

## Original Research Article

# A retrospective observational study of traumatic orthopaedic related infections in Cambodia

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### ABSTRACT

**Background:** The objective of this study was to establish the type of microbiology along with antimicrobial resistance related to orthopedic related trauma infections in this area in order to help guide diagnosis and treatment regimens.

**Methods:** This study evaluated the microbial etiology of orthopedic-related infections (ORI) between September 2015 and September 2016 in three tertiary hospitals in Phnom Penh, Cambodia. Clinical records were for clinical features and demographics. Standard laboratory bacteriology was used to recover, identify and perform antibiotic susceptibility testing (AST) by disk diffusion or broth microdilution.

**Results:** 119 patients were categorized as ORI cases. In the cases identified, median interquartile range (IQR) age was 38 (IQR: 26-46) years and 80.0% were male. Of the 119 ORI cases, a total of 156 bacterial strains were recovered, identified and after review, 128 of these pathogenic bacterial strains underwent AST. Among the gram-positive pathogens, the following susceptibilities were as follows: *Staphylococcus aureus* (n=57) (Methicillin-resistant *S. aureus* (n=35; 61.4%), (Methicillin-sensitive *S. aureus* (n=22; 38.6%)), coagulase-negative *staphylococcus* (all MS-CoNS; n=6) and four isolates of *Enterococcus* sp. (non-VRE). A total of 44 gram-negative pathogens were recovered and AST was performed. Among these 44, a total of nine extended-spectrum beta-lactamase (ESBL) producing strains (20.5%) were discovered including *Escherichia coli* (n=8), *Klebsiella pneumoniae* (n=1) and carbapenemase-resistant *Enterobacteriaceae* (CRE) (*Morganella morganii*). In addition, a single *E. coli* isolate contained both the ESBL and CRE genotypes was noted.

**Conclusions:** This data suggests that ORI rates in Cambodia appear to be comparable to other studies in the literature. However, further studies need to be done in order to establish definitive data related to orthopedic infections in the region.

**Keywords:** Cambodia, Orthopedic related infections, Microbiology, Antimicrobial resistance

## INTRODUCTION

Infections remain a significant cause of morbidity and mortality in orthopedic surgery which frequently involve the placement of artificial implants and sometimes are associated with related infections (National Healthcare Safety Network; NHSN).<sup>1</sup> Such infections continue to remain a complicated issue to treat, especially in patients with concomitant co-morbidities and underlying illnesses.<sup>2,3</sup> The most common pathogen in orthopedic-related infections (ORI) is *Staphylococcus spp.* in both developed and developing countries NHSN.<sup>4-7</sup> Species of the genus *Enterobacteriaceae* are becoming an increasingly global healthcare concern due to development of multiple-drug resistant (MDR) phenotypes, including orthopedic patients.<sup>7-13</sup>

Risk factors for ORIs include advancing age, previous surgeries, recent surgeries in other sites, urinary tract infections, nursing home admissions and previous antibiotics.<sup>14,15</sup> In addition to these risk factors, developing countries tend to have additional problems such as the lack of accurate data collection, lack of adequate microbiological facilities and lack of availability of appropriate antibiotics to treat MDR pathogens.

The objective of this study was to establish the type of microbiology along with antimicrobial resistance related to orthopedic related trauma infections in this area in order to help guide diagnosis and treatment regimens.

## METHODS

This study was conducted as a cross-sectional observational study of ORI cases enrolled from September 2015 through September 2016 from two regional hospitals in Phnom Penh, Cambodia: Children’s Surgical Services, and the Preah Ketmealea Military Hospital (no ORI cases were enrolled from the Kampong Cham Provincial Hospital). For all ORI cases, clinical data, including available demographics (age, sex, white blood cell counts, etc.) and comprehensive laboratory

results, including the identification of pathogens and antibiotic susceptibility testing (AST) results, were merged, validated and statistically analyzed. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). Continuous variables were determined to be non-normally distributed and as such, non-parametric testing was conducted. Continuous variables were expressed as the median value straddled by the interquartile range. All categorical variables were reported as counts and percentage. Clinical specimens were collected by a standardized method.<sup>16</sup> Bacterial isolates were identified based on standardized laboratory bacteriology methods.<sup>17</sup> Once the pathogen(s) were identified, appropriate AST was performed and antibiotic break-points were interpreted based on the clinical and laboratory standards institute (CLSI) guidelines.<sup>18</sup> No anaerobic bacteriology was performed for this study.

Inclusion criteria for this study requires the definite diagnosis of an ORI with the documented recovery, identification and AST of bacterial pathogen recovered from clinical specimens collected from the wound.<sup>16,17</sup>

Exclusion criteria for this study was based on an indeterminate or negative diagnosis of an ORI and the failure to recover pathogenic bacterial specimens or the recovered and identification of bacteria determined to be a contaminant. Since the study did not include patients but only laboratory data with no patient identification, there was no need for ethical approval for this study.

