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Original Article

Surgical management of chronic osteomyelitis: Organisms, recurrence and treatment outcome

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ABSTRACT

Purpose: The study aimed to identify the risk factors of recurrence in chronic osteomyelitis (COM) and to document the microbiological patterns pre- and intra-operatively and at recurrence, if any.
Methods: We performed retrospective review on COM patients treated with surgical debridement and a 6-week course of antibiotics. The patients with symptoms of osteomyelitis for at least 6 weeks, present or past episodes of discharging sinus, documentation of bone sequestration in operative notes or preoperative images were included in the study. Patients with symptoms of osteomyelitis < 6 weeks, lack of history of discharging sinus or lack of evidence of sequestration in preoperative images or intraoperative notes were excluded. Logistic regression models were used to assess the impact of risk factors of recurrence. Cohen-Kappa scores were derived to see the concordance between pre-operative and intra-operative isolates and at recurrence.
Results: Totally, 147 COM patients (115 males and 32 females, mean age (33 ± 19) years) were included in this study. Recurrence was noted in 28 patients (19.0%). Polymicrobial growth and extended spectrum beta-lactamase producing *Enterobacteriaceae* increased the chance of recurrence. Cierny-Mader stage-1, hematogenous aetiology and negative intraoperative culture reduced the chance of recurrence. Concordance between pre-operative and intra-operative cultures was 59.85% (Kappa score 0.526, $p < 0.001$) and between index surgery and at recurrence was 23.81% (Kappa score 0.155, $p < 0.001$). Lack of knowledge of causative organism preoperatively did not affect outcome. At mean follow-up (42 ± 15) months, all patients were apparently infection free for at least 1 year.
Conclusion: Polymicrobial growth and multi-drug resistant organisms increase the risk of recurrence in COM. Patients' age, gender, diabetes mellitus, previous failed treatment, duration of symptoms, haemoglobin, white cell count, C-reactive protein and erythrocyte sedimentation rate at presentation did not have any impact on the recurrence of infection. Pre-operative isolation of organism is of questionable value. Recurrences of infections do occur and are more of re-infections than relapses. Diligent isolation of organism must be attempted even in re-debridements. Even patients with recurrences do well with appropriate debridement and antibiotic therapy.

Introduction

Chronic osteomyelitis (COM) is a disease in transition, with ongoing changes in predisposing factors, causative organisms and treatment. It is generally secondary to neglected or incompletely treated hematogenous osteomyelitis (OM), inadequately treated open fractures or postoperative infectious complications. The incidence of hematogenous OM is declining, but the increasing number of implant surgeries and joint replacements contributes to increased incidence of posttraumatic and periprosthetic infections. There has also been a steady evolution in diagnostic modalities, newer antibiotics, biomaterials and reconstructive surgeries.[1] The available studies on management of COM differ widely with respect to surgical and antibiotic regimens and treatment outcomes. This leaves us with no scope to identify the most effective treatment

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regimen or recommend the best suitable treatment approach in COM.[2]

The biggest challenge in treatment of COM is the fact that eradication of infection is never certain. Many patients relapse over time, requiring multiple operations and prolonged hospitalizations, adding to a huge economic burden on patients and health care systems.[3] The reported recurrence rate of COM varies from 0[4,5] – 48%.[6] Factors leading to recurrence of infection in COM are sparingly addressed in literature.[7]

The study by Tice et al.[8] comprehensively reviewed the risk factors associated with recurrence in 454 patients who had a recurrence rate of 30.6%. But their mode of treatment was community based parenteral antibiotic therapy, surgery being reserved only for recurrent cases. Antibiotic therapy alone will not suffice because of its poor kinetics in bone with sequestrae and fistulae. Currently the trend is shifting towards surgical debridement as the predominant option with minimal[9] or no systemic antibiotics[5] with or without local antibiotics. There are limited reports on the risk factors of recurrence in OM treated with surgery and antibiotics.[10–15] These studies differ from one another with regard to age of patients, aetiology of COM treated and treatment protocols adopted, and have come out with non-uniform conclusions. Similarly, there are reports pertaining to the pre– and intra-operative identification of causative organisms, but microbiological patterns of recurrences after surgical treatment of COM are not well documented.[16]

In this background we undertook this study with the primary objective to identify the risk factors of recurrence in COM managed by surgery and antibiotics. The secondary objective was to document the microbiological patterns of disease and recurrences, including pre-operative isolation from pre-operative sinus tract cultures.

