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Treatment of infection following intramedullary nailing of tibial shaft fractures—results of the ORS/ISFR expert group survey

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Abstract

Objective The lack of universally accepted treatment principles and protocols to manage infected intramedullary (IM) nails following tibial fractures continues to challenge us, eliciting a demand for clear guidelines. Our response to this problem was to create an ORS/ISFR taskforce to identify potential solutions and trends based on published evidence and practices globally.

Materials and methods A questionnaire of reported treatment methods was created based on a published meta-analysis on the topic. Treatment methods were divided in two groups: A (retained nail) and B (nail removed). Experts scored the questionnaire items on a scale of 1–4 twice, before and after revealing the success rates for each stage of infection. Inter- and intra-observer variability analysis among experts' personal scores and between experts' scores was performed. An agreement mean and correlation degree between experts' scores was calculated. Finally, a success rate report between groups was performed.

Results Experts underestimated success rate of an individual treatment method compared to published data. The mean difference between experts' scores and published results was + 26.3 ± 46 percentage points. Inter-observer agreement mean was poor (< 0.2) for both rounds. Intra-observer agreement mean across different treatment methods showed a wide variability (18.3 to 64.8%). Experts agree more with published results for nail removal on stage 2 and 3 infections.

Conclusions Experts' and published data strongly agree to retain the implant for stage 1 infections. A more aggressive approach (nail removal) favoured for infection stages 2 and 3. However, literature supports both treatment strategies.

Evidence Clinical Question

Keywords Tibia infection · Intramedullary nailing · Nonunion tibia · Tibia fractures · Treatment algorithm · Survey on nonunion

Introduction

Intramedullary (IM) nailing is the gold standard of treatment for unstable and displaced tibial shaft fractures in the adult. Incidence of infection following IM nailing is relatively uncommon, ranging from 0.9 to 3.8% [1, 2]. In a series review that included 1106 tibial shaft fractures treated by reamed IM nailing, the incidence of infection was 1.9% for closed fractures and 7.7% for open fractures [3].

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Management of both acute and chronic deep infections following IM nailing of the tibia can be challenging, and there is no standardized treatment protocol for these patients. Diverse treatment strategies have been described depending on the status of fracture union, extent of infection, time of onset of infection after nailing, and the host status [4]. Through a "three-stage" bone and joint infection classification proposed by Romano et al. [24], Makridis and colleagues classified infections following IM nailing of tibial shaft fractures into three stages (Table 1). Results from the meta-analysis guided the proposal of a treatment algorithm, based on the success rates of individual treatment methods.

Our aim was to analyze the status of various reported methods for treating infection after IM nailing of tibial shaft

Table 1 Different stages of infection after IM nailing (Makridis et al.)

Stage 1	Early bacterial cellulitis	2–6 weeks after IM nailing
Stage 2	Delayed wound healing, discharge, and necrosis. May show impaired fracture healing	2–9 months after IM nailing
Stage 3	Established intramedullary osteomyelitis.	> 9 months

fractures by performing a survey among orthopaedic trauma experts around the world. Our objective was to assess (i) the degree of inter-observer agreement in their chosen treatment options to study the variability in treatment methods across peers and regions and (ii) to assess correlation between expert opinions and published treatment methods to understand the current practices in treating infection after IM nailing of tibial fractures. We hypothesized that there will be poor inter-observer agreement among experts and poor correlation between expert scores and published treatment methods.

Measuring the degree of correlation between expert scores and published methods may help to categorize stage-specific treatment methods in line with current practice and potentially support the formulation of clear guidelines for treatment of infection after IM nailing of tibial shaft fractures.

Methods

A survey was performed on an international cohort of ten practicing orthopaedic trauma experts in attendance at the Orthopedic Research Society - International Section of Fracture Repair workshop on segmental bone defects in Marseille, France, in June 2017. All ten experts are specialized in orthopaedic trauma surgery and are currently practicing in level I trauma centres.

