ORIGINAL RESEARCH

Critical Bone Defect Affecting the Outcome of Management in Anatomical Type IV Chronic Osteomyelitis

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Abstract

Background: The Cierny and Mader classification assists with decision-making by stratifying host status and the pathoanatomy of the disease. However, the anatomical type IV represents a heterogenous group with regard to treatment requirements and outcomes. We propose that modification of the Cierny and Mader anatomical classification with an additional type V classifier (diffuse corticomedullary involvement with an associated critical bone defect) will allow more accurate stratification of patients and tailoring of treatment strategies.

Methods: A retrospective review of 83 patients undergoing treatment for Cierny and Mader anatomical type IV osteomyelitis of the appendicular skeleton at a single centre was performed.

Results: Risk factors for the presence of a critical bone defect were female patients [OR 3.1 (95% CI, 1.08–8.92)] and requirement for soft tissue reconstruction [OR 3.35 (95% CI, 1.35–8.31)]; osteomyelitis of the femur was negatively associated with the presence of a critical bone defect [OR 0.13 (95% CI, 0.03–0.66)]. There was no statistically significant risk of adverse outcomes (failure to eradicate infection or achieve bone union) associated with the presence of a critical-sized bone defect. The median time to the bone union was ten months (95% CI, 7.9–12.1 months). There was a statistically significant difference in the median time to bone union between cases with a critical bone defect [12.0 months (95% CI, 10.2–13.7 months)] and those without [6.0 months (95% CI, 4.8–7.1 months)].

Conclusion: This study provided evidence to support the introduction of a new subgroup of the Cierny and Mader anatomical classification (Type V). Using a standardised approach to management, comparable early outcomes can be achieved in patients with Cierny and Mader anatomical type V osteomyelitis. However, to achieve a successful outcome, there is a requirement for additional bone and soft tissue reconstruction procedures with an associated increase in treatment time.

Keywords: Cierny and Mader classification, Chronic osteomyelitis, Critical bone defect.

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Introduction

The management of chronic osteomyelitis is challenging and resource-intensive for both patients and healthcare providers.[1–4] Accurate decision-making is critical to achieving optimal outcomes for patients. Furthermore, an accurate understanding of treatment outcomes and duration is necessary for patients to make informed choices about their care.

The Cierny and Mader classification assists with decision-making by classifying the host status of the patient and the morphology of anatomical involvement.[5] The host component identifies patients with sound immune systems and vascularity (Type A), those with systemic (Type Bs) or local (Type Bl) compromise, and those in which the risks of surgical treatment exceed that of the disease (Type C).[5] Modification to this host classification system has been shown to improve outcomes for high-risk patients.[6] By improving the stratification of patients, treatment strategies were refined to suit the needs of the high-risk patient resulting in outcomes comparable to that of lower-risk patients.[6]

The anatomical component described four morphological patterns in osteomyelitis of the long bones; type I medullary involvement, type II cortical involvement only, type III localised corticomedullary involvement, and type IV diffuse corticomedullary involvement.[5] The Cierny and Mader anatomical type IV is arguably the most complicated to manage as these individuals have two concurrent treatment goals; curing infection and achieving bone union.[7] A recent review of the management and outcome of chronic osteomyelitis reported that anatomical type IV cases were associated with the most heterogeneous anatomical parameters, treatment strategies, and outcomes.[7] When these cases are associated with critical-sized bone defects, the reconstructive treatment pathway may potentially be significantly more complex and associated with poor outcomes.[8] There is no consensus definition of a critically-sized bone defect.[8] However, a review of the current literature concluded that those greater than 2.5 cm in length were associated with adverse outcomes.[8] This effect on outcome has been demonstrated in the treatment of primary fracture fixation and fracture-related infection.[9,10] There is a paucity of published data describing the effect of bone defects on the outcome following treatment for chronic osteomyelitis.[7]

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In this study, we propose that modification of the Cierny and Mader anatomical classification with an additional type V classifier (diffuse corticomedullary involvement with an associated critical bone defect) will allow more accurate stratification of patients and tailoring of treatment strategies. We aimed to demonstrate that whilst patients with diffuse chronic osteomyelitis and a critical bone defect require additional reconstructive intervention and experience a different clinical course, comparable outcomes can still be achieved.