Methods

This was a retrospective study of all COM cases treated from January 2014 to December 2018 (5 years) in the orthopaedic department of a tertiary level charitable super-speciality teaching hospital in south India. The study was performed by reviewing all available medical records and radiographs of eligible patients. The inclusion criteria were symptoms of OM for at least 6 weeks, present or past episodes of discharging sinus, documentation of bone sequestration in operative notes or preoperative images. The exclusion criteria were duration of symptoms less than 6 weeks, lack of history of discharging sinus and lack of evidence of sequestration in preoperative images or intraoperative notes. Cases of acute OM, septic arthritis, acute post-operative infections and subacute forms of OM like Brodie's abscess (without history of draining sinus) were not considered. The patients with at least 1 year of follow-up from the date of last surgical debridement only were included, while the ones with less than 1 year of documented follow-up were excluded. In recurrent cases where multiple debridements were performed, we ensured that follow-up was available from the last attempt of infection eradication.

The study was performed according to the World Medical Association Declaration of Helsinki. Approval of the Institutional Ethics Committee was not required, considering the observational, non-interventional and retrospective nature of the study from medical records. All patients at the time of their respective admissions had given signed informed consent that their clinical data, radiological images and clinical photographs could be used for research and scientific publications.

All patients were planned for surgical debridement under anaesthesia, during which all antibiotics were stopped if the patients were already on. Apart from thorough clinical assessment, biplanar radiographs were obtained in all cases. Selected cases (especially the ones without metallic implants) had CT or MRI to assist surgical planning. For the patients who had discharging sinus at the time of presentation, we obtained samples for bacterial culture and sensitivity. After cleaning the local area thoroughly with saline, sample was obtained with swab from deeper parts of the sinus. In patients with abscess, aspiration was performed with sterile precautions to obtain pre-operative sample. The purpose of this examination was to decide on the antibiotic therapy in the first 2 – 3 days after surgical debridement (till reports of culture from sequestrum are available). No antibiotics were administered till deep samples were obtained for microbiological analysis during surgical debridement. An antibiotic-free period of at least 3 weeks was ensured prior to debridement to ensure good yield of intraoperative organisms.

All debridements were performed under regional or general anaesthesia. The sinuses were demarcated by injecting methylene blue. Radical excision of all unhealthy and nonviable tissues including sequestrectomy was performed. Metallic implants were removed too. Bony sequestrum with the surrounding unhealthy granulation tissue was submitted as the “deep sample” for intraoperative microbiological analysis. The field was irrigated with copious amounts of saline. Antibiotic beads were inserted (and kept for 6 weeks) in patients who had dead space at the end of debridement. In patients of intramedullary OM of long bones with wide medullary canal, antibiotic nails (fabricated on table over long K-wire) were inserted at the end of debridement. Wounds were closed over suction drains and bone was stabilized with plaster slab or external fixator depending on the amount of bone resected. The drains were retained till the discharge was less than 25 mL per day.

Post-operatively, single antibiotic was given intravenously for a period of 1 week, selected from pre-operative culture and modified as per-intraoperative culture, after which single and sensitive oral antibiotic was administered for the next 5 weeks (to make 6 weeks of total duration). If no sensitive oral agents were available, patients were administered out-patient based single antibiotic injections, but the duration was shortened to 4 weeks, if the patient did not have any signs of infection with a falling trend of C-reactive protein. If the patient grew more than 1 organism intraoperatively, 2 antibiotics were used covering all organisms (if a single antibiotic did not cover all organisms). Clindamycin was the antibiotic of choice in culture negative cases.

Ilizarov method was used as the predominant reconstruction modality for cases with significant cortical defect following debridement or associated issues like nonunion. Cases with cortical defect less than one-third of the circumference of the cortex were treated with plaster. Bone graft was added to cortical defect between one-third to half of circumference at 6 weeks, usually timed with removal of antibiotic beads. These patients were kept on non-weight bearing for the next 6 weeks, after which gradual weight bearing was started. Defects more than half of the diameter were additionally stabilized with Ilizarov fixator (along with bone graft at 6 weeks) and allowed full weight bearing (till this time, they were kept on plaster and non-weight bearing). Infected nonunions that could be acutely docked with shortening less than 3 centimetre were managed by mono focal osteosynthesis with Ilizarov method, without any attempt to lengthen the bone. We accepted the shortening as it could be managed easily by shoe raise, whereas lengthening would unnecessarily prolong the external fixator time. In cases of infected nonunion with more than 3 centimetre of defect, bifocal osteosynthesis or bone transport was used, depending on the length of defect. Wherever possible, bifocal osteosynthesis was given preference over bone transport considering its lesser incidence of technical challenges and complications.[17] Most of these cases required bone grafting at the docking

site. Four children with major defect of femur or tibia were managed with the special strategy called "fibula plus Ilizarov" reported previously.[18]

After completion of treatment, all patients were followed up every 3 months in the first year, every 6 months in the second year and yearly thereafter. During the period, the patient was asked to return immediately in case of any recurrence symptoms.