A 16-item questionnaire was designed to incorporate the various reported treatment options for each stage of infection (Table 2). The following steps were followed to implement the survey; first, the three stages of infection after IM nailing of the tibia and various treatment methods reported for treatment of the problem were discussed and agreed upon. At this stage, the success rate reported in literature for each treatment option

Table 2 Questionnaire used for the experts' survey

Stage	Treatment	Rate from 1 to 4
Stage 1 infection	Retain nail and antibiotics +/− soft tissue debridement	
Stage 2 (infection)	Retain nail with suppressive antibiotics and removal after union	
	Nail removal and antibiotic nail insertion	
	Retain nail with soft tissue debridement and antibiotics	
	Retain nail and antibiotics and remove nail at union with intramedullary debridement	
	Exchange nailing with antibiotics	
	Nail removal, intramedullary debridement, and Ilizarov application	
Stage 2 (infected nonunion)	Exchange nailing and antibiotics +/− bone grafting	
	Nail removal and plate fixation	
	Nail removal and Ilizarov/external fixator frame application	
	Retain nail with debridement and antibiotics	
Stage 3 (infection)	Nail removal, antibiotics, and debridement	
	Exchange nailing, antibiotics, and debridement	
	Retain nail, excision of necrotic bone, and antibiotics	
Stage 3 (infected nonunion)	Retain nail, suppressive antibiotics, debridement, and removal when healed	
	Nail removal and Ilizarov frame application	

was not revealed. Experts were then asked to complete the questionnaire by scoring each treatment option on a scale of 1–4, in which 1 = poor agreement with treatment option and 4 = high agreement with treatment option. After completing the first round of the expert survey, the success rates for all treatment options reported by Makridis et al. [4] were disclosed. Experts were then asked to complete a second round of the same survey and were given the chance to change or keep their scores for each treatment option after having seen published results.

Data analysis and statistics

The scores by experts on a scale of 1–4 were scaled to a 1–100 scale to be comparable to the percentage success rates reported in literature.

Data was analyzed for consistency among expert scores and comparability to literature reported evidence. Variability in scores among the ten experts for each treatment was assessed separately at baseline. Inter-observer variability was calculated using kappa statistics. The classic interpretation of kappa statistics was implemented, in which 0.00 to 0.20 = poor, 0.21 to 0.40 = fair, 0.41 to 0.60 = moderate, 0.61 to 0.80 = substantial, and 0.81 to 1.00 = almost perfect agreement [6].

The coefficient of variation was calculated to assess the intra-observer variability in the response scores for each expert. The mean of the expert scores was compared to the estimates reported from meta-analyses. Correlation between expert scores and success rates in literature across all treatment methods was assessed.

The treatment methods reported in the meta-analysis were divided in to two groups: (i) group A—methods that retain the implant and (ii) group B—more aggressive methods that remove the implant and look at alternate fixation. The mean difference and the degree of correlation between experts' scores and reported success rates with regard to these two groups were calculated for each stage of infection. Spearman's rank correlation was used to assess the correlation among the different groups of treatments.

Results

All ten orthopaedic trauma experts completed the survey. Two are currently practicing in Japan, two in South Korea, two in Germany, two in the USA, and one each in France and Greece. High degree of inter-observer variability was noted in both rounds with regard to the scoring of individual treatment options. Inter-observer agreement ranged from poor to moderate in round 1 and poor to fair in round 2. The mean inter-observer agreements in both rounds were poor (Table 3). The coefficient of variation calculated to assess intra-observer variability showed a high degree of variation ranging from 18 to 65% (Table 4). The intra-observer variability was lowest for nail retention with debridement and antibiotics for stage 1 infection and highest for retention of nail with suppressive antibiotics and debridement for stage 3 infected nonunion.

Table 3 Inter-observer variability

	Kappa (κ)	
	Round 1	Round 2
Range	0.143–0.570	0.126–0.391
Mean ± SD	0.180 ± 0.179	0.140 ± 0.134

The average difference between expert ratings and the rates reported in literature was + 26 percentage points with a standard deviation of 46. Experts underestimated success rates for all treatment methods by a wide margin. There was a lot of variability in the estimates (coefficient of variation (CoV)—160%), but the values were not highly correlated (rho = − 0.2). If two items with 0% success rates in literature were removed from the calculations, the mean difference rose to 39 (std. dev—23) with variability reduced (CoV—59%) and poorer correlation (rho = − 0.13). Overall, expert ratings were poorly correlated with the success rates reported in literature.