Methods

All patients presenting with chronic osteomyelitis of the appendicular skeleton between January 2016 and November 2022 were reviewed. Patient demographics, aetiology and site of infection, type of dead space management technique, isolated pathogens, follow-up period and outcome in terms of resolution of infection and bone reconstruction were collected. Patients with Cierny and Mader anatomical stage IV were included.[3] Patients with fewer than six months of follow-up were excluded from the study.

Chronic osteomyelitis was defined as an infection of the bone with associated necrosis with a duration of at least ten days, where the pathogens were thought to have resisted either intracellularly or interstitially in biofilm-or persister-states.[11] Patient records and laboratory investigations assisted in stratifying the host into A, B, or C types according to the modified Cierny and Mader classification proposed by Marais et al.[6,12] Patients without critical bone defect underwent debridement, acute reduction and skeletal stabilisation. Patients with critical bone defects underwent debridement, skeletal stabilisation, and soft tissue reconstruction in addition to a dedicated bone defect reconstruction strategy: acute shortening, induced membrane technique or bone transport, as indicated by Ferreira and Tanwar.[13]

Laboratory studies were used to obtain and identify isolates. Deep samples of infected tissue and/or biofilm obtained intraoperatively were submitted for bacterial culture. Tissue samples were crushed, inoculated onto solid media and incubated for at least 48 hours. Tryptose blood, boiled blood and MacConkey agar (for aerobic/CO_2-enriched conditions) and Brucella and/or tryptose blood agar (for anaerobic conditions) were used for solid media. Cooked meat medium or tryptic soy broth was used as liquid media. Pre-culture sonication or vortexing of samples, in the absence of prosthetic material, was not performed.

All pure cultures were identified. Mixed cultures were reviewed by a pathologist and discussed with the surgical team to determine clinical relevance. Identification and susceptibility testing were performed using the VITEK 2 automated system (bioMérieux, Marcy-l'Étoile, France). Where appropriate, rapid biochemical or antigen-based identification and disk or gradient diffusion antibiotic susceptibility testing were also performed. Antibiotic susceptibility results were interpreted in line with guidelines from the Clinical Laboratory and Standards Institute. For the purposes of this study, pathogens with an intermediate laboratory susceptibility to a given agent were categorised as resistant, as *in vivo* antimicrobial activity was likely to be suboptimal.

Intravenous broad-spectrum empiric antibiotics were given postoperatively and changed to six weeks of directed oral or intravenous antibiotics based on antibiogram results. Resolution of infection was defined as the absence of clinical signs at a minimum of 6 months following surgery. Treatment failure was defined as failure to achieve remission, including ongoing clinical signs of infection, unplanned reoperation, or amputation.

A critical bone defect was defined as a bone defect (>20 mm) that will not heal if left untreated, with segmental defects of more than 60 mm generally regarded as large defects.[8,14,15] Non-union was defined as fractures that failed to unite nine months after the injury or showed no radiological progression to union in three consecutive months. Treatment success was defined as bone union and resolution of infection. Treatment failure was defined as either failing to achieve union or recurrence of infection.

Statistical analysis was performed using Stata 16.1 (StataCorp, College Station, Texas), EpiCalc 2000 v1.02 (Brixton Books, UK), MiniTab v19, MiniTab LLC, PA, USA, and SPSS v25, IBM Corp, Armonk, NY, USA. Parametric data were reported as mean with standard deviation (SD) or 95% confidence intervals (CI), where appropriate. Non-parametric data were reported with median, interquartile range and range. Categorical data were expressed as frequencies and/or counts, with 95% CI, where appropriate. Depending on the distribution, associations were investigated using an independent *t*-test or a Mann–Whitney *U*/Median test. Pearson Chi-squared test (or Fisher's Exact test, where appropriate) was used to detect significant differences between groups. Estimation of time to bone union was performed using Kaplan–Meier statistics, and comparisons were made using Log-rank analysis.

Results

Between January 2016 and October 2022, 83 patients underwent surgical treatment for Cierny and Mader anatomical type IV chronic osteomyelitis, with all patients eligible for inclusion. The cohort comprised 59 males and 24 females, with a median age of 33 years (range 8–71) (Table 1). The anatomical site of infection was predominated by tibias ($n = 55$, 67%). The full distribution of involved anatomical sites is displayed in Figure 1.