All surgeries were performed by a team of 2 orthopaedic consultants with special interest in bone infection and Ilizarov method. Data was retrieved from a prospectively maintained surgical database and validated by the same 2 consultants by review of all medical records.

The data was analysed using IBM SPSS Statistics (Version 25) predictive analytic software. Continuous variables were expressed as mean (SD) and categorical variables were summarized as number (percent). For the primary objective, i.e., to analyse the impact of risk factors of recurrence of infection, we used the logistic regression models. Treatment outcome with any episode of recurrence of infection was coded as "1" and lack of recurrence of infection throughout the follow-up period was coded as "0". The risk factors considered in the study were: (1) demographic and clinical factors including Cierny-Mader stage and type of OM; and (2) number and type of organisms isolated in intra-operative culture.

To account for multiple categories while analysing the impact of type of Cierny-Mader stage, type of OM, number of organisms isolated and the type of organism isolated, we used categorical dummies in each of these cases. For example, while studying the impact of the number of organisms isolated in intra-operative culture, there were 3 categories: culture negative, single bacterial growth, and poly bacterial growth. Since we needed to choose 1 of the 3 categories as the base and in our analysis, we chose "culture negative" as the base category. Then a dummy each D_{1i} and D_{2i} was created for capturing the impact of single bacterial and poly bacterial growths respectively, such that, D_{1i} took the value "1" in those cases where only 1 organism was isolated and the rest were coded "0". Similarly, D_{2i} took the value "1" when more than 1 organism was isolated and the others took the value "0". It is noteworthy that D_{1i} and D_{2i} were "0" wherever the culture was negative and the constant term accounted for the impact of the base group. In this way, when we had n categories, there were n-1 dummies. Variables or categories having p values less than 0.05 were considered statistically significant. R-squared values measured the goodness of fit and also pseudo-R-square as we resorted to logistic regression. However, unlike the R-squared values in for normal regression, the measures of the pseudo-R-square as expected were found to be low.[19]

The second objective was to test the agreement between the organisms isolated in pre-operative cultures (from sinus) and the organisms isolated from intra-operative bone specimens. We noted that the pre- and intra-operative culture reports of all the patients who underwent surgical debridement for primary and recurrent infections. This analysis was not possible for the patients whose skin was intact preoperatively because the preoperative sampling was not possible. For the patients who had relapse of infection, we wanted to assess the agreement between the organisms isolated during the index surgery and recurrence. For the patients who had more than 1 recurrence, paired comparison was made between organism(s) isolated at every recurrence with those at index surgery. For the purpose of statistical analysis, partial agreement in polymicrobial growths was taken as disagreement. To assess agreement between paired isolates we used the Cohen-Kappa score. We coded each organism and specific group of organisms with unique numerical values. Kappa score ranges between 0 and 1: 0.00 – 0.40 was a marginal agreement; 0.41 to 0.60 was moderate agreement; 0.61 to 0.80 was substantial agreement; 0.81 to 1.00 was perfect agreement. Further, observed agreement was considered better than the expected agreement by chance if the p values are significant at 0.05.

Retrospectively, we identified the patients where the pre-operative culture showed growth and agreed completely with the growth in intra-operative culture sample. These patients had the advantage of the right antibiotic therapy till reports of the intra-operative culture were available. We used logistic regression to see if lack of correct identification of causative bacteria resulted in increased chance of recurrence of infection.

Results

Out of 162 eligible patients screened for inclusion to the study, 11 patients did not have the required follow-up. The medical records were incomplete in 4 patients. Eliminating these 15 patients, we enrolled 147 patients.

All patients were classified by Cierny-Mader staging system and managed with a combination of surgical debridement and post-operative antibiotic therapy. The demographic and pre-operative clinical characteristics of the patient cohort are summarized in Table 1. Forty-seven patients (32.0%) were children or adolescents (< 18 years). The majority of cases were related to metallic implants. Tibia and femur were the common bones involved and 36 patients had history of failed surgical debridements, of which 5 patients had more than 1 attempt to eradicate infection. Three children presented with pathological fractures, 2 in femur and 1 in tibia.

Table 1
Demographic and clinical characteristics of the patient cohort.

Variables	Value
Age (year)[a]	33 (19)
Gender	
Male	115 (78.2)
Female	32 (21.8)
Diabetic	15 (10.2)
Type of osteomyelitis	
Hematogenous	47 (31.9)
Exogenous	26 (17.7)
Implant associated	74 (50.3)
Bone involved	
Tibia	59 (40.1)
Femur	49 (33.3)
Humerus	7 (4.8)
Fibula	8 (5.4)
Ulna	6 (4.1)
Foot	4 (2.7)
Ilium	3 (2.0)
Patella	3 (2.0)
Radius	3 (2.0)
Radius and ulna	2 (1.4)
Calcanuem	2 (1.4)
Clavicle	1 (0.7)
Adjacent joint involvement	10 (6.8)
Ankle	3 (2.0)
Hip	3 (2.0)
Knee	2 (1.4)
Joints of foot	1 (0.7)
Elbow	1 (0.7)
Duration of symptoms (month)[a]	16 (20)
History of past surgical debridements	36 (24.5)
Cierny-Mader grade	
1	42 (28.6)
2	32 (21.8)
3	23 (15.6)
4	50 (34.0)
Duration of follow-up (month)[a]	42 (15)

[a] Data presented as mean (SD), excepted as n (%).

Pre-operative microbiological sample obtained in 103 out of 147 patients (70.1%) (the rest did not have a discharging sinus or a palpable abscess). Local antibiotic therapy could be delivered in 90 patients (61.2%) (the rest did not have any dead space). Debridement alone was enough in 86 patients (46.3%), the rest required secondary surgeries, depending on the extent of bone resection. The spectrum of reconstructive surgeries employed are summarized in Table 2.

The mean follow-up available was (42 ± 15) months. Recurrences were classified as "early" if they happened within a month of index debridement and "late" if later than 1 month. Recurrence of infection was noted in 28 out of 147 patients (19.0%) and 11 (7.5%) had more than 1 recurrence (2 recurrences in 8 patients and 3 recurrences in 3 patients). Out of 42 recurrences that happened, 9 (27.3%) were classified as early and the rest 33 (72.7%) were late. The mean duration from debridement to first evidence of relapse was 10 months (range, 2 weeks to 84 months). All recurrences were debrided surgically and were subjected to the same of pre-, intra- and post-operative management protocols as for the primary cases, including antibiotic administration.

Even though 19.0% of cases required reoperations to eradicate infection, all patients were apparently cured (with 1 year free of symptoms) at the time of the final follow-up. Though many patients had associated bony deformity, none of them merited a surgical correction as all of them were functional. Eradication of infection was the only aim in these patients for fear of corrective osteotomies going for non-union, considering poor local blood supply and sclerosis. All patients with infected nonunion achieved union, though many of them had residual shortening less than 3 centimetre.

As with the organisms grown from the intra-operative bone samples, 20 samples did not grow any organism, 117 samples grew single organisms, 8 samples grew 2 organisms and 2 samples grew 3 organisms (Table 3).

The results from the logistic regression, revealed that the demographic and clinical factors like age, gender, co-existing diabetes mellitus, history of past failed treatment, duration of symptoms, haemoglobin, white cell count, C-reactive protein and erythrocyte sedimentation rate levels at presentation did not have an impact on the chance of recurrence of infection. The impact of C-reactive protein and erythrocyte sedimentation rate were estimated independently as the data was not available for all patients, the sample sizes being 111 and 117, respectively. Among the Cierny-Mader stages, it was evident that the constant capturing the impact of stage 1 significantly reduced the risk of recurrence ($p < 0.001$). Among stages 2, 3 and 4, we noted that it was only stage 4 that could be considered marginally significant as its p value neared level of significance (0.056). A positive sign for stage 4 would imply it adding to risk of recurrence when compared to stage 1. For analysing the impact of type of COM, we took hematogenous OM as the base category. Results revealed that hematogenous variety significantly reduced the risk of recurrence ($p < 0.001$) when compared to exogenous and implant-associated varieties of OM (Table 4).

Table 3
Summary of bacterial growth isolated from intraoperative bone samples.

Growth isolated in intraoperative culture ($n = 147$)	Number (%)
Culture negative	20 (13.6)
Single organism isolated	117 (79.6)
Methicillin Sensitive *Staphylococcus aureus*	47 (32.0)
Methicillin Resistant *Staphylococcus aureus*	28 (19.1)
Coagulase Negative *Staphylococci*	16 (10.9)
ESBL producing *Enterobactericiae*	8 (5.4)
ESBL producing *Klebsiella pneumoniae*	3 (2.0)
ESBL producing *Escherichia coli*	3 (2.0)
ESBL producing *Enterobacter* sp.	2 (1.4)
Enterobactericiae	6 (4.1)
Proteus vulgaris	3 (2.0)
Enterobacter sp.	3 (2.0)
Pseudomonas aeruginosa	5 (3.4)
Streptococcus pyogens	3 (2.0)
Enterococcus sp.	3 (2.0)
Achromobacter denitrificans	1 (0.7)
Polymicrobial growth isolated	10 (6.8)
Two organisms grown	8 (5.4)
Three organisms grown	2 (1.4)

ESBL: extended spectrum beta-lactamase.

When we studied the impact of the organisms isolated in intra-operative culture samples, culture negative OM was found to be reducing the risk of recurrence (captured by the constant). While, the impact of having 1 or more than 1 organism (polymicrobial growth) added to risk of recurrence, it was only polymicrobial growth that was found to be statistically significant. Finally, among the type of organism present in the isolate, having no organism as seen earlier reduced the chance of recurrence. Compared to this, extended spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* was found to be significantly riskier as its coefficient is found to be positive with statistical significance ($p = 0.048$). In this context, we also note that *methicillin resistant staphylococcus* was also a potential threat towards recurrence with its $p = 0.063$ (nearing statistical significance) (Table 5). Even though we isolated *Streptococcus pyogens*, *Enterococcus spp*. and *Achromobacter denitrificans* in our isolates, their impact could not be studied due to their infrequent occurrence.

The agreement between the organisms isolated in pre-operative sinus cultures and intra-operative bone cultures (137 paired pre-operative *vs.* intra-operative samples, wherever pre-operative sampling was possible in both primary and recurrence settings) was found to be moderate with the Kappa score at 0.526. In case of organism(s) isolated at index surgery and at recurrence (there were 42 paired isolates at index surgery *vs.* at recurrence), evidence suggested that the agreement was just marginal as the Kappa score at 0.155. In either case the agreement was statistically significant

Table 2
Spectrum of reconstructive surgeries performed post-eradication of infection for cortical defects or associated pathologies.

Secondary reconstructive surgery	Number (%)
No reconstruction (including 2 pediatric femoral pathological fractures that united in spica)	86 (58.5)
Bone graft for cortical defect	10 (6.8)
Bone graft plus Ilizarov for cortical defect	7 (4.8)
Ilizarov monofocal osteosynthesis (including one case of pediatric tibial pathological fracture)	29 (19.7)
Ilizarov bifocal osteosynthesis	6 (4.1)
Ilizarov bone transport	1 (0.7)
Fibula plus Ilizarov	4 (2.7)
Arthrodesis (knee-2, subtalar-1)	3 (2.0)
Ilizarov hip reconstruction	1 (0.7)

Table 4
Results of logistic regression to assess the impact of clinical and demographic factors on the chance of recurrence of infection.

Variables	Demographic and clinical factors			Stage of osteomyelitis	Type of osteomyelitis
	Equation 1	Equation 2	Equation 3		
Constant[a]	1.17 (0.542)	-1.15 (<0.001)[b]	-1.41 (<0.001)[b]	-1.60 (<0.001)[b]	-1.74 (<0.001)[b]
Age	-0.01 (0.401)	-	-	-	-
Gender	-1.08 (0.113)	-	-	-	-
Diabetes mellitus	-0.13 (0.898)	-	-	-	-
History of previous failed treatment	0.82 (0.083)	-	-	-	-
Duration of symptoms	-0.005 (0.71)				
Hemoglobin level	-0.06 (0.650)	-	-	-	-
WBC count	-0.0001 (0.06)	-	-	-	-
C-reactive Protein	-	-0.01 (0.204)	-	-	-
Erythrocyte sedimentation rate	-	-	0.001 (0.801)	-	-
Cirney-Mader stage 2	-	-	-	-1.09 (0.190)	-
Cirney-Mader Stage 3	-	-	-	-0.74 (0.321)	-
Cirney-Mader stage 4	-	-	-	0.94 (0.056)	-
Type of osteomyelitis - exogenous	-	-	-	-	0.53 (0.384)
Type of osteomyelitis – implant related	-	-	-	-	0.37 (0.446)
R Square	0.07	0.02	0.0005	0.09	0.006

WBC: white blood cell.
[a] Constant captured by Cirney-Mader stage 1 in "Stage of osteomyelitis" category and hematogenous osteomyelitis in "Type of osteomyelitis" category
[b] Statistically significant.

Table 5
Results of logistic regression to assess the impact of the number and type of organism isolated from intraoperative culture on chance of recurrence of infection.

Variables	No. of organisms isolated (*p* value)	Type of organism isolated (*p* value)	Preoperative isolation of correct organism (*p* value)
Constant[a]	−2.94 (<0.001)[b]	−2.94 (<0.001)[b]	−1.75 (<0.001)[b]
Single bacterial growth	1.44 (0.172)	–	–
Polybacterial growth	2.58 (0.023)[b]	–	–
Methicillin sensitive *Staphylococcus aureus*	–	1.02 (0.359)	–
Coagulase negative *Staphylococci*	–	0.23 (0.871)	–
Pseudomonas	–	1.55 (0.304)	–
Enterobactericiae	–	1.33 (0.373)	–
Methicillin resistant *Staphylococcus aureus*	–	2.02 (0.063)	–
ESBL producing Enterobactericiae	–	2.43 (0.048)[b]	–
Lack of knowledge of causative organism preoperatively	–	–	0.50 (0.275)
R square	0.06	0.08	0.01

ESBL: extended spectrum beta-lactamase.
[a] Constant captured by culture negative category both in number and type of organism isolated. Regarding whether preoperative isolation of organism was useful, Constant is captured by the category of samples that grew organism in preoperative culture and agreed with those of intraoperative culture.
[b] Statistically significant.

($p < 0.001$), thereby meaning that the observed agreement was better than the expected agreement by chance (Table 6). The knowledge of correct organism was available pre-operatively in 61 out of 147 patients. In the remaining 86 patients, pre-operative sampling could not be done in 41 patients, was culture negative in 13 patients and did not agree with the intra-operative culture with 32 patients. However, lack of knowledge of the right organism before surgery did not affect the chance of recurrence of infection (Table 5).

Discussion

COM is a complex and potentially devastating condition. Appropriate therapy is multimodal and surgical debridement is the cornerstone of management for this challenging problem. Despite best efforts, recurrence continues to be the challenge faced by the treating surgeons. Newer technologies like novel antibiotic laden biomaterials are made available with a view to reducing this complication. Further additions to the armamentarium aiming at reduction of recurrence include: use of artificial intelligence for diagnostics,[20] predictive modelling for risk factors,[21] genomic characterisation for virulence and antibiotic resistance,[22] novel 3D printed customised implants[23] and aggressive, and combined osteo-plastic surgical strategies.[24]

The incidence of recurrence varies from 0% to 48% (Table 7) and depends on many factors like patient age, type and severity of OM, virulence and load of the offending bacteria, immunity of the host

Table 6
Assessment of agreement of the intraoperative bacterium isolated with preoperative sample and those at recurrence.

Parameters	Agreement	Expected agreement	Kappa score	Probability
Agreement between preoperative sinus culture and intraoperative bone culture	59.85%	15.25%	0.526	<0.001[a]
Agreement between organism(s) isolated at index surgery and at recurrence	23.81%	9.81%	0.155	<0.001[a]

[a] Statistically significant.

Table 7
Summary of all studies on chronic osteomyelitis reporting recurrence rate as available in literature.

Study (year)	Inclusion criteria	Sample size (*n*)	Surgical debridement	Local antibiotics	Systemic antibiotics	Recurrence rate (%)
Ellur et al.[4] (2020)	CHOM, age ≤ 15 years	31	Yes	Antibiotic loaded calcuim sulfate pellets	5 weeks	0
Lowneberg et al.[9] (2019)	All ages and aetiologies	127	Yes	None	2 – 6 days	1.6
Petfield et al.[11] (2019)	Posttraumatic COM tibia following wartime open fracture	112	Yes	None	Yes, no mention of duration	28
Masrouha et al.[5] (2018)	Infected non-union	13	Yes	Antibiotic loaded calcuim sulfate pellets	3 – 5 days	0
Jerzy et al.[28] (2018)	All ages and aetiologies	30	Yes	Topically during surgery	6 weeks	5
Pozo et al.[13] (2018)	All ages and aetiologies	116	In 107 patients	None	3 – 4 weeks	22.4
Jorge et al.[14] (2017)	Post traumatic COM, age >12 years	193	Yes	None	Yes, no mention of duration	19.8
Laghmouche et al.[32] (2017)	COM caused by *Pseudomonas aeuroginosa*	67	Yes	None	3 – 13 weeks	20.9
Chadayammuri et al.[12] (2017)	Posttraumatic COM	142	Yes	None	6 weeks	34.5
McNally et al.[26] (2016)	All ages and aetiologies	100	Yes	Gentamicin loaded calcuim sulfate hydroxyapatite biocomposite	6 – 12 weeks	4
Marais et al.[27] (2016)	All ages and aetiologies	26	12 patients in curative, no surgery for 14 patients in palliative group	Antibiotic loaded PMMA beads in 4 patients	6 weeks in curative group, 3 – 6 months in palliative group	4.8
Mondal et al.[29] (2015)	All ages and aetiologies	30	Yes	PMMA beads	2 doses	6.7
Fergeuson et al.[30] (2014)	All ages and aetiologies	195	Yes	Antibiotic loaded calcium sulfate	6 – 12 weeks	9.2
Baldan et al.[33] (2014)	All ages and aetiologies	71	Yes	None	4 weeks	33
Ikpeme et al.[34] (2013)	All ages and aetiologies	44	Yes	Antibiotic loaded PMMA beads in 18 patients	6 weeks	34.1
Mantero et al.[10] (2011)	Age <18 years, all aetiologies	90	Yes	None	6 weeks	12.2
Beckless et al.[31] (2010)	CHOM, age ≤15 years	167	Yes	None	6 weeks	16
Agaja et al.[25] (2008)	All ages and aetiologies	107	Yes	None	6 weeks	2.8
Biruk et al.[6] (2007)	All ages and aetiologies	73	Yes	None	4 – 6 weeks	48
Tice et al.[8] (2003)	All ages and aetiologies	454	None	None	2 – 6 weeks	30.6

COM: chronic osteomyelitis; CHOM: chronic hematogenous osteomyelitis; PMMA: polymethyl methacrylate.

and treatment strategy adopted.[4–6,8–14,25–34] Various authors have tried to study the factors causing recurrence of OM.

Tice et al.[8] in their study on 454 cases of COM treated by outpatient based parenteral therapy alone reported that both initial pathogen and type of antibiotic selected for treatment determined recurrence. *Pseudomonas aeruginosa* posed more than double the risk associated with *Staphylococcus aureus*. Arias et al.[15] conducted an interesting ambispective cohort study in 129 patients with COM. They concluded that patients treated with orthopaedist alone resulted in more recurrence rate than when treated in consultation with an infection disease consultant. In addition, the following factors determined recurrence: age ≥ 57 years, long bone involvement, fracture, monotherapy, receiving less than 4 weeks of antibiotics and inadequate treatment. In their study on 130 cases of posttraumatic OM of tibia, Petfield et al.[11] opined that bone loss, presence of devascularised bone and duration of antibiotic therapy determined recurrence. Chadayammuri et al.[12] in a series of 142 cases of posttraumatic OM determined polymicrobial growth and lack of skin cover to be determining adverse outcome. Sequential administration of parenteral and oral antibiotic therapies was associated with reduced incidence of adverse outcome. Jorge et al.[14] performed a retrospective cohort study in 192 patients with posttraumatic OM. Their view was that elderly patients, intra-operative blood transfusions and *Pseudomonas aeruginosa* were associated with recurrence. Pozo et al.[13] concluded that duration of OM more than 3 months, bone exposure and requirement of additional procedures like flaps contributed to the chance of recurrence. Our data revealed that polymicrobial infection and multi-drug resistant organism (especially ESBL producing *Enterobacteriaceae*) significantly increase the risk of recurrence in COM. Cierny-Mader stage 1, hematogenous variety and culture negative OM were factors reducing the chances of recurrence compared to other respective categories.

The value of pre-operative isolation of bacteria from sinus tract culture is a matter of debate. Some studies have demonstrated excellent agreement between culture from sinus tracts and from sequestra.[35–37] Some others have concluded that sinus tract samples as not reliable as sequestra.[38–41] The low accuracy of sinus tract samples is attributed contamination by skin commensal or external organisms yielding false results. A recently done meta-

analysis demonstrated a concordance rate of 59.41% (with statistical significance) between sinus tract and bone cultures. The concordance was the most with *Staphylococcys aureus* and least with *Enterococcus*.[42] Our data also suggested a concordance rate of 59.85% and moderate agreement as per Kappa value, within the paired sinus and bone samples available. But its value was reduced by the inability to perform sinus culture (41 patients) and lack of growth in sinus culture (13 patients) that puts the value of pre-operative isolation of organism to question. We further found that lack of pre-operative isolation of the correct organism did not increase the chance of recurrence, in spite of the delay in starting the correct antibiotic as per intra-operative sequestrum sample. We believe that the practice of sampling from sinuses may be avoided, especially in resource challenged settings, without any impact on the treatment outcome.