The overall mean difference between experts' scores and reported success rates for treatment methods in group B was much lower compared to that for methods in group A for both stage 2 and 3 infections. The difference was + 22 compared to + 54 percentage points for stage 2 infections and + 26 compared to + 66 percentage points for stage 3 infections. This showed that even though experts underestimated the overall success rates of different treatment methods, they tend to prefer and agree more with literature for techniques that are aggressive in terms of eradicating infection by removing the nail and use alternate fixation for both stage 2 and 3 infections (Table 5).

In addition, the calculated difference in percentage points for reported success rates between the two groups for both stage 2 and 3 infections was much less compared to the difference in percentage points of experts' scores (Table 6). This shows that though the literature tends to support both groups of treatment methods for stage 2 and 3 infections with reasonably high success rates, the experts tend to favor more aggressive treatment methods and have a low level of acceptability for methods that retain the nail.

The Spearman's rank correlation was 0.74 for group A methods in stage 2 infection indicating a higher degree of consistency in expert evaluation and 0.2 (low consistency) for group B methods in stage 2 infection. Correlation was not performed for stage 3 infection since the samples available were low.

Table 4 Coefficient of variation in two rounds of expert scores to assess intra-observer variability

Stage	Treatment	Mean expert scores in % Round 1/round 2	Standard deviation	Coefficient of variation
Stage 1	Retain nail + debridement + antibiotics	78	14	18%
		85	18	21%
Stage 2	Retain nail + suppressive antibiotics + removal of nail after union	35	18	50%
		43	21	48%
	Nail removal + antibiotic nail	73	18	25%
		78	18	24%
	Retain nail + debridement + antibiotics	33	12	37%
		43	12	28%
	Retain nail + antibiotics + removal of nail after union with reaming	38	18	47%
		52	25	47%
	Exchange nailing + antibiotics	65	27	41%
		75	24	31%
	Nail removal + Ilizarov/ external fixator	65	34	52%
		68	33	50%
Stage 2 infected nonunion	Exchange nailing + antibiotics + bone grafting	58	33	58%
		70	26	37%
	Nail removal + plate fixation	45	26	57%
		43	21	48%
	Nail removal + Ilizarov/external fixator	78	32	41%
		73	28	38%
	Retain nail + debridement + antibiotics	33	17	52%
		43	17	40%
Stage 3	Nail removal + antibiotics + debridement	85	21	25
		80	23	29
	Exchange nailing + antibiotics + debridement	63	21	34
		68	17	25
	Retain nail + necrotic bone excision + antibiotics	35	18	50%
		45	28	63%
Stage 3 infected nonunion	Retain nail + suppressive antibiotics + debridement + remove nail after union	33	12	37%
		38	24	65%
	Nail removal + Ilizarov frame	78	30	39%
		78	30	39%

Discussion

Treatment of infection following IM nailing of tibial fractures is challenging. Treatment options are diverse [5, 20], and the choice of treatment is often made on a case basis rather than following established protocols. Current literature about treatment options for infection after IM nailing of tibia was analyzed and summarized in a meta-analysis by Makridis et al. [4]. Results of our survey demonstrated high intra-observer and inter-observer variability among experts regarding those treatment options reported in the literature.

Our study helped us confirm that there are no standards for the treatment of infection after IM nailing of tibial fractures. Our first hypothesis was proved true as evident by the marked variability in expert opinions among them as well as with what is published. The second hypothesis was also proved partly true in that we were able to categorize different treatment methods based on both the expert scores and published results using our analysis. We cannot however formulate evidence-based guidelines or algorithm for treatment because of the limited quality of evidence available at present. However, this study can serve as a platform for further research on the topic. Developing an evidence-based algorithmic treatment to deal with infection after IM nailing will be difficult due to the lack of robust level I trials comparing different methods. Additionally, the presence of too many variables influencing outcomes such as age, comorbidities, smoking history, host immune status, type of fracture (open vs. closed fractures), fracture union status, microorganisms involved, appropriate isolation and their response to treatment, the extent of infection, and the application of a proposed infection classification also makes developing a protocol-based treatment difficult [6–10, 22]. In fact, this represents most of the limitations of this study. Therefore, analyzing particular variables in this population could add important information for future references.

