cases where pathogens are isolated, cultured, and return sensitivities, the importance of a collaborative team approach in association with infectious disease specialists cannot be over emphasized. Their addition of expertise for guiding antibiotic administration, duration of antibiosis, and monitoring for eradication versus the need for chronic suppression is simply unparalleled. Furthermore, their field is more inclined to follow trends of virulent organisms and geographic distributions of resistant strains. We believe this will be an important area for directed treatment in the future; better understanding for the inciting microorganisms we are fighting. This remains no small feat, however, as evidenced just by this study alone where 23 unique pathogenic organisms were identified. Traditionally, much focus has been attended to SA and associated methicillin and antibiotic resistant strains. We should highlight, though, that the incidence of SA was exceeded by Staphylococcus epidermidis [SE] in this study. There is also increasing evidence that SE should be considered as an opportunistic pathogen(*15*) which has developed highly resistant, hospital-associated, clones.(*5; 33*)

There are several limitations to this study. In order to enhance the power of this study we grouped fractures of all long bone types together. Although the core tenants of surgical management were consistent between surgeons, there was no standard protocol or algorithm employed for this study. Furthermore, we did not account for differences in treatment methods in our analyses. Concerning microbial eradication, the research protocol was not standardized to assess secondary aspirations/ cultures or serial inflammatory markers at the time of follow-up assessment(s). Thus, we are limited in our ability to comment regarding rates of persistent culture positivity. Finally, concerning the definition of an infected nonunion, while each positive culture represents a colonization of an anatomic site that should be sterile, we considered these as infected nonunions. Some consider only the biologic response to that colonization (purulence, drainage, warmth etc..) to indicate the presence of an infection. Thus, the true importance of a positive culture can be placed into question.

Ultimately, culturing positive at any time during nonunion surgery or through the course of post-operative management has significant implications for the surgeon and patient, alike. PCPs should be educated regarding the significance of wound complications and strict regimented antibiotic use. Specifically, these patients should understand that their ultimate outcomes and functional activities might be constrained by the complications associated with infection and/or subsequent infectious treatment. Although patients who culture positive for bacteria at the time of nonunion surgery appear to achieve satisfactory levels healing, other outcome measures, including the need for potential return to the operating room and poorer long-term functional status, appear to be associated consequences. Hospitals and staff should also be educated on these issues as "pay-for-performance" initiatives are instituted throughout the health care system. Given the rates of follow-up complications, including length of antibiotic use, re-admission, and re-operation rates, these findings have significant implications for institutional measures of quality and pay-for-performance metrics.

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