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Systematic review of the microbiology of osteomyelitis associated with war injuries in the Middle East and North Africa

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ABSTRACT
Osteomyelitis is a serious complication associated with war-related limb injuries requiring complicated treatment regimens and management. Few reports have been published from the Middle-East and North-Africa regions about the microbial aetiology of osteomyelitis caused by war injuries. The aim of this review is to collect published data about the microbiology of osteomyelitis in war-related injuries in the region and to derive targeted treatment regimens to manage these serious and limb-threatening infections. A thorough literature search was done using six search engines for pertinent articles. Articles with a minimum of five cases of osteomyelitis from war wounds, citation of microbial aetiology and mention of the timing of cultures obtained in relation to injury were included. Nine studies that met the eligibility criteria were included, involving 1644 patients and a total of 2332 cultures. Gram-negative bacteria were isolated from 1184 cultures, and Gram-positive bacteria were identified from 1148 cultures. Antibiotic coverage should be tailored for Gram-negative organisms in the early stages and Gram-positives in the chronic phase, respectively, with broader coverage reserved for critically ill patients. There is a dire need for further and larger studies about osteomyelitis from war injuries for targeted treatment.

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KEYWORDS War; conflict; infection; injury; osteomyelitis; drug resistance

Introduction

Wars are notorious for the devastating injuries they produce, causing massive destruction to various aspects of the community. War wounds are extremely hard to manage due to the mode of injury, whether

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blasts or gunshot wounds, in addition to other challenges to care such as inadequately equipped primary care centres and the wide array of microbiological pathogens involved (Belmont, Owens, and Schoenfeld 2016). Wars affect a large number of people and result in major population displacement and an influx of patients to unprepared medical centres. This negatively affects the quality of care provided, ranging from primary to tertiary care endpoints (Toole 1995). Conflict wounds have been increasingly associated with multi-drug resistant (MDR) bacteria resulting in increased morbidity and treatment costs; infections with MDR bacteria are difficult to treat and warrant longer antibiotic courses (Sahli, Bizri, and Abu-Sittah 2016).

Experience gained over the past years and technological advances have led to the adoption of several measures in order to improve survival in modern conflicts. Armoured vehicles, individual body armour, and casualty care and resuscitation have all been intensively developed. These measures have improved survival rates and decreased limb amputations from war injuries. This came with the cost of salvaging injured limbs with extensive damage and infections. A major burden of war-related infections comes from osteomyelitis, the treatment of which may incur multiple surgical procedures and long courses of antibiotics, further complicated by MDR bacteria (Burns et al. 2012). In the literature, acute osteomyelitic infections caused by war injuries have been associated with Gram-negative bacteria, while chronic cases have been mostly associated with Gram-positive bacteria (Davis et al. 2005). The treatment of this serious condition in the presence of MDR bacteria poses major challenges stemming from the use of expensive and potentially toxic antibiotics and prolonged treatment courses (Murphy et al. 2011). The morbidity associated with osteomyelitis remains uncomfortably high despite the advanced treatment modalities used.

Aim of the study

Although osteomyelitis is a complex phenomenon caused by many factors contributing to its occurrence and severity, the microbiology of osteomyelitis is important and carries significant epidemiological and therapeutic implications. In this review, we try to identify the pathogens most associated with osteomyelitis in conflict wounds. This would facilitate the initiation of appropriate antibiotic therapy in patients with war wound osteomyelitis and may prove to be lifesaving, especially in critically ill patients. This is the first review of all published reports of war-related osteomyelitis in the Middle East and North Africa (MENA) region.

Methods

A thorough literature review of the following six databases was carried out to find pertinent articles: Cochrane Library, EMBASE, Global Health Library, Scopus, Medline and PubMed. The article search was based on all articles ever published including any MeSH (Medical Subject Headings) terms of war AND osteomyelitis up to 2021. A flowchart for the selection of articles is shown in Figure 1. Two researchers independently went over the article titles and abstracts. Relevant articles were read thoroughly for any citation of the microbiology of osteomyelitis in war and combat wounds. The search criteria for including an article in our review were as follows: a minimum of 5 cases of osteomyelitis from war wounds, citation of microbial aetiology and mention of the chronology of cultures obtained. Information extracted from the articles included the time range from injury to culture, number of patients in the study, geographic location where the injuries occurred, and the culture results. Data regarding multi-drug resistance from the isolated organisms were not stated in all the reviewed papers and are mentioned in our text only where available. Data were further divided into acute and chronic osteomyelitis cases based on the presentation provided by the study designs, with 2 weeks being the dividing time. All articles had level of evidence 2b based on the Oxford Centre for Evidence-Based Medicine Levels of Evidence (2009) (Groll, Woods, and Salcido 2018).

Results

A total of 2332 cultures from 1644 patients were obtained from nine included studies. Gram-negative bacteria were isolated from 1184 cultures, and Gram-positive bacteria were isolated from 1148 cultures, as shown in Table 1. Culture results divided by acute vs. chronic osteomyelitis are shown in Tables 2 and 3.