Published treatment methods are based on two principles: (i) a conservative approach aiming to retain the nail until fracture union by suppressing infection using debridement and antibiotics and (ii) a more radical approach aimed at eradicating infection, which involves bone resection and nail removal plus an alternate fixation technique [4, 11, 12]. For stage 1 infection, both the published results and our experts seem to agree on a conservative approach [4]. For stage 2 and 3

Table 5 Stage-specific difference in experts' mean and published success rates for the two treatment groups

Infection stages	Treatment method	Mean expert score (%)	Published success rate % (success/no. of cases)	Difference in % points
Stage 1	Retain nail + debridement + antibiotics	78	100% (4/4)	23
Stage 2	Methods that retain the nail:			
	i) Retain nail + suppressive antibiotics + removal of nail after union	35	85% (6/7)	50
	ii) Retain nail + debridement + antibiotics	32	87% (34/39)	55
	iii) Retain nail + antibiotics + removal of nail after union with reaming	38	100% (8/8)	63
	Methods that remove the nail:			
	i) Nail removal + antibiotic nail	73	90% (18/20)	18
	ii) Exchange nailing + antibiotics	65	100% (8/8)	35
	iii) Nail removal + Ilizarov/ external fixator	71	69% (9/13)	−2
	iv) Nail removal + plate fixation	45	0% (0/1)	−45
	v) Exchange nailing + antibiotics + bone grafting	58	96% (24/25)	39
Stage 3	Methods that retain the nail:			
	i) Retain nail + necrotic bone excision + antibiotics	35	100% (1/1)	65
	ii) Retain nail + suppressive antibiotics + debridement + remove nail after union	32	100% (4/4)	68
	Methods that remove the nail:			
	i) Nail removal + antibiotics + debridement	85	0% (0/1)	−85
	ii) Exchange nailing + antibiotics + debridement	63	91% (10/11)	29
	iii) Nail removal + Ilizarov frame	78	100% (9/9)	23

infections, the literature shows reasonably high success rates with both the approaches [4]. On the contrary, experts' scores from our survey favoured the more radical approach for both stage 2 and 3 infections. This shows the current trend in clinical practice to lean towards a more radical approach. Reasons for this change in practice may be due to a larger armamentarium selection, plus an improved understanding of different treatment methods available to deal with bone defects, soft tissue coverage, vacuum-assisted wound closure, bioburden control, and bone grafting techniques [13–15, 21, 23]. However, alternative treatment methods still need further investigation to support their use [16–18].

The meta-analysis, on which this study is based upon, is the most recent and comprehensive one on the topic, but it has limitations [4]. For this study, all expert decisions were based only on a proposed classification for infections after IM nailing of the tibia. We did not take into account other important factors that might influence decision-making. A protocol-based treatment would be difficult to develop if all factors that potentially impact decision-making were included. There is

Table 6 Stage-specific difference in experts' scores and published success rates for the two treatment groups

Stage of infection	Mean % points (experts' scores)		Mean % points (published success rates)	
	Group A	Group B	Group A	Group B
Stage 1	78	NA	100	NA
Difference in % points	NA		NA	
Stage 2	35	62	91	89
Difference in % points	27		2	
Stage 3	34	75	100	96
Difference in % points	41		5	

no clear definition of fracture-related infection and thus renders existing studies difficult to compare [19]. We performed a correlation test between two different variables (expert scores and success rates in literature). A more powerful analysis would be performing correlation tests between two groups showing success rates or two groups showing experts' scores. Most of the studies included were retrospective with small number of patients and treatment methods were poorly defined. Some treatment methods were rarely reported, and a few were reported only once. Therefore, the rates of success published in the meta-analysis by Makridis et al. [4] may not actually represent the accurate success rates. Some treatment methods were considered as absolute success or failures based on single outcome reports, which may not be a fair reflection of the technique. Because of the small samples considered, we relied on correlational analysis and descriptive statistics and refrained from further statistical analysis, which could be misleading in these situations. The expert survey in this setting becomes very helpful to understand and reflect the exact utility of different described techniques to treat the problem. It may also help develop a consensus and contribute to important knowledge on treatment methods used to treat infection after IM nailing of tibial fractures.