Critical bone defects were present in 47 patients with a median defect size of 40 mm (range 25–120 mm, SD 24.2). Bone defects were predominantly located in the tibia ($n = 35$, 74%), and 32 patients (68%) with bone defects had associated soft tissue defects that required reconstruction. In contrast, 14 patients (39%) who did not present with a bone defect required soft tissue reconstruction.

Risk factors for the presence of a critical bone defect were female patients [OR 3.1 (95% CI, 1.08–8.92, $p = 0.05$] and requirement for soft tissue reconstruction [OR 3.35 (95% CI, 1.35–8.31), $p = 0.014$]; osteomyelitis of the femur was negatively associated with the presence of a critical bone defect [OR 0.13 (95% CI, 0.03–0.66), $p = 0.014$].

Pathogens were isolated in 64 cases (77%) (Table 2). A single organism was isolated in 46 (55%), while 18 (22%) patients showed polymicrobial growth. Staphylococcus aureus was the most common isolate identified in 21 patients (25%).

Circular external fixation was used as definitive skeletal stabilization in the majority of patients ($n = 43$, 52%) and the most common fixation method in patients with critical bone defects. Bone transport was the most commonly employed bone defect reconstruction technique ($n = 23$, 49%).

The median time to bone union was ten months (95% CI, 7.9–12.1 months) (Table 1). There was a statistically significant difference ($p < 0.001$) in the median time to bone union between cases with a critical bone defect [12.0 months (95% CI,10.2–13.7 months)] and those without [6.0 months (95% CI, 4.8–7.1 months)] (Fig. 2). In cases

Table 1: Demographics of included patients

	Cierny and Mader anatomical type IV			
	Without CBD (n = 36)	*With CBD (n = 47)*	*Total (n = 83)*	*p-value*
% Male (*n*)	83% (30)	62% (29)	71% (59)	**0.05**
Median age (Range, SD)	36.5 (8–61, 13.3)	33.0 (12–71, 14.7)	33.0 (8–71, 14.1)	0.751
Host status				
C & M Class A	31% (11)	21% (10)	25% (21)	**0.019**
C & M Class B_S	31% (11)	9% (4)	18% (15)	**(0.010)**
C & M Class B_L	19% (7)	40% (19)	31% (26)	**(0.041)**
C & M Class $B_{L/S}$	19% (7)	30% (14)	25% (21)	
Anatomy (%, *n*)				
Humerus	6% (2)	0% (0)	2% (2)	**0.015**
Humerus + Ulna	0% (0)	4% (2)	2% (2)	
Radius/Ulna	3% (1)	9% (4)	6% (5)	
Femur	25% (9)	4% (2)	13% (11)	
Femur + Tibia	0% (0)	4% (2)	2% (2)	**(0.006)**
Tibia	56% (20)	74% (35)	67% (55)	
Tibia + Talus	11% (4)	4% (2)	7% (6)	
Soft tissue envelope (%, *n*)				
Not needing reconstruction	61% (22)	32% (15)	45% (37)	**0.014**
Needing reconstruction	39% (14)	68% (32)	55% (46)	
Bacteriology (%, *n*)				
Culture-negative	22% (8)	23% (11)	23% (19)	1.000
Pure culture	61% (22)	51% (24)	55% (46)	0.383
Polymicrobial	17% (6)	26% (12)	22% (18)	0.424
Median time to union (months) (95% CI,)	6.0 (4.8–7.1)	12.0 (10.2–13.7)	10.0 (7.9–12.1)	**<0.001**
% Non-union (*n*)	6% (2)	11% (5)	8% (7)	0.693
% Recurrence of infection (*n*)	3% (1)	6% (3)	5% (4)	0.629
% Failure to achieve treatment goal (*n*)	6% (2)	13% (6)	10% (8)	0.456
Median follow-up (months) (Range, SD)	12.0 (6.0–36.0, 8.1)	13.0 (6.0–38.0, 8.0)	12.0 (6.0–38.0, 8.0)	0.203

All *p*-values at or below 0.05 are marked in bold as these show statistical significance. CBD, critical bone defect, C & M, Cierny and Mader; CI, confidence interval