The most commonly isolated bacterium overall was *Staphylococcus aureus* followed by coagulase-negative *Staphylococcus* and *Escherichia coli*. *Acinetobacter* dominated in acute-phase isolates, while *Staphylococcus aureus* dominated in chronic-phase isolates. Most studies reviewed revealed dominance of Gram-negative organisms in early stages of infection in comparison to later stages where Gram-positive bacteria, mainly *Staphylococcus* species, dominated (Burns et al. 2012; Murphy et al. 2011; Brown, Murray, and Clasper 2010; Oxford Centre for Evidence-Based Medicine 2009; Mody et al. 2009; Johnson et al. 2007). The geographical locations of injury were Iraq, Afghanistan, and Libya.

Most articles screened mentioned the predominance of MDR bacteria but did not go further into identifying them, making it impractical to statistically analyse the significance of various MDR bacterial species isolated.

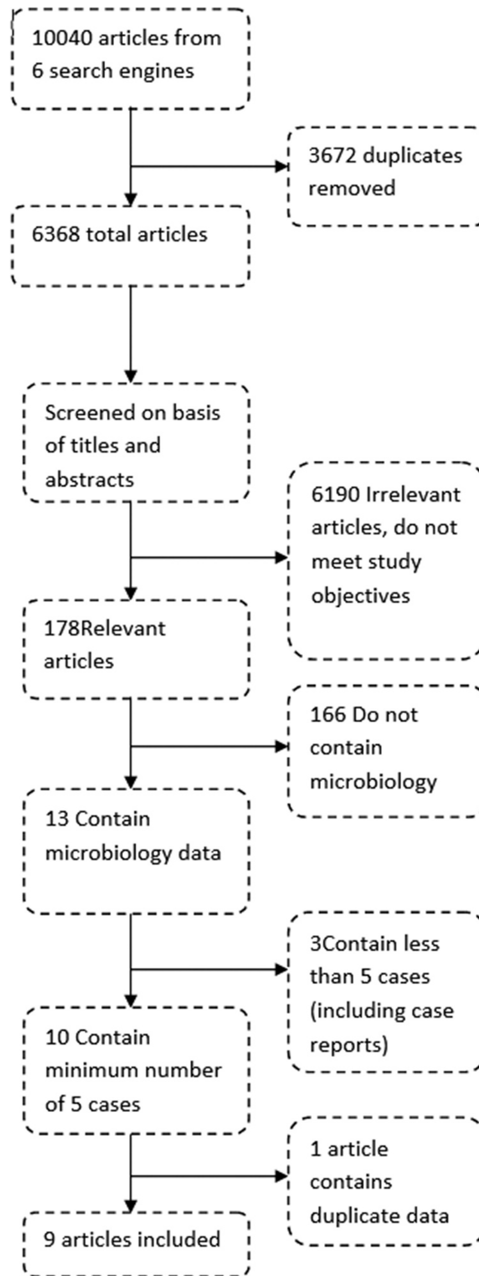

Figure 1. Flowchart of study selection.

Table 1. War osteomyelitis total cultures.

Article	Brown et al.	Johnson et al.	Burns et al.	Davis et al.	Yun et al.	Rahbar et al.	Wadi et al.	Geiger et al.	Hérard et al.	Total
Gram positive										**1148**
Staphylococcus aureus	1	7	8		8	9			540	573
Coagulase-negative Staphylococcus		10	16		13			4	343	386
Streptococcus viridans									96	96
MRSA	3	5	10		14	6	1	2		41
Enterococcus species		3	17		13		3	3		39
Bacillus species	1					1		1		3
Streptococcus					2					2
Other		6				2				8
Gram negative										**1184**
Escherichia coli	1	3			5	10	5		308	332
Pseudomonas aeruginosa	2	8	13		25	5	4		224	281
Acinetobacter		13	67	18	71	3	6	9	38	225
Klebsiella pneumoniae		3	19		20	10	6	1	120	179
Proteus						6			99	105
Enterobacter	1	6	17		21	1	3	5		54
Morganella morganii						3				3
Stenotrophomonas species	1	1								2
Citrobacter							1			1
Other		1				1				2
Level of evidence	2b	2b	2b	2b	2b	2b	2b	2b		

Table 2. War osteomyelitis acute-phase isolates.

Article	Brown et al.	Johnson et al.	Burns et al.	Davis et al.	Yun et al.	Geiger et al.	Total
Gram positive							**78**
Enterococcus species		3	13		12	3	31
Coagulase-negative staph		3	6		8	4	21
MRSA	3	1			8	2	14
Staphylococcus aureus	1	2			5		8
Other		2					2
Bacillus species	1					1	2
Gram negative							**306**
Acinetobacter		13	57	18	70	9	167
Enterobacter	1	6	17		18	5	47
Pseudomonas aeruginosa	2	5	13		25		45
Klebsiella pneumoniae		3	13		19	1	36
Escherichia coli	1	2			5		8
Stenotrophomonas species	1	1					2
Other		1					1

Table 3. War osteomyelitis chronic-phase isolates.