Recurrence of OM after a long symptom free interval has been reported even after 50 years.[43] Many authors believe that bone once infected is infected forever and the outcome of treatment may be expressed as “arrest” or “remission” rather than “cure”. The microbiological patterns of recurrence are not well documented in literature.[44] Recurrence with the same isolate of organism may be called “relapse” and with a different or additional strain may be termed “re-infection”. Contrary to the more popular belief of relapse of dormant infection, Uçkay et al.[45] in their report of 3 cases suggested the possibility of re-infection with different strains without any obvious source. Rather than reactivation of dormant infection, they suggested that the bone once infected becomes a vulnerable area of bacterial adhesion when transient bacteraemia occurs due to any reason, whether obvious or not. This theory strongly resembles the established facts about altered valvular surfaces and infectious endocarditis. One cannot exclude, however, that during surgery another bacterium was introduced that remained dormant for many years.[45] Wang et al.[46] performed reconstruction with induced membrane technique in 424 patients declared to be “cured” of infection. Among them, 52 patients had recurrence of infection. Among them, only 10 (27.8%) patients had the same bacterium as that of original infection. Our data also showed a concordance of 23.81% between organisms isolated at primary and recurrent settings (with poor agreement as per Kappa value), suggesting that re-infection was a stronger reason for recurrence than relapse.

Our study has many limitations. It was retrospective in nature. Patients were not directly assessed as part of the study. Assessment bias is likely as surgeons themselves assessed the outcome. The study population was heterogenous in that many patients had in addition, previous failed treatment, metallic implants, joint involvement, pathological fracture, deformity and nonunion. There was no way to assess retrospectively the adequacy of surgical debridement performed, though all debridements were performed by the same 2 surgeons experienced in bone infection. In cases labelled as relapse, colony variations could not be assessed as samples were not stored. Samples were not subjected for histopathological examination. We also feel that despite clear-cut protocols, there could have been therapeutic bias based on individual variations in clinical presentation and response to treatment. We also acknowledge that we did not have access to the absorbable antibiotic impregnated calcium sulfate pellets. Being a tertiary level charitable super speciality hospital giving treatment completely free of cost to patients coming mostly from poor socio-economic background, its availability was limited by its high cost. We used poly methyl methacrylate cement beads loaded with Vancomycin and Ceftazidime for broad spectrum coverage.[47] To save cost, we pre-fabricated these beads in batches, sterilized them with ethylene oxide and stored them in a sterile manner till they could be completely utilised.[48] Keeping in mind the need for second surgery for removal, we applied antibiotic beads only in cases where there was obvious soft tissue dead space. We are also unable to study the impact of these beads on outcome due to the significant selection bias of using them in cases that were probably severe than the rest.

In patients with COM treated with surgical debridement and post-operative antibiotics, polymicrobial growth and multi-drug resistant organisms, in particular ESBL producing *Enterobacteriaceae*, increase the chance of recurrence. Cierny-Mader stage 1, hematogenous variety and lack of bacterial growth in intra-operative samples reduce the chance of recurrence compared to other respective categories. The concordance between pre-operative sinus culture and intra-operative bone culture is only moderate. Preoperative isolation of organism is of questionable value as lack of this information does not have impact on the outcome. Recurrences of infection do occur and they are more of re-infections than relapses. Diligent isolation of organism must be attempted even in re-debridements. In spite of recurrence, repeat surgical debridement along with appropriate antibiotic therapy yields apparent remission if infection over a reasonable period of follow-up.

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Ethical statement

The study was performed according to the World Medical Association Declaration of Helsinki. Approval of the Institutional Ethics Committee was not required, considering the observational, non-interventional and retrospective nature of the study from medical records. All patients at the time of their respective admissions had given signed informed consent that their clinical data, radiological images and clinical photographs could be used for research and scientific publications.

Declaration of competing interest

All authors declare that they have no conflict of interests.

Author contributions

Koushik Narayan Subramanyam: Conceptualization of study, design of study, verification and cleaning of collected data, analysis of data, writing of manuscript, review and approval of manuscript; Abhishek Vasant Mundargi: Design of study, verification and cleaning of collected data, analysis of data, writing of manuscript, review and approval of manuscript; Milind Vittal Prabhu: Collection of data, writing of manuscript, review and approval of manuscript; K U Gopakumar: Analysis of data, writing of manuscript, review and approval of manuscript; D S Ankush Gowda: Collection of data, writing of manuscript, review and approval of manuscript; Devagiri Raviteja Reddy: Collection of data, writing of manuscript, review and approval of manuscript.

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