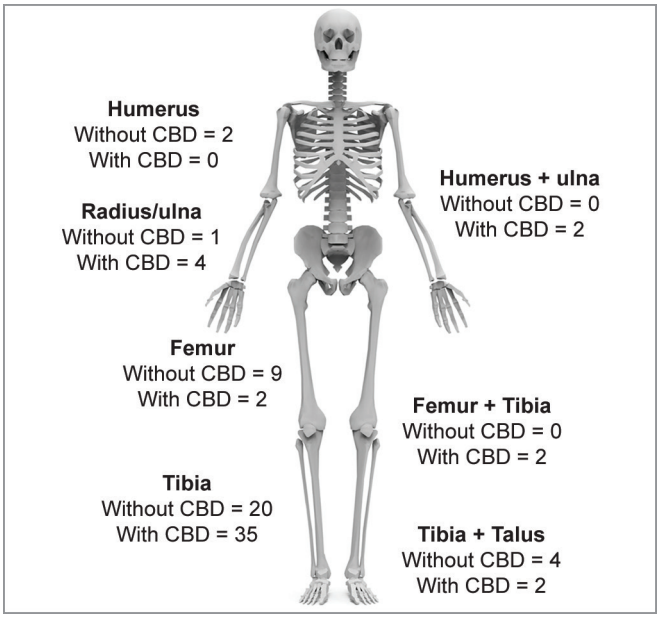

Fig. 1: Anatomical distribution of affected sites

with a critical-sized bone defect, there were statistically significant differences in the median time to union between reconstructive strategies ($p < 0.001$) (Table 3 and Fig. 3).

Discussion

Cierny and Mader provided a classification system that stratifies patients into management strategies and expected treatment outcomes.[5] The anatomical type IV group comprises a heterogeneous group. Whilst in this present study, no statistical difference was found in the risk of adverse outcomes (failure to eradicate infection or achieve bone union), there was a clinically and statistically significant prolonged time to bone union in the presence of a critical-sized bone defect due to the requirement for additional reconstructive techniques for both the bone and soft tissues. Associated risk factors for the presence of critical-sized defects include; females, soft tissue defects requiring reconstruction, and involvement of anatomical regions outside the femur.

Similar results have been reported in the published literature. Wu et al. reported the outcome of 36 patients with Cierny and Mader type IV chronic osteomyelitis treated using a staged-induced membrane technique with a minimum of two years follow-ups.

Table 2: Treatment and outcomes of bone defects ($n = 47$)

	Shortening (n = 7)	*Induced membrane (n = 17)*	*Bone transport (n = 23)*	*Total (n = 47)*
% Male (*n*)	(4)	59% (10)	(15)	62% (29)
Median age (Range, SD)	31.0 (16–53, 15.1)	37.0 (24–71, 16.2)	30.0 (12–57, 12.8)	33.0 (12–71, 14.7)
Median defect size (Range, SD)	28.6 (25–30, 2.4)	60.6 (25–120, 33.3)	48.7 (25–80, 14.2)	40.0 (25–120, 24.2)
Anatomy (%, *n*)				
Humerus	0% (0)	0% (0)	0% (0)	0% (0)
Humerus + Ulna	0% (0)	12% (2)	0% (0)	4% (2)
Radius/Ulna	14% (1)	18% (3)	0% (0)	9% (4)
Femur	0% (0)	12% (2)	0% (0)	4% (2)
Femur + Tibia	0% (0)	12% (2)	0% (0)	4% (2)
Tibia	71% (5)	47% (8)	96% (22)	74% (35)
Tibia + Talus	14% (1)	0% (0)	4% (1)	4% (2)
Definitive fixation (%, *n*)	14% (1)	18% (3)	0% (0)	9% (4)
Plate and screws	0% (0)	35% (6)	0% (0)	13% (6)
IM nail Circular external fixator	29% (2)	47% (8)	100% (23)	70% (33)
Hexapod external fixator	43% (3)	0% (0)	0% (0)	6% (3)
Monolateral external fixator	14% (1)	0% (0)	0% (0)	2% (1)
Median time to union (95% CI)	6.0 (4.9–10.2)	12 (9.8–14.2)	16.0 (11.5–20.4)	12.0 (10.2–13.7)
% Non-union (*n*)	29% (2)	6% (1)	9% (2)	11% (5)
% Recurrence of infection (*n*)	0% (0)	6% (1)	9% (2)	6% (3)
% Failure to achieve treatment goal (*n*)	29% (2)	12% (2)	9% (2)	13% (6)