Article	Johnson et al.	Burns et al.	Yun et al.	Rahbar et al.	Hérard et al.	Wadi et al.	Total
Gram positive							**1070**
Staphylococcus aureus	5	8	3	9	540		565
Coagulase-negative staph	7	10	5		343		365
Streptococcus viridans					96		96
MRSA	4	10	6	6		1	27
Enterococcus species		4	1			3	8
Other	4			2			6
Streptococcus			2				2
Bacillus species				1			1
Gram negative							**877**
Escherichia coli	1			10	308	5	323
Pseudomonas aeruginosa	3			5	224	4	236
Klebsiella pneumoniae		6	1	10	120	6	143
Proteus				6	99		105
Acinetobacter		10	1	3	38	6	58
Enterobacter			3	1		3	7
Morganella morganii				3			3
Other				1			1
Citrobacter						1	1

Discussion

In general, more Gram-negative bacteria were isolated than Gram-positive bacteria when considering the total number of isolates identified in the reviewed reports. However, the role of Gram-positive bacteria in chronic osteomyelitis was more significant despite the persistent dominance of Gram-negative bacteria. This finding is close to what is cited in most of the papers

reviewed where Gram-negative bacteria dominated in acute-phase osteomyelitis cultures and Gram-positive bacteria in the chronic-phase osteomyelitis (Burns et al. 2012; Murphy et al. 2011; Brown, Murray, and Clasper 2010; Mody et al. 2009; Johnson et al. 2007; Yun, Branstetter, and Murray 2008).

Acinetobacter species was the most common amongst Gram-negative bacteria in acute osteomyelitis, a feature that has earned its sobriquet of 'Iraqibacter', being the dominant bacteria in war injuries from Iraq (Jones et al. 2006). In one of the papers, and before Operation Iraqi Freedom, only two cases of *Acinetobacter* infection, one of which was MDR, were recognized over a 14-month period from Brooke Army Medical Center in San Antonio, Texas. In the same report, and following the start of Operation Iraqi Freedom, 48 deployed soldiers in Iraq were admitted over a 15-month period with clinical infection caused by MDR A*cinetobacter* (Davis et al. 2005). In addition, and at the same facility, no cases of *Acinetobacter* osteomyelitis were encountered before the Iraqi war compared to 23 cases after the start of war (Davis et al. 2005).

In chronic osteomyelitis, the most common Gram-negative bacteria isolated were *E. coli,* while the most common Gram positive bacteria were *Staphylococcus aureus*. Methicillin-resistant *Staphylococcus aureus* (MRSA) represented 7.2% (41 cases) of cases of *Staphylococcus aureus* in total. This significant figure has therapeutic implications where there is a high need to utilize antibiotics that cover *Staphylococcus aureus* including MRSA.

Gram-positive bacteria were isolated much more commonly in cases with recurrent osteomyelitis. Johnson et al. and Yun et al. believe that it is unlikely that Gram-positive bacteria, if present originally in the wound, will be missed in most cultures, suggesting that they are acquired at later stages of care especially in patients with osteomyelitis recurrence (Johnson et al. 2007; Yun, Branstetter, and Murray 2008). In addition, Scott et al. stated that nosocomial transmission is a main factor in the spread of MDR bacteria, including MRSA (Scott et al. 2007). It was observed that antibiotics given in the initial period of osteomyelitis should have covered for Gram-positive bacteria mainly *Streptococcus* and methicillin-sensitive *Staphylococcuss* (Yun, Branstetter, and Murray 2008). In some cases, vancomycin, which covers for MRSA, was used in the initial coverage, further supporting the idea that these organisms are acquired at a later stage rather than being missed in the initial phases (Yun, Branstetter, and Murray 2008). These figures point towards the acquisition of bacteria involved in chronic osteomyelitis secondarily in battlefields and primary care centres.

It is mentioned in five articles that most of the cases included grew MDR pathogens in the cultures (Davis et al. 2005; Murphy et al. 2011; Yun, Branstetter, and Murray 2008; Wadi et al. 2013; Rahbar et al. 2010). This emphasizes the potential for increased morbidity among war injuries, mainly in osteomyelitis cases because of the burden posed by MDR bacteria as compared to non-war injuries and trauma. This information could not be

further elaborated on due to the lack of detail regarding MDR bacteria in the articles.

The treatment of osteomyelitis is usually surgical debridement followed by a long course of 4–6 weeks of antibiotics (Hatzenbuehler and Pulling 2011; Hogan, Heppert, and Suda 2013). The choice of antibiotics depends on the infecting organism and whether it is an MDR bacterium or not. *Acinetobacter* is an emerging organism recognized as a nosocomial and war pathogen, especially from the Middle Eastern region. Carbapenems, sulbactam, and tigecycline are the treatment of choice in *Acinetobacter* infections (Karageorgopoulos and Falagas 2008; Waites, Duffy, and Dowzicky 2006). