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Original Research Article

Orthopaedic implant infections: interplay of associated factors

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ABSTRACT

Background: Medical implants are devices that are placed inside or on the surface of the body for functional, cosmetic or therapeutic purposes. Orthopaedic implants are usually associated with infections which lead to devastating complications for the patients. The study was conducted to evaluate the association of various factors considered to affect orthopaedic implant infections.
Methods: The 100 patients with orthopaedic implant infections were included. Various patient parameters including risk factors, intervention form and type of onset of infection were recorded. Microbiological workup was done by standard techniques along with biofilm detection.
Results: Early onset of infection was prevalent in cases with open fractures. Smoking and tissue destruction were the major risk factors. Longer duration of surgery was associated with early onset and polymicrobial infections. 15.5% of the isolates were strong biofilm producers. *Staphylococcus aureus* was the predominant biofilm producer. More biofilm producing organisms were recovered from stainless steel implants.
Conclusions: Orthopaedic device-related infections lead to extreme morbidity in patients and puts a great encumberance on hospital resources. Various factors affect the outcome of orthopaedic implants. Appropriate infection control and institution specific interventions will help in reducing the magnitude of the problem.

Keywords: Biofilm, Implant, Infection, Prosthetic

INTRODUCTION

Implants are devices that are intended to replace missing body parts or deliver medication, monitor body function or provide support to organs and tissues.[1] Orthopaedic implants can be used to replace or provide fixation of bone, or articulating surfaces of a joint. These include prosthetic joint implants (PJI) and the fracture fixation devices.[2] The implants are highly susceptible to microbial infections which are associated with high rate of morbidity and medical costs.[3] Patients can suffer many interventions (implantation, removal, and re-implantation) along with long term anti-microbial treatment which in turn can be associated with complications such as prolonged hospitalization and a possibility of renewed disability.[4]

Implant related infections can be classified as early (<2 weeks in fixation implants or <3 months in PJI), delayed (2-10 weeks in fixation implants or 3-24 months in PJI) and late (>10 weeks in fixation implants or >24 months in PJI), depending upon the duration of onset of symptoms.[5] Existence within a biofilm is a basic survival mechanism by which microorganisms resist the host immune system and anti-microbial agents. The formation of biofilms is mediated by mechanical, biochemical and genetic

factors.[6] Various risk factors play a role in orthopaedic implant infections which include;

- Location of the implant, open or closed wound.[7]
- Patient modalities (like obesity, diabetes, advanced age, smoking, use of corticosteroids, psoriasis, SLE, hemophilia, rheumatoid arthritis, iron deficiency, etc.).[7]
- Surgical techniques, extended operative duration, higher number of operating room personnel, post operative care and cleanliness.[8]
- Biocompatibility of the material, implant surface properties and design.[8]

Diagnosis of orthopaedic implant related infections remains challenging and a strategy is required with a clear view of the pathogenesis of implant-related infections, with a special attention on the alarming phenomenon of antibiotic resistance.[9] This study was conducted to evaluate the relationship of various factors which are associated with orthopaedic implant infections.

METHODS

It was a cross sectional study conducted in the Department of Microbiology and Department of Orthopaedics, Sher-i-Kashmir Institute of Medical Sciences (SKIMS), a tertiary care institute from August 2014 to February 2016. 100 Orthopaedic implant patients of any age group were included.

Inclusion criteria

Patients presenting with clinical features of infection like fever, local persisting pain, erythema, hematoma, wound healing disturbance in case of early infections; joint pain, loosening of implant in delayed infections; sinuses, aseptic loosening and sepsis in case of late infections were included. The patient demographic characteristics, co-morbid conditions, nature of trauma, type of implant, type and duration of procedure were recorded. Open fractures were classified according to the Revised Gustillo and Anderson classification.[10]

Specimens included were pus (55%) (from implant site/sinus tract), implants (30%), aspirates (8%), tissue specimens (4%) and drain tips (3%). Samples were collected with proper aseptic precautions and subjected to conventional microbiological techniques along with biofilm detection.

Procedures

The basic procedures included Gram staining, followed by identification of the isolates using standard microbiological techniques.[11] Biofilm detection was done by Tissue Culture Plate method described by Christensen et al.[12]

Tissue culture plate method

Organisms isolated from fresh nutrient agar plates were inoculated in 10mL of trypticase soy broth (TSB) with 1% glucose. Broths were incubated at 37ºC for 24 hours and then diluted 1:100 with fresh medium. Individual wells of sterile 96 well-flat bottom polystyrene tissue culture plates were filled with 200µL of these diluted cultures. Negative control wells contained un-inoculated sterile broth. The plates were incubated at 37ºC for 24 hours. After incubation, contents of each well were removed by gentle tapping and then washed with 0.2mL of phosphate buffer saline (pH 7.2) four times to remove the free floating bacteria. Biofilm formed by bacteria adherent to the wells were fixed by 2% sodium acetate and stained by crystal violet (0.1% w/v). Excess stain was removed using de-ionized water and plates kept for drying. Optical density (OD) of stained adherent biofilm was obtained using micro ELISA auto-reader (BIO RAD iMark™ Microplate Reader, Series No.13272) at the wavelength of 570nm. Biofilm interpretation was done with Stepanovic Method as detailed in Table 1.[13]

Table 1: Interpretation of biofilm production.

Average OD value	Biofilm production
≤ ODc / ODc < ~ ≤ 2x ODc	Non/weak
2x ODc < ~ ≤ 4x ODc	Moderate
> 4x ODc	Strong
Optical density cut-off value (ODc) = average OD of negative control + 3x standard deviation (SD) of negative control.	

Statistical analysis was done by SPSS version 12. The results obtained were discussed on 5% level of significance and p-value <0.05 was considered significant.

RESULTS

Among 100 patients, the most commonly affected site was femur [34(%)], followed by tibia [27(%)], humerus [11(%)], and other sites [19(%)]. Depending upon the type of procedures, 91 patients had insertion of fixators and 9 had prosthesis insertion. The surgical procedures involved were categorized as fixation and replacement procedures (Table 2).

Table 2: Distribution of various surgical procedures in patients.

Orthopaedic Implant Procedures	N (%)
Extra Medullary Fixation	58 (%)
Intra Medullary Fixation	33 (%)
Total Knee Replacement (TKR)	5 (%)
Total Hip Replacement (THR)	4 (%)
Total	100

In our study 55 patients underwent secondary surgical procedures. Average duration to revision procedure was 22.14 weeks from the date of implant insertion (Table 3).

Table 3: Distribution of revision/secondary surgical procedures in patients with orthopaedic implants.

Total Patients	N=100(%)
Total secondary surgical procedures	55(%)
> 1 secondary surgical procedure	17(%)
Removal of implant	45(%)
Drainage/ debridement	10(%)
Insertion of other implant	14(%)

Emergency surgeries had been done in 69 (%) patients and 26 (28.6%) cases had extensive trauma (Table 4) Stainless steel implants were used in 64 (%) patients, titanium in 26 (%) and miscellaneous in 10 (%) patients. 32 (%) cases had early onset, 47 (%) had delayed and 21 (%) cases had late onset of infection.

Of the 100 patients 97 isolates were recovered. Methicillin resistant *Staphylococcus aureus* (MRSA) and coagulase negative *Staphylococcus* (CoNS) were the most prevalent organisms in early onset infection and Methicillin sensitive *Staphylococcus aureus* (MSSA) in delayed onset. However, in late onset infection *Citrobacter* spp. (19%) and *Enterococcus* spp (19%) were most prevalent (Table 5).

Patients with fixation procedures developed more of early [43(47.3%)] and delayed [32 (35.2%)] onset infections and these infections [delayed (27) and early (10)] were common among younger age group (20-39 yrs) (Table 6). The joint replacement procedures had more of late onset infections [5(55%)] and were more among higher age groups [60 yrs and above] in which the insertion of prosthesis is common (Table 7).

Table 4: Distribution of type of injury in patients and various orthopaedic interventions.

Type of Injury (fractures)	N=91(%)
Open fractures	41 (45.1%)
Closed fractures	50 (54.9%)
Open fractures with extensive trauma (Gustillo classes IIIa (N=14) and IIIb (N=12)	26 (28.6%)
Type of initial surgical intervention	**N=100 (%)**
Emergency surgeries	69 (%)
Elective surgeries	31 (%)
Fracture fixation surgeries	**N=91(%)**
Open reduction	69 (75.8%)
Closed reduction	22 (24.2%)

Smoking (38), anemia (28%), extensive trauma (26%) and diabetes (13%) were the major risk factors associated with our cases (Table 8). Early onset of infection [25 (61%)] was predominant in open fractures followed by delayed [10 (24.4%)] and late onset [6(14.6%)] infections. However, in case of closed fractures, delayed onset of infection [N=33(66%)] was more prevalent than late [10 (20.0%)] and early onset [7(14.0%)] infections.

Comparing the onset of infection for each class in Gustillo's classification of open fractures, it was seen that early onset infections were more prevalent in classes II, IIIa and IIIb respectively.[10] No patient was reported in class IIIc in our study (Table 9).

Table 5: The prevalence of various Gram positive and Gram negative organisms cultured from different samples in relation to the onset of infection.

Organism	Early (N)	%	Delayed (N)	%	Late (N)	%
MRSA	6	20.0	9	19.6	3	14.3
MSSA	5	16.7	10	21.7	3	14.3
CoNS	6	20.0	1	2.2	3	14.3
Enterococcus spp.	2	6.7	1	2.2	4	19.0
Acinetobacter spp.	3	10.0	5	10.9	1	4.8
Citrobacter spp.	3	10.0	9	19.6	4	19.0
Escherichia coli	3	10.0	3	6.5	2	9.5
Klebsiella spp.	0	0.0	3	6.5	1	4.8
Pseudomonas spp.	0	0.0	3	6.5	0	0.0
Serratia spp.	2	6.7	1	2.2	0	0.0
Enterobacter spp.	0	0.0	1	2.2	0	0.0

A significant relationship between the duration of surgery and onset of infection was observed. When the duration was greater than 60 minutes, early onset infections (44.2%) were predominant as compared to delayed onset infections in surgeries performed in less than 60 minutes (69.2%) (Table 10).

Table 6: Comparison of age group distribution in relation to the onset of infection for patients with fracture/fixators.

Fixators	Onset of infection			
Age Group (in years)	**Early (< 2 weeks)**	**Delayed (2-10 weeks)**	**Late (>10 weeks)**	**Total**
0-19	10	4	2	16
20-39	10	27	5	42
40-59	9	7	9	25
60 or above	3	5	0	8
Total N (%)	32 (35.2%)	43(47.3%)	16 (17.6%)	91

Table 7: Comparison of age group distribution in relation to the onset of infection for patients with prosthetic implants.

PJI	Onset of infection			
Age Group (in years)	**Early (<3 months)**	**Delayed (3-24 months)**	**Late (>24 months)**	**Total**
0-19	0	0	0	0
20-39	0	0	0	0
40-59	0	1	2	3
60 or above	0	3	3	6
Total N (%)	0	4 (45%)	5 (55%)	9

Table 8: Associated risk factors and their relationship to the onset of infection.

Risk factor	Early		Delayed		Late		Total
	N	**%**	**N**	**%**	**N**	**%**	
Smoking	15	39.5%	15	39.5%	8	21.1%	38
Anemia	9	32.1%	12	42.9%	7	25.0%	28
Hypertension	8	29.6%	10	37.0%	9	33.3%	27
Extensive Trauma	9	34.6%	9	34.6%	8	30.8%	26
Diabetes	1	7.7%	4	30.8%	8	61.5%	13
Osteoarthritis	2	15.4%	7	53.8%	4	30.8%	13
Obesity	1	8.3%	8	66.6%	3	25.0%	12
UTI	0	0.0%	4	33.3%	8	66.7%	12
COPD	4	33.3%	4	33.3%	3	25.0%	11
Osteomyelitis	1	20.0%	2	40.0%	2	40.0%	5
Extra articular infection	0	0.0%	2	50.0%	2	50.0%	4
Dental Infection	1	33.3%	2	66.7%	0	0.0%	3
Malignancy	0	0.0%	0	0.0%	2	100.0%	2
Psoriatic Arthritis	1	50.0%	1	50.0%	0	0.0%	2
Renal failure	0	0.0%	2	100.0%	0	0.0%	2
Cardiac Failure	2	100.0%	0	0.0%	0	0.0%	2
Immunosuppression	0	0.0%	1	100.0%	0	0.0%	1

Dominance of poly-microbial infections with isolation of more than one organism was seen in infected patients who had undergone surgical procedures with duration of more than 60 minutes (72.7%). However, when the duration of surgery was less than 60 minutes, mono-microbial infections (42.7%) were predominant (Table 11).

In cases where stainless steel implants were used, delayed onset of infection comprised of 53.13% followed by early onset infection (32.8%) and in cases using titanium implants early onset were predominant (38.4%) followed by delayed onset (34.6%) infections (Table 12).

Citrobacter spp. (20.6%) was found to be more prevalent in cases where orthopaedic implantation was done under emergency conditions.

In cases where elective procedures were performed, *Staphylococci* spp. [MSSA (24.1%)], MRSA (17.2%) and CoNS (6.9%)] were mostly isolated (Table 13).

The biofilm detection method was carried in all the 97 isolates. 15 (15.5%) isolates were strong biofilm producers, 4 (4.1%) were moderate and 78 (80.4%) were non/weak biofilm producers.

Table 9: Comparison of onset of infection in relation to Gustillo's classification of open fractures.

Gustillo Class (N)	Early N (%)	Delayed N (%)	Late N (%)
I (5)	1 (20.0%)	4 (80.0%)	0 (0.0%)
II (10)	5 (50.0%)	2 (20.0%)	3 (30.0%)
IIIa (14)	11 (78.6%)	2 (14.3%)	1 (7.1%)
IIIb (12)	8 (66.7%)	2 (16.7%)	2 (16.7%)
IIIc (0)	0 (0%)	0 (0%)	0 (0%)

Table 10: Onset of infection in relation to the duration of surgical procedure.

Duration of surgery in minutes	Early N (%)	Delayed N (%)	Late N (%)
< 60 minutes (N=37)	7 (12.8%)	23 (69.2%)	7 (17.9%)
> 60 minutes (N=63)	25 (44.2%)	24 (32.7%)	14 (22.9%)
Total	32	47	21

Table 11: Comparison of duration of surgical procedure in relation to poly/mono-microbial infections.

Duration of Surgery	Mono-microbial (N=75)	Poly-microbial (N=11)	Culture Negative (N=14)
< 60 minutes (N=37)	32 (42.7%)	3 (27.3%)	2 (14.3%)
> 60 minutes (N=63)	43 (57.3%)	8 (72.7%)	12 (85.7%)

Table 12: Comparison of onset of infection in relation to the material of orthopaedic implant.

Material of Implant	Early N (%)	Delayed N (%)	Late N (%)
Stainless steel	21 (32.8%)	34 (53.1%)	9 (14%)
Titanium	10 (38.4%)	9 (34.6%)	7 (26.9%)
Others	1 (10.0%)	4 (40.0%)	5 (50.0%)

Table 13: Prevalence of different organisms cultured in relation to the elective or emergency surgical procedure.

Organism	Emergency Surgery (N=68) (%)	Elective Surgery (N=29) (%)
Acinetobacter spp.	7 (10.3%)	2 (6.9%)
Citrobacter spp.	14 (20.6%)	2 (6.9%)
Escherichia coli	4 (5.9%)	4 (13.8%)
Enterobacter spp.	1 (1.5%)	0 (0.0%)
Enterococcus spp.	4 (5.9%)	3 (10.3%)
Klebsiella spp.	2 (2.9%)	2 (6.9%)
CoNS	8 (11.8%)	2 (6.9%)
Pseudomonas spp.	1 (1.5%)	2 (6.9%)
Serratia spp.	3 (4.4%)	0 (0.0%)
MRSA	13 (19.1%)	5 (17.2%)
MSSA	11 (16.2%)	7 (24.1%)
Total	68	29

Table 14: Comparison of Biofilms detected in relation to the material of orthopaedic implants.

Material of implant	Implants, N	Organisms, N	Strong N (%)	Moderate N (%)	Weak N (%)
Steel	64	65	11 (16.92%)	2 (3.08%)	52 (80.00%)
Titanium	26	24	2 (8.33%)	1 (4.17%)	21 (87.50%)
Others	00	8	2 (25.00%)	1 (12.50%)	5 (62.50%)

It was seen that stainless steel implants produced more strong biofilms (16.92%) as compared to the titanium implants (8.33%) (Table 14).

DISCUSSION

Orthopaedic implant surgeries are quite common in the modern era.[14] Fixation implants are temporarily required while as prosthetic joints replace the irreversibly damaged articulating surfaces of a joint in patients with osteoarthritis or inflammatory arthritis.[15] Microorganisms attached to these implants defy removal by host defenses.[16] Patient may suffer multiple surgeries with a prolonged period of disability. [17]

In our study 47 (47%) patients presented with delayed onset of infection, 32 (32%) with early and 21 (21%) presented with late onset infections. Giulieri SG et al, also found delayed onset (41%) of infections more frequent among 60 arthroplasty patients in their study.[18] However early onset of infection (72.9%) was most common in a study by Khosravi et al. including 165 patients with orthopaedic implant infections.[19]

The preponderance of early and delayed infections is attributed to the fact that these infections are exogenously acquired and may be related to inadequate infection control practices . It was also seen that the most common organisms in early and delayed onset infections were the hospital acquired bugs like MRSA, CoNS and *Citrobacter* spp.

Late onset infections are associated with prosthetic joints which remain susceptible to hematogenous seeding during their entire lifetime.[20] In our study, late onset infections (21%) were predominant in cases of prosthesis insertion. However, due to small sample size of these patients, it was not found to be statistically significant. Similar findings have been reported by Fernandes et al in their study.[3] However Laffer reported early onset (45%) as most prevalent in patients with prosthetic infections.[21] *Enterococcus* spp. and *Citrobacter* spp. were the main organisms isolated in our patients with prosthetic infections.

Further in our study, early infection was seen to be more common in patients with open fractures belonging to the Gustillo's wound class III A and III B. In case of open fractures, extensive tissue damage and break down of the tissue barrier between the fracture zone and the environment leaves the underlying bone prone to direct contact with contaminating agents. The management of such fractures thus continues to be a challenge for the orthopaedic surgeons. With early appropriate antibiotic administration, meticulous irrigation and debridement, the rates of infection can be dramatically decreased. Early closure of open fractures should also be done to decrease the rate of infection.

In this study most of the early and delayed onset infections were seen in the 20-39 years age group in fracture patients. This was found to be statistically significant. It may be because majority of our patients were from this age group which is more likely affected by open fractures and hence earlier infections. Similar findings were reported by Arruda et al who found the maximum number of open fractures in the working age group of 21 -30 years, presenting with early onset complications.[22]

Secondary surgical procedures as well as revision surgeries are quite common in orthopaedic implant infections. In our study 55% patients had undergone secondary surgical procedures which included removal of the implant in 45% and drainage /debridement in 10%. Similarly, Fernandes et al reported removal of the implants in 50% patients in their study.[3]

The risk of infection in a patient with orthopaedic implant is affected by the patient's co-morbidities. In our study the major patient associated risk factors were diabetes, smoking, anemia and extensive trauma. Similar associated factors were reported in a study by Jain BK et al.[23] Infection in diabetic patients is higher due to increased biofilm formation in the presence of elevated glucose levels, impaired leukocyte function or micro-vascular changes which may influence wound healing and lead to superficial surgical site infections.[24]

It was seen that 38% of the cases in our study were smokers. Smoking is reported as a factor responsible for increasing the risk of surgical site infection as nicotine, nitric oxide, carbon monoxide directly alter the wound healing process.[26] Peri-operative smoking cessation seems to be an effective measure to reduce postoperative complications. In orthopedic infections smoking has been reported as an important risk factor in studies by Durand F and Singh JA.[25,26]

Duration of the surgical procedure has also a direct bearing on the onset of infection. It was seen that in cases where the surgery duration was more than 60 minutes, the patients presented with more of the early onset infections [N=25(44.26%)]. This was in sharp contrast to the lower percentage of early onset infection [N=7 (12.82%)] in the patients where the duration of surgery was less than 60 minutes. It was found to be statistically significant and could be attributed to the fact that greater the duration of the surgery, more is the time period during which the operating site is exposed and thus more chances of getting infected by the organisms present in the surroundings. Ercole FF et al, has reported the duration of surgery as an important factor in surgical site infections.[27] Longer duration surgeries are also associated with team fatigue, enhanced technical errors and decreased systemic defenses leading to increasing infections.[28]

There are higher rates of infection in emergency surgeries as compared to the elective ones. It is due to insufficient

preoperative preparation, underlying conditions predisposing to emergency surgery and higher frequency of contaminated wounds in emergency surgeries. In our study more emergency surgical procedures were performed than the elective ones. *Citrobacter* spp. which are generally considered as contaminants were prevalent among these emergency cases followed by other Gram negative organisms. However, in elective procedures *Staphylococci* spp. which are generally colonizers were predominant. Thus, there is an urgent need of microbiological surveillance to find out the cause of this occurrence and the main source of these contaminants in our hospital. Source of contaminants have been traced to the hospital design or hospital resources as reported by Moges F et al.[29]

Implant materials can act as an avenue for both bacterial contamination and colonization. In our study, both stainless steel and titanium implants were associated more with early and delayed onset than late onset infections. The difference in the onset and rate of infection between the two materials which is otherwise well known was not seen in our study. This could be due to the presence of nosocomial organisms in higher percentage in our hospital environment and also because of inadequate infection control practices, thus making titanium equally vulnerable to the infecting organisms as stainless steel, though titanium has been known to have better biomechanical properties. Arens S et al, have reported higher stainless steel implant infection rates as compared to titanium implants.[30]

Biofilms play a pivotal role in healthcare-associated infections, particularly in the implantation of medical devices. A worrying feature of such infections is represented by higher antibiotic resistance of bacterial and fungal cells growing as biofilms as compared with planktonic cells.[31] In the present study, biofilm detection was done by Christensen's tissue culture method which has been reported to be quantifiable and reliable method of detecting biofilms.

Properties of the substrate (chemical composition, surface charge, hydrophobicity, surface roughness) are thought to be important in the initial bacterial attachment process.[2] In this study there was a higher percentage of strong biofilm producing organisms in cases with stainless steel (16.92%) as compared to titanium implants (8.33%). Clauss M et al, in their study also reported that titanium implants had lesser degree of biofilm production.[32]

CONCLUSION

It is evident from our study that multiple institution specific interventions along with proper infection control measures need to be taken on priority basis to decrease the infection rates in orthopaedic implant patients. The relationship and interplay of different variables will require focus and longer duration studies to increase knowledge related to our settings in order to improve the orthopaedic as well as the microbiological management of the infections associated with orthopaedic implants.

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