## RESULTS

A total 119 ORI cases met the study inclusion criteria, resulting in the recovery and identification of 156 bacterial strains. From the 156 isolates, it was determined that 128 bacterial specimens would undergo AST testing. There were two ORI patients with concomitant bacteremia (*Escherichia coli* (n=1) and *Enterobacteriaceae cloacae* (n=1)). Tables 1 and 2 summarize the microbiological data obtained in this study along with the AST.

**Table 1: Orthopedic-related infections - gram positive pathogens antimicrobial susceptibility testing results; *Staphylococcus sp.* and *Streptococcus sp.***

Antibiotics	<i>Staphylococcus aureus</i> (n=57)	<i>Staphylococcus</i> (Coag-Neg) (n=6)	<i>Streptococcus sp.</i> (n=14)
	Susceptible (n/N%)	Susceptible (n/N%)	Susceptible (n/N%)
Cefepime	NA	NA	3/5 (60.0%)
Ceftriaxone	NA	NA	2/5 (40.0%)
Chloramphenicol	47/57 (82.5%)	5/6 (83.3%)	NA
Ciprofloxacin	25/57 (43.9%)	6/6 (100.0%)	NA
Clindamycin	17/57 (29.8%)	5/6 (83.3%)	7/9 (77.8%)
Erythromycin	18/57 (31.6%)	3/6 (50.0%)	6/10 (60.0%)
Gentamicin	32/34 (56.1%)	5/6 (83.3%)	NA
Oxacillin	24/57 (42.1%)	5/6 (83.3%)	NA
Penicillin G	NA	NA	11/11 (100%)
Tetracycline	27/46 (58.7%)	6/6 (100.0%)	NA

Continued.

Antibiotics	<i>Staphylococcus aureus</i> (n=57)	<i>Staphylococcus</i> (Coag-Neg) (n=6)	<i>Streptococcus</i> sp. (n=14)
	Susceptible (n/N%)	Susceptible (n/N%)	Susceptible (n/N%)
SXT	38/57 (67.8%)	6/6 (100.0%)	NA
Vancomycin	NA	NA	5/5 (100%)

Note: Not all recovered isolates were tested for antimicrobial susceptibility.

**Table 2: Orthopedic-related infections - gram negative pathogens antimicrobial susceptibility testing stratified by glucose fermenters.**

Antibiotics	Gram negative - glucose fermenters <sup>a</sup>		Gram negative - glucose non-fermenters <sup>b</sup>
	ESBL-CRE (n=9) <sup>c</sup>	Non-ESBL (n=32)	
Amoxicillin	4/9 (44.4%)	11/20 (55.0%)	1/1 (100.0%)
Ampicillin	9/9 (100%)	3/19 (15.8%)	0
Ampicillin-sulbactam	NA	NA	1/1 (100.0%)
Aztreonam	NA	NA	6/14 (42.9%)
Cefazolin	0/9 (0.0%)	5/19	NA
Ceftazidime	2/9 (22.2%)	NA	5/5 (100.0%)
Ceftriaxone	0/9 (0.0%)	15/20	0/1 (0.0%)
Chloramphenicol	8/9 (33.3%)	11/19	NA
Ciprofloxacin	3/9 (33.3%)	NA	4/4 (100.0%)
Colistin	NA	NA	2/2 (100.0%)
Doxycycline	NA	NA	3/3 (100.0%)
Gentamicin	3/9 (33.3%)	NA	2/4 (50.0%)
Imipenem	7/9 (77.8%)	NA	5/5 (100.0%)
Meropenem	8/9 (88.9%)	19/19 (100.0%)	1/1 (100.0%)
Piperacillin	NA	NA	2/2 (100.0%)
Tetracycline	1/9 (11.1%)	3/6 (50.0%)	NA
SXT	1/9 (11.1%)	5/10 (50.0%)	NA
Tobramycin	NA	NA	8/10 (80.0%)

a. *Aeromonas* sp. (n=2), *Citrobacter* sp. (n=1), *Enterobacter* sp. (n=12), *Escherichia* sp. (n=63), *Klebsiella* sp. (n=8), *Morganella* sp. (n=4), *Proteus* sp. (n=7); b. *Achromobacter* sp. (n=3), *Acinetobacter* sp. (n=1), *Bordetella* sp. (n=1), *Burkholderia* sp. (n=1), and *Pseudomonas* sp. (n=11); c. *Klebsiella pneumoniae* (n=4) and *E. coli* (n=52). Carbapenemase-resistant *Enterobacteriaceae* (CRE).

The NHSN report showed that the overall rate of surgical site infection after open reduction and internal fixation of tibial plateau fractures during the seven years of this study was 7.8%.<sup>19-21</sup> At the present time, there is no data available in Cambodia documenting the rates of ORI nor the types of pathogens causing these infections and the antibiotic susceptibility patterns, except for one study that described MDR in wounds at a surgical center in 2011-2013.<sup>4</sup>

## DISCUSSION

ORIs are primarily caused by bacteria growing and producing biofilms on foreign material and in necrotic bone tissue. This makes it extremely difficult to collection a proper clinical specimen which can lead to unreliable laboratory results. Cultures taken from an open wound at the time of initial fracture fixation do not correlate with an eventual later infection and should be avoided. This is a mistake that is often repeated in clinical practice and leads to false positive cultures and often misuse of antibiotics.<sup>22</sup> In addition, repeated swab cultures at the time of revision surgery do not necessarily reflect the pathogens in the bone and are therefore not recommended.<sup>23</sup> Hence, in cases where infection is

suspected, at least three bone biopsies should be taken in the regions of suspected infection such as necrotic bone tissue or non-unions.<sup>24</sup> Repeated growth of the same pathogen, cultured in at least two separated biopsies, is believed to be relevant. This method can be used in developing countries where the availability of advanced molecular procedures is severely limited. There is some data to suggest that in cases of virulent species such as *S. aureus* or *E. coli*, a single positive biopsy may be adequate to suggest a true infection.<sup>24</sup> Standard laboratory guidelines set a duration of wound culture incubation from 7 up to 14 day.<sup>17</sup>

The polymerase chain reaction (PCR) to rapidly identify the wound etiology or even possible to identify pathogens that may be unculturable, including aerobic incubation is becoming a gold standard test in many areas of the laboratory; although published reports on its use in ORI is still being debated due to its low sensitivity and the polymicrobial nature of wounds.<sup>25</sup> It is increasingly being used to identify difficult to culture or non-culturable bacteria, especially after antibiotic pre-treatment.<sup>26,27</sup> At the present time, antibiotic loaded implants and devices are used as options in developing countries as an alternative to intravascular administration of antibiotics due to cost saving considerations. These may, over time,

become contraindicated in countries with high endemic rates of MDR.<sup>28</sup> Other options include the use of silver due to low resistance rates in clinical isolates. Antimicrobial peptides are also emerging as possible options since at the present time; they do not seem to induce resistance within pathogens after exposure.<sup>29</sup> Finally, antibiotic loaded hydrogels may offer benefits in treating complex wounds and tissue infections, although further studies need to be done to validate this approach.

In developing countries, complications due to skin and soft tissue infections (SSTI) and osteomyelitis result in the majority of would-associated orthopedic infections. In addition, it has to be noted that hardware related infections appear to cause of number of wound infections as well.<sup>19,20,30</sup> Thus, the conditions of skin and soft tissues overlying fractures or hardware may be significantly different in different clinical scenarios. For example, in trauma, there may be significant damage to overlying tissues, with extensive vasculature compromise and bacterial infection. Such vascular and tissue damage can impair tissue healing as well as host defenses. Furthermore, trauma patients may also require repeated surgical interventions for definitive fixation, debridement, and plastic surgery reconstruction, which are not routine in primary arthroplasty.

The US CDC classification divides SSTIs into superficial, deep incisional, and organ/space infections, and this is a useful concept when treating hardware and trauma wounds.<sup>31</sup> In this study, some patients had both superficial SSTI, and hardware related infections. The pathogens associated with ORI range from *Staphylococcus* in most of the series to gram-negative pathogens including ESBL.<sup>4,19,30</sup> In a study done by Ercole and colleagues, *Staphylococcus* species were found to be the most prevalent etiological agents in orthopedic infections, representing 75.3% of all infections with 78.1% of the isolates obtained from the orthopedic hardware group, closely followed by *Staphylococcus epidermidis* in the presence of a foreign body.<sup>6</sup> In this cohort, we noted that the *Staphylococcus* species also appeared to be the predominant species isolated in all ORIs. MDR (including ESBL) was also seen in this study and appeared to be comparable to the current medical literature.<sup>12,32,33</sup>

## CONCLUSION

Developing countries face several challenges that are not usually met in the developed world, including poorly developed public health systems where accurate data is not maintained, poor follow up after surgery with inaccurate documentation of post-op infections, poor hygiene and wound care postoperatively, inadequate microbiological diagnosis and lack of appropriate antibiotic therapy to treat infections. Limitations to this study include a lack of robust numbers with all the clinical data needed to make reproducible studies, and a lack of outcome data. Despite these issues, progress has

been made in countries like Cambodia, where orthopedic implants are now being increasingly done. Some recommendations can be made based on this limited study, such as using one of two regional hospitals for orthopedic surgeries where the appropriate technical, laboratory and medical expertise is available to support the service. Quality control measures need to be implemented to make sure that antibiotic susceptibilities of the pathogens are accurately documented, and then based on accurate data, the hospital will need to acquire the appropriate antibiotics to treat acquired infections. Treating ORI in developing countries results in significant socio-economic costs to the health care system and recovery is protracted in many cases due to other factors such as lack of medications, access to the hospitals and appropriate antimicrobials and diagnostic tools.

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