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Factors associated with adverse postoperative outcomes in patients with long bone post-traumatic osteomyelitis

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Abstract

Aims To evaluate short-term clinical and functional outcomes following operative treatment of long bone post-traumatic osteomyelitis (PTOM).

Methods We retrospectively analyzed a consecutive cohort of 142 adult patients undergoing operative treatment of long bone PTOM at our Level I trauma center over a 10-year study period. In addition to subjective patient evaluations, surveyed postoperative outcomes included incidence of residual infection, fracture malunion or nonunion, and requirement for limb amputation. All included patients had a minimum follow-up of 12 months postoperatively.

Results Patients suffering an adverse postoperative outcome tended to have a higher incidence of polymicrobial infection (25.4 vs. 11.4%, $p = 0.042$) and requirement for skin grafting (58.1 vs. 37.9%, $p = 0.024$) and free-flap procedures (43.6 vs. 19.5%, $p = 0.003$) compared to those achieving complete healing. Sequential administration of parenteral and oral antibiotic therapies was associated with a reduced incidence of adverse postoperative outcome ($p = 0.047$).

Discussion Patients with long bone PTOM and extensive soft tissue defects often fail to develop complete remission of their symptoms by 12 months postoperatively. Sequential administration of parenteral and oral antibiotics may help to limit infection recurrence. Further research is required to inform optimal treatment strategy.

Keywords Osteomyelitis · Treatment · Flap · Antibiotic

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Introduction

Long bone post-traumatic osteomyelitis (PTOM) is a relatively frequent complication following surgical fixation of long bone fractures that poses many complex challenges [1–3].

A wide range of treatment strategies are described in the literature, including radical debridement, local antibiotic therapy (antibiotic-impregnated beads, spacers, cements, or intramedullary nails), soft tissue grafting (free flap, myocutaneous flap, skin graft), bone transport, acute limb shortening, and two-staged reconstruction [1, 4–9]. Unfortunately, standardized treatment guidelines remain to be established. The lacking consensus regarding optimal treatment strategies is, in part, attributed to the relative paucity of high-powered studies and randomized-controlled trials investigating long-term treatment of long bone PTOM [3].

The purpose of the present study was to identify factors associated with poor clinical and functional outcomes in patients undergoing surgical management of long bone PTOM at our Level I trauma center. The hypothesis was that patients treated with local antibiotic therapy and early soft tissue grafting procedures would demonstrate improved postoperative outcomes as compared to all other surveyed treatment strategies.

Patients and methods

Study population

Following institutional board review (IRB) approval, we retrospectively analyzed a consecutive cohort of 142 adult patients presenting with long bone PTOM to our Level I trauma center between January 1, 2003, and December 31, 2013. The diagnosis of osteomyelitis was made in accordance with the Center for Disease Control and Prevention (CDC) criteria [10], given by: (1) pathogenic growth on direct bone cultures, (2) evidence of osteomyelitis on direct examination of the bone during invasive procedures or histopathologic examination, or (3) at least 2 signs of infection (temperature >38 °C, localized edema, erythema, tenderness, or purulent drainage) in addition to positive blood cultures, laboratory tests, or imaging findings suggestive of infection. Additionally, patients had to demonstrate infection localized to long bones (humerus, radius, ulna, femur, tibia, or fibula) and minimum clinical follow-up of 1 year to be included in this study. The following criteria were reasons for exclusion: diabetic foot infection, septic arthritis, or osteomyelitis of the hand, spine, or pelvis.

Intervention

Patients with long bone PTOM were treated operatively to achieve infection control, fracture fixation, and bridging of soft tissue defects. Deep-seated infections of the bone were radically debrided and stabilized with external fixation, internal fixation, or a delayed two-staged reconstruction. In cases involving wide diaphyseal defects exceeding 6 cm in size, a two-staged reconstruction technique was performed that involved the use of an antibiotic-impregnated spacer to maintain dead space volume during temporary joint-bridging external fixation [7]. Choice of antibiotic was predicated on the results of culture and sensitivities as previously described [11]. Soft tissue defects were treated with skin graft, pedicled flap, or free-flap transfer at the microvascular surgeon's discretion. Patients with long bone PTOM also underwent antibiotic therapy delivered parenterally, orally, or both, depending upon extent of bone/tissue involvement and results of antimicrobial susceptibility tests. The choice of antibiotic therapy was determined by a dedicated musculoskeletal infectious disease specialist and the treating orthopedic team. As the standard of care, duration of antibiotic therapy totaled 6 weeks following last debridement.

Data collection

Demographic variables including age, gender, height, weight, body mass index (BMI), clinical diagnoses, history of substance abuse (alcohol, tobacco, cocaine, marijuana, heroin/opiates), fracture location, and AO Foundation and Orthopaedic Trauma Association (AO/OTA) fracture classification [12] were retrieved for all patients.

All subjects were evaluated at outpatient clinics by fellowship-trained orthopedic trauma surgeons at regular intervals of 1.5, 3, 6, months and 1 year postoperatively. At each follow-up visit, patients underwent a standardized series of evaluations including clinical outcome review (reoperation, infection, nonunion, and subjective pain score), physical examination, and anteroposterior (AP) and lateral radiographic imaging of the involved bone.

Main outcome measures

The primary outcome measure was postoperative complication, defined as 2 or more signs of recurrent infection (as previously described), non-healing wound, fracture malunion or nonunion, or requirement for limb amputation. The secondary outcome measure was subjective patient evaluation of functional outcome, graded as "poor" (debilitating pain that precluded performance of daily activities of living), "fair" (residual pain but preserved functional capacity to perform in daily activities of living), or "good" (no complaints of pain and ability to resume pre-injury level of activity).

Statistical analysis

All variables were evaluated for distribution of normality using a combination of histograms, *Q*–*Q* plots, and the Shapiro–Wilk tests. Descriptive statistics were summarized as means and standard deviations for quantitative variables and as counts and frequencies for categorical variables. The significance of mean differences between quantitative variables was evaluated using the independent samples *t* test (normally distributed) or Mann–Whitney *U* test (non-normally distributed), and between categorical variables using the Chi-square test or Fisher's exact test (expected cell count <5). All significant ($p < 0.05$) and near-significant ($p < 0.10$) univariate trends were entered into a backwards stepwise multivariate logistic regression model to determine independent predictors of adverse postoperative outcome. Statistical significance for all comparisons was set at $p < 0.05$ (two-tailed). All analyses were conducted using IBM SPSS Statistics (version 22.0, IBM, Inc.).

Results

Participants and descriptive data

The study cohort comprised 142 patients (91 males, 51 females) with a mean follow-up of 20 months (range 12–120 months). Fifty-five patients (38.7%) reported an adverse clinical or functional postoperative outcome. Baseline demographic characteristics did not vary significantly between patients with and without adverse postoperative outcomes (Table 1). Open fractures constituted 40.2% of initial injuries in patients without adverse postoperative outcomes and 45.5% in patients with adverse postoperative outcomes ($p = 0.602$). In both cohorts, the most common site of involvement was the tibia (66.6% and 80.0%, respectively; $p = 0.125$). Additional demographic data are summarized in Table 1.

Infection characteristics

Patients reporting at least one adverse postoperative outcome had a significantly higher prevalence of infection due to polymicrobial (mixed) flora compared to patients without adverse postoperative outcomes (25.4 vs. 11.4%, respectively; $p = 0.042$). The frequency of all other pathogenic species underlying osteomyelitis infection did not vary significantly between the two cohorts.

Table 1 Demographic and clinical characteristics of patients with long bone PTOM ($N = 142$)

Patient variables	No adverse outcomes ($N = 87$)	One or more adverse outcomes ($N = 55$)	p value
Age, mean (SD), years	45.3 (12.6)	49.1 (12.6)	0.086
Male, *n* (%)	56 (64.4)	35 (63.6)	1.000
Height, mean (SD), cm	172.8 (10.6)	172.3 (11.8)	0.793
Weight, mean (SD), kg	84.6 (21.5)	84.8 (25.4)	0.951
BMI, mean (SD), kg/m^2	28.4 (7.5)	28.5 (7.7)	0.757
Open fracture, *n* (%)	35 (40.2)	25 (45.5)	0.602
Site of long bone involvement, *n* (%)			
Tibia	58 (66.6)	44 (80.0)	0.125
Fibula	14 (16.0)	13 (23.6)	0.280
Femur	19 (21.8)	6 (10.9)	0.116
Ulna	4 (4.5)	4 (7.2)	0.711
Radius	9 (10.3)	2 (3.6)	0.203
Humerus	8 (9.1)	4 (7.2)	0.766
Fracture localization, *n* (%)			
Diaphysis	38 (43.6)	24 (43.6)	1.000
Metaphysis	33 (37.9)	24 (43.6)	0.598
Both	16 (18.3)	7 (12.7)	0.485
Causative pathogen, *n* (%)			
Staphylococcus	49 (56.3)	28 (50.9)	0.485
Anaerobic bacteria	13 (14.9)	10 (18.1)	0.645
Polymicrobial (mixed flora)	10 (11.4)	14 (25.4)	**0.042***
Streptococcus	8 (9.1)	7 (12.7)	0.585
Enterobacteria	2 (2.2)	2 (3.6)	1.000
Gram-negative bacteria	4 (4.5)	2 (3.6)	1.000
Bacillus	1 (1.1)	0 (0.0)	1.000
Corynebacteria	2 (2.2)	0 (0.0)	0.518
Propionibacteria	2 (2.2)	1 (1.8)	1.000
Fungal	2 (2.2)	3 (5.4)	0.355

BMI body mass index

* Statistically significant, $p < 0.05$. Presented in bold

Overall, the most common cause of osteomyelitis infection was *Staphylococcus* species (56.3.4 and 50.9%, respectively, $p = 0.485$), followed by anaerobic bacteria (14.9 and 18.1%, respectively, $p = 0.645$) and Streptococci species (9.1 and 12.7%, respectively, $p = 0.585$). The rate of infection due to enterobacteriaceae, unspecified gram-negative bacteria, propionibacteria, corynebacteria, or Bacillus species comprised less than 5% of all deep bone infections in our study cohort.

Short-term postoperative outcomes in patients with long bone PTOM

After a minimum of 12 months postoperatively, forty-nine patients (34.5%) demonstrated recurrent signs of infection: 12 (8.4%) had persistent purulent drainage, 9 (6.3%) had persistent erythema, and 28 (19.7%) had residual edema. Twenty patients (14.1%) demonstrated signs of persistent non-healing: 4 (2.8%) had wound dehiscence, while 16 (11.3%) had fracture mal-/non-union. Ultimately, eleven patients (7.7%) required limb amputation.

Subjectively, twenty-four patients (16.9%) reported a good clinical outcome entailing return to pre-injury levels of physical activity; 94 patients (66.1%) reported a “fair” clinical outcome with mild residual, non-debilitating pain; and 23 (16.1%) patients reported “poor” clinical outcome given by severe, debilitating pain that precluded independent performance of daily activities of living (Tables 2, 3).

Table 2 Functional outcomes in patients treated for long bone PTOM

Outcome variables	No. of positive cases, n (%)
Functional deficit	
None	24 (16.9)
Moderate	94 (66.1)
Severe (debilitating)	23 (16.1)
Signs of recurrent infection	
Purulent drainage	12 (8.4)
Erythema	9 (6.3)
Edema	28 (19.7)
Signs of chronic non-healing	
Open wound	4 (2.8)
Non-healing fracture	16 (11.2)
Amputation	11 (7.7)
Tibial	11
Tibia–fibula	5
Tibia–femur	2

Effect of route of antibiotic delivery on postoperative outcome

Retrospective analysis identified that sequential administration of parenteral and oral antibiotic therapy occurred more frequently among patients without adverse postoperative outcomes compared to those with (54.0 vs. 36.3%, $p = 0.047$). In contrast, patients with adverse postoperative outcomes had a higher frequency of usage of antibiotic spacers (45.4 vs. 28.7%, $p = 0.049$) and external fixators (42.5 vs. 63.6%, $p = 0.016$) during the initial stages of treatment. There was also an increased incidence of skin grafting (58.1 vs. 37.9%, $p = 0.024$) and free-flap procedures (43.6 vs. 19.5%, $p = 0.003$) in patients suffering adverse postoperative outcomes compared to those without (Table 3).

Multivariate analysis of independent factors predicting adverse postoperative outcomes in patients with long bone PTOM

Multivariate logistic regression analysis identified the requirement for free-flap transfer [odds ratio (OR) 4.32; 95% confidence interval (CI) 1.86–9.63; $p = 0.001$] as the strongest independent variable associated with adverse postoperative outcome. In contrast, sequential administration of parenteral and oral systemic antibiotic therapy significantly reduced the risk of adverse postoperative outcome (OR 0.38; 95% CI 0.18–0.82; $p = 0.014$; Table 4).

Discussion

Long bone PTOM is a challenging clinical entity with a high rate of recurrence, underscoring the importance of establishing standardized treatment guidelines [3, 13]. The results of the present study demonstrate that patients with extensive soft tissue defects often fail to achieve complete recovery despite undergoing various treatments including staged fixation, local antibiotic delivery, and free-flap transfer. Moreover, requirement for free-flap reconstruction was the single-most important predictor of adverse postoperative outcome. Taken together, these findings suggest that patients with long bone PTOM and wide soft tissue defects should be cautioned that their treatment course will likely involve multiple surgeries, a prolonged hospital stay, and a significant risk for recurrence.

Indeed, optimal treatment outcomes for free-flap reconstruction are reported for soft tissue defects lesser than 6 cm [3, 7]. For wider soft tissue defects, extirpation of infection often requires amputation. Less aggressive strategies such as radical debridement and local antibiotic

Table 3 Adverse postoperative outcomes per various treatment strategies

Category	Treatment modality	No adverse outcome ($N = 87$)	One or more adverse outcome ($N = 55$)	*p* value
Local antibiotics	Antibiotic bead, *n* (%)	39 (44.8)	33 (60.0)	0.087
	Antibiotic cement, *n* (%)	5 (5.7)	2 (3.6)	0.706
	Antibiotic spacer, *n* (%)	25 (28.7)	25 (45.4)	0.049
Systemic antibiotics	IV antibiotics, *n* (%)	33 (37.9)	27 (49)	0.224
	PO antibiotics, *n* (%)	7 (8.0)	7 (12.7)	0.396
	Sequential IV and PO antibiotics, *n* (%)	47 (54)	20 (36.3)	0.047
Fixation	External fixation, *n* (%)	37 (42.5)	35 (63.6)	0.016
	Internal fixation, *n* (%)	77 (88.5)	48 (87.2)	1.000
Wound coverage	Bone graft, *n* (%)	32 (36.7)	19 (34.5)	0.858
	Skin graft, *n* (%)	33 (37.9)	32 (58.1)	0.024
	Microvascular free flap, *n* (%)	17 (19.5)	24 (43.6)	0.003
	Pedicled muscle flap, *n* (%)	7 (8.0)	5 (9.0)	1.000
	Vacuum-assisted closure therapy, *n* (%)	38 (43.6)	33 (60)	0.085
Overall	Total no. of surgical procedures, median (IQR)	5 (4)	7 (8)	0.012

Table 4 Results of logistic regression identifying significant predictors of poor postoperative outcome in patients with long bone PTOM

Predictor variable	Odds ratio	95% CI	*p* value
Free flap (1 vs. 0)	4.32	1.86–9.63	<0.001
IV and PO antibiotics (1 vs. 0)	0.38	0.18–0.82	0.014

R^2 model = 0.115; sensitivity = 43.6%, specificity = 81.7%, PPV = 61.5%; NPV = 68.4%

delivery often achieve suppression, but not eradication, of infection. This challenge is further compounded by the lack of reliable clinical methods or markers to establish treatment success [14]. In support, two recent studies reported rates of recurrence of 8 and 20%, respectively, in patients with osteomyelitis undergoing aggressive debridement, definitive fixation, and free-flap reconstruction [15, 16].

Interestingly, patients in our study that underwent sequential parenteral and oral systemic antibiotic therapies suffered significantly fewer adverse postoperative outcomes compared to those treated by a single route of antibiotic delivery. This could be, in part, due to distinct advantages associated with each route of drug delivery. Parenteral antibiotics generally achieve a higher local concentration in bone compared to oral antibiotics; however, oral administration circumvents line-infection—cited to be as high as 11–15%—that limits prolonged use of intravenous antibiotics in patients with osteomyelitis [17–19]. Sequential antibiotic therapy (involving both routes of administration) has been shown to be cost-effective and potentially reduces patient non-compliance [20]. Specific guidelines on the optimal time to transition from parenteral to oral antibiotic therapy have been well established [20, 21]. Empirically, the authors also recommend adjunct local antibiotic therapy to further limit biofilm formation and maintain dead space volume in avascular areas that are inaccessible by systemic routes of drug delivery [14, 22].

Strengths of the present study include its relatively large sample size and surveillance of a wide variety of treatment strategies. However, we acknowledge several important limitations. The retrospective design of our study inherently limits the scientific objectivity of our findings. Additionally, the presented cohort was largely comprised of a medically indigent population Therefore, our findings may not be generalizable to all clinical settings. Finally, an equal proportion of patients undergoing free-flap transfer in the presented study demonstrated fracture union versus malunion/nonunion at 1-year follow-up (56.3 vs. 43.8%, respectively). Additional studies are required to determine whether long-term clinical outcomes differ among patients with free-flap transfers that go on to develop complete bone healing compared to those who do not.

Conclusion

The successful treatment of long bone PTOM is complex, necessitating a careful and standardized approach to care. Patients with long bone PTOM and extensive soft tissue defects often fail to develop complete remission of their symptoms at 12 months postoperatively, despite undergoing various soft tissue coverage procedures. Sequential administration of parenteral and oral antibiotics may help to limit infection recurrence. Further research is required to inform optimal treatment strategies for long bone PTOM.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest in relation to the presented body of research.

Ethical approval Institutional board review (IRB) approval was obtained prior to the initiation of this study.

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