CI, confidence interval; IM, intra-medullary

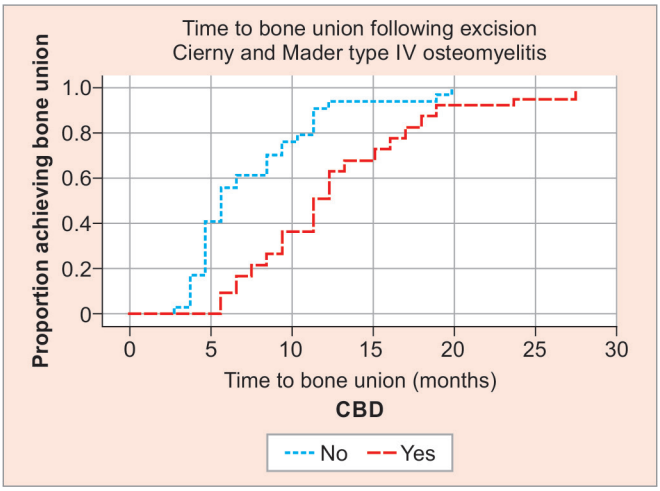

Fig. 2: Kaplan–Meier curve comparing time to bone union following excision of Cierny and Mader type IV osteomyelitis between cases with a critical-sized bone defect (CBD) and those without. The log-rank analysis demonstrated statistically significant differences ($p < 0.001$)

They reported that all patients achieved bone union, and clinical eradication of osteomyelitis was achieved in 97% of patients. Whilst the defect size did not predict bone union, increasing age and tibial involvement were found to predict ongoing non-union.[7] Despite these findings, an instructional review on the management of bone defects from the French Society of Orthopedic Surgery and Traumatology, which included the creator of the induced membrane technique, recommended bone transport in cases where bone loss exceeded 10 cm.[16,17]

Sigmund et al. compared bone reconstructive techniques (bone transport and acute shortening with re-lengthening) to manage infected segmental defects of the tibia.[18] Ultimately, there was no difference in the risk of recalcitrant infection or ongoing non-union between the two techniques. However, 15 of 27 bone transport cases required unplanned surgeries, including docking site procedures, to achieve bone union. The two groups had no difference in overall time in the fixator or the external fixator index.[18] It should be noted that patients undergoing acute shortening in this present study did not undergo re-lengthening (median defect size 28.6 mm) and thus experienced a significantly shorter treatment time compared to patients undergoing bone transport (median defect size 48.7 mm).

Marais and Ferreira reported the outcomes of patients undergoing staged bone transport through an induced membrane in treating Cierny and Mader type IV osteomyelitis of the tibia.[19] All patients achieved eradication of infection at a mean follow-up of 28 months; one patient failed to achieve bone union and consolidation of bone regeneration due to poor compliance with the transport programme and ultimately underwent amputation. The median time in the frame was 77 weeks, with an external fixator index of 81 days/cm.[19] Mifsud et al. described the outcomes of 57 consecutive patients undergoing single-stage excision and reconstruction in the treatment of tibial infection.[20] Of the 57 cases, 49 had Cierny and Mader anatomical type IV involvement; Ilizarov bone reconstruction included mono-focal compression, mono-focal distraction, acute shortening and re-lengthening, bone transport, and a protective frame; soft tissue reconstructions were all free muscle flaps. Recurrence of infection was experienced in 2/57 cases, and failure to achieve union was reported in 5/57 cases. The mean time in the frame for patients undergoing mono-focal compression was 5.0

Table 3: Organisms isolated from intraoperative samples in patients with chronic osteomyelitis ($n = 82$)

	Cierny and Mader anatomical stage		
	Without CBD	*With CBD*	*Total*
Staphylococci			
Methicillin-susceptible *S. aureus*	12	9	21
Methicillin-resistant *S. aureus*	0	0	0
Streptococci			
Group A *Streptococcus*	5	1	6
Group B *Streptococcus*	1	0	1
Enterococci			
Enterococcus faecalis	1	1	2
Enterobacterales			
Proteus mirabilis	1	7	8
Proteus hauseri	0	1	1
Proteus penneri	0	2	2
Enterobacter cloacae	4	4	8
Klebsiella pneumoniae	1	0	1
Serratia marcescens	2	1	3
Providencia stuartii	0	1	1
Escherichia coli	2	5	7
Morganella morganii	0	5	5
Non-fermenting gram-negative bacilli			
Pseudomonas aeruginosa	2	8	10
Acinetobacter baumannii	0	2	2
Miscellaneous gram-negative bacilli			
Aeromonas hydrophlia/caviae	1	1	2
Anaerobes			
Bacillus cereus	0	1	1
Finegoldia magna	1	0	1
	33	49	82

months (range 2.9–9.7 months) and bone transport 9.4 months (range 6.5–13.1). The mean defect size in the bone transport group was 61 mm.[20]

Cierny and Mader anatomical type IV osteomyelitis represent a heterogeneous group requiring different treatment strategies and experiencing different clinical courses. This study provided evidence to support a modification of the Cierny and Mader anatomical classification, with the addition of an "anatomical type V" subclassification for diffuse corticomedullary osteomyelitis with an associated critical-sized bone defect.

When interpreting these results, it is essential to acknowledge that they are reported at a median follow-up of 12.0 months. Whilst it may be that cases of recurrent infection may yet still present, a previous

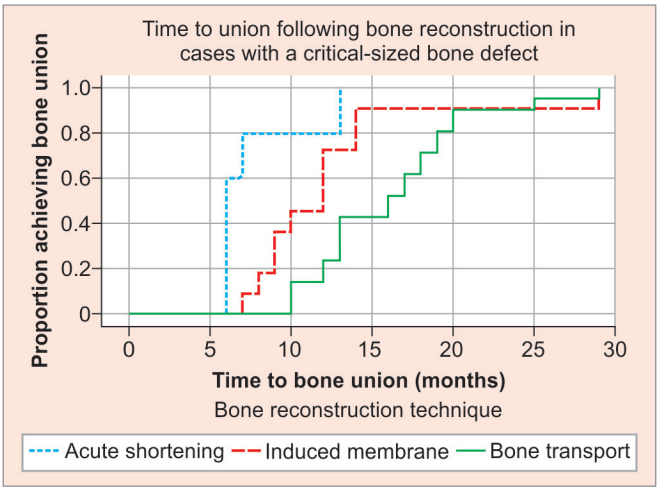

Fig. 3: Kaplan–Meier curve comparing time to bone union following different bone reconstruction options in cases with a critical-sized bone defect. The log-rank analysis demonstrated statistically significant differences ($p < 0.001$)

study demonstrated that ~50% of cases of recurrent osteomyelitis present within the first twelve months of surgery.[21] The overall risk of recurrent osteomyelitis in that series of Cierny and Mader type III and type IV cases was 6%. In this present study, recurrence occurred in 4/83 cases; even if another four cases of recurrent infection were to present in a group with a critical-sized bone defect, the difference would still not be statistically significant ($p = 0.129$). Therefore, we can confidently say that there is no statistically significant difference in the eradication of infection between the two groups that have been missed due to the length of follow-up.

Conclusion

This study provided evidence to support the introduction of a new subgroup of the Cierny and Mader anatomical classification (type V). Using a standardised approach to management, comparable early outcomes can be achieved in patients with Cierny and Mader anatomical type V osteomyelitis. However, to achieve a successful outcome, there is a requirement for additional bone and soft tissue reconstruction procedures with an associated increase in treatment time.

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References

1. Walter N, Rupp M, Hierl K, et al. Long-term patient-related quality of life after fracture-related infections of the long bones. Bone Joint Res 2021;10(5):321–327. DOI: 10.1302/2046-3758.105.BJR-2020-0532.
2. Walter N, Rupp M, Baertl S, et al. Prevalence of psychological comorbidities in bone infection. J Psychosom Res 2022;157. DOI: 10.1016/j.jpsychores.2022.110806.
3. Ferguson J, McNally M, Stubbs D. The financial burden of treating osteomyelitis in the UK. Orthop Proc 2019;101-B(SUPP_14):65–65. DOI: 10.1302/1358-992X.2019.14.065.

4. Jiang N, Wu HT, Lin QR, et al. Health care costs of post-traumatic osteomyelitis in China: Current situation and influencing factors. J Surg Res 2020;247:356–363. DOI: 10.1016/j.jss.2019.10.008.
5. Cierny G, Mader JT, Penninck JJ. A clinical staging system for adult osteomyelitis. Contemp Orthop 1985;(10):17–37. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12966271.
6. Marais LC, Ferreira N, Aldous C, et al. A modified staging system for chronic osteomyelitis. J Orthop 2015;12(4):184–192. DOI: 10.1016/j.jor.2015.05.017.
7. Wu H, Shen J, Yu X, et al. Two stage management of Cierny-Mader type IV chronic osteomyelitis of the long bones. Injury 2017;48(2):511–518. DOI: 10.1016/j.injury.2017.01.007.
8. Schemitsch EH. Size Matters: Defining critical in bone defect size! J Orthop Trauma 2017;31(Suppl 5):S20–S22. DOI: 10.1097/BOT.0000000000000097.8.
9. Keating JF, Simpson AH, Robinson CM. The management of fractures with bone loss. J Bone Joint Surg Br 2005;87(2):142–150. DOI: 10.1302/0301-620x.87b2.15874.2.
10. Bezstarosti H, Metsemakers WJ, van Lieshout EMM, et al. Management of critical-sized bone defects in the treatment of fracture-related infection: A systematic review and pooled analysis. Arch Orthop Trauma Surg 2021;141(7):1215–1230. DOI: 10.1007/s00402-020-03525-0.
11. Lew DP, Waldvogel FA. Osteomyelitis. N Engl J Med;336(14):999–1007. DOI: 10.1056/NEJM199704033361406.
12. Marais LC, Ferreira N, Aldous C, et al. The management of chronic osteomyelitis: Part II – Principles of post-infective reconstruction and antibiotic therapy. SA Orthop J 2014;13(3):32–39. ISSN: 2309-8309.
13. Ferreira N, Tanwar YS. Systematic approach to the management of post-traumatic segmental diaphyseal long bone defects: Treatment algorithm and comprehensive classification system. Strateg Trauma Limb Reconstr 2020;15(2):106–116. DOI: 10.5005/jp-journals-10080-1466.
14. Roddy E, DeBaun MR, Daoud-Gray A, et al. Treatment of critical-sized bone defects: clinical and tissue engineering perspectives. Eur J Orthop Surg Traumatol 2018;28(3):351–362. DOI: 10.1007/s00590-017-2063-0.
15. Sanders DW, Bhandari M, Guyatt G, et al. Critical-sized defect in the Tibia: Is it critical? Results from the sprint trial. J Orthop Trauma 2014;28(11):632–635. DOI: 10.1097/BOT.0000000000000194.
16. Karger C, Kishi T, Schneider L, et al. Treatment of posttraumatic bone defects by the induced membrane technique. Orthop Traumatol Surg Res 2012;98(1):97–102. DOI: 10.1016/j.otsr.2011.11.001.
17. Rigal S, Merloz P, Le Nen D, et al. Bone transport techniques in posttraumatic bone defects. Orthop Traumatol Surg Res 2012;98(1):103–108. DOI: 10.1016/j.otsr.2011.11.002.
18. Sigmund IK, Ferguson J, Govaert GAM, et al. Comparison of ilizarov bifocal, acute shortening and relengthening with bone transport in the treatment of infected, segmental defects of the Tibia. J Clin Med 2020;9(2):279. DOI: 10.3390/jcm9020279.
19. Marais LC, Ferreira N. Bone transport through an induced membrane in the management of tibial bone defects resulting from chronic osteomyelitis. Strateg Trauma Limb Reconstr 2015;10(1):27–33. DOI: 10.1007/s11751-015-0221-7.
20. Mifsud M, Ferguson JY, Stubbs DA, et al. Simultaneous debridement, Ilizarov reconstruction and free muscle flaps in the management of complex tibial infection. J Bone Jt Infect 2020;6(3):63–72. DOI: 10.5194/jbji-6-63-2020.
21. McNally MA, Ferguson JY, Scarborough M, et al. Mid- to long-term results of single-stage surgery for patients with chronic osteomyelitis using a bioabsorbable gentamicin-loaded ceramic carrier. Bone Joint J 2022;104-B(9):1095–100. DOI: 10.1302/0301-620X.104B9.BJJ-2022-0396.R1.