Overall, our results revealed more variability about the best treatment options for different stages of infected IM nailing of the tibia. This signifies the lack of standards in literature and in clinical practice, where treatment options are chosen mainly, if not only, based on surgeons' preferences. Though randomized controlled trials on larger population of patients are needed to postulate clear guidelines, our experts' survey shows a consensus towards a more radical approach aimed at eradicating bone infection and concurrently dealing with resultant bone defects in stage 2 and 3 infections. The consensus generated from top experienced trauma surgeons from all parts of the world opens future important research questions that required to be answered before developing a protocol-based treatment for tibial infection following IM nailing.

To conclude, various treatment options have been reported for infection following IM nailing of the tibia, and no consensus about the appropriate management is available in literature, nor in the current practice of expert trauma surgeons. In addition, experts' opinions do not very well correlate with current published literature. Given the paucity and inconsistency of published material on the topic, this study adds more knowledge on the current status of different treatment methods used to treat these patients. Based on the expert scores and the published success rates of different treatment methods, we suggest retention of the nail with local debridement and antibiotics for stage 1 infections and a more radical approach with removal of the nail, debridement, antibiotics, and alternate fixation techniques for stage 2 and 3 infections.

References

1. Court-Brown CM, Keating JF, McQueen MM (1992) Infection after intramedullary nailing of the tibia. Incidence and protocol for management. J Bone Joint Surg Br 74(5):770–774
2. Tsang STJ, Mills LA, Frantzias J et al (2016) Exchange nailing for nonunion of diaphyseal fractures of the tibia. Bone Joint J 98(4): 534–541
3. Court-Brown CM (2004) Reamed intramedullary tibial nailing: an overview and analysis of 1106 cases. J Trauma 18(2):96–101
4. Makridis KG, Tosounidis T, Giannoudis PV (2013) Management of infection after intramedullary nailing of long bone fractures: treatment protocols and outcomes. Open Orthop J 14(7):219–226. https://doi.org/10.2174/1874325001307010219.
5. Chaudhary MM (2017) Infected nonunion of the tibia. Indian J Orthop 51(3):256–268. https://doi.org/10.4103/ortho.IJOrtho_199_16
6. Calori GM, Philips M, Jeetle S, Tagliabue L, Giannoudis PV (2008) Classification of nonunion: need for a new scoring system? Injury 39(2):S59–S63. https://doi.org/10.1016/S0020-1383(08)70016-0
7. Torbert JT, Joshi M, Moraff A, Matuszewski PE, Holmes A, Pollak AN, O'Toole RV (2015) Current bacterial speciation and antibiotic resistance in deep infections after operative fixation of fractures. J Orthop Trauma 29(1):7–17. https://doi.org/10.1097/BOT.0000000000000158.
8. Graves DT, Alblowi J, Paglia DN, O'Connor JP, Lin S (2011) Impact of diabetes on fracture healing. J Exp Clin Med 3(1):3–8. https://doi.org/10.1016/j.jecm.2010.12.006
9. Patel RA, Wilson RF, Patel PA, Palmer RM (2013) The effect of smoking on bone healing: a systematic review. Bone Joint Res 2(6): 102–111. https://doi.org/10.1302/2046-3758.26.2000142.
10. Chadayammuri V, Herbert B, Hao J et al (2017) Diagnostic accuracy of various modalities relative to open bone biopsy for detection of long bone posttraumatic osteomyelitis. Eur J Orthop Surg Traumatol 27(7):871–875. https://doi.org/10.1007/s00590-017-1976-y
11. Schenker ML, Yannascoli S, Baldwin KD, Ahn J, Mehta S, (2012) Does timing to operative debridement affect infectious complications in open long-bone fractures? A systematic review. J Bone Joint Surg Am, (94)12 p. 1057–64. doi:https://doi.org/10.2106/JBJS.K.00582.
12. Kadhim M, Holmes L, Gesheff MG, Conway JD (2017) Treatment options for nonunion with segmental bone defects: systematic review and quantitative evidence synthesis. J Orthop Trauma 31(2): 111–119. https://doi.org/10.1097/BOT.0000000000000700.
13. Yang Y, et al., (2013) Modified classification and single-stage microsurgical repair of posttraumatic infected massive bone defects in lower extremities. J Recon Microsurg, 29(9) p. 593–600. doi: https://doi.org/10.1055/s-0033-1348064.
14. Bose D, Kugan R, Stubbs D, McNally M (2015) Management of infected nonunion of the long bones by a multidisciplinary team. Bone Joint J 97(6):814–817. https://doi.org/10.1302/0301-620X.97B6.33276.
15. McNally MA, Ferguson JY, Lau ACK, Diefenbeck M, Scarborough M, Ramsden AJ, Atkins BL (2016) Single-stage treatment of chronic osteomyelitis with a new absorbable, gentamicin-loaded, calcium sulphate/hydroxyapatite biocomposite. Bone Joint J 98(9):1289–1296. https://doi.org/10.1302/0301-620X.98B9.38057
16. Samuel G, Menon J, Thimmaiah S, et al., (2017) Role of isolated percutaneous autologous platelet concentrate in delayed union of long bones. Eur J Orthop Surg Traumatol. doi.org/10.1007/s00590-017-2077-7.
17. Leighton R, Watson JT, Giannoudis P, Papakostidis C, Harrison A, Steen RG (2017) Healing of fracture nonunions treated with low-

intensity pulsed ultrasound (LIPUS): a systematic review and meta-analysis. Injury 48(7):1339–1347. https://doi.org/10.1016/j.injury.2017.05.016

18. Kertzman P, Császár NB, Furia JP, Schmitz C, (2017) Radial extra-corporeal shock wave therapy is efficient and safe in the treatment of fracture nonunions of superficial bones: a retrospective case series. J Orthop Res, 12(1) p.164. doi: https://doi.org/10.1186/s13018-017-0667-z.
19. Metsemakers WJ, Morgenstern M, McNally MA, et al., (2017) Fracture-related infection: a consensus on definition from an international expert group. Injury. doi.org/10.1016/j.injury.2017.08.040.
20. Mioc ML, Prejbeanu R, Deleanu B, Anglitoiu B, Haragus H, Niculescu M, (2018) Extra-articular distal tibia fractures-controversies regarding treatment options. A single-centre prospective comparative study. Int Orthop. 2018 Jan 22. doi: https://doi.org/10.1007/s00264-018-3775-4.
21. Bao T, Han F, Xu F, Yang Y, Shu X, Chen K, Qi B, Wei S, Yu A (2017) Papineau technique combined with vacuum-assisted closure for open tibial fractures: clinical outcomes at five years. Int Orthop 41(11):2389–2396. https://doi.org/10.1007/s00264-017-3620-1
22. Seng P, Traore M, Lavigne JP, Maulin L, Lagier JC, Thiery JF, Levy PY, Roger PM, Bonnet E, Sotto A, Stein A (2017) Staphylococcus lugdunensis: a neglected pathogen of infections involving fracture-fixation devices. Int Orthop 41(6):1085–1091. https://doi.org/10.1007/s00264-017-3476-4.
23. Olesen UK, Pedersen NJ, Eckardt H, Lykke-Meyer L, Bonde CT, Singh UM, McNally M (2017) The cost of infection in severe open tibial fractures treated with a free flap. Int Orthop 41(5):1049–1055. https://doi.org/10.1007/s00264-016-3337-6.
24. Romano CL, Romano D, Logoluso N, Drago L (2011) Bone and joint infections in adults: a comprehensive classification proposal. Eur Orthop Traumatol 1(6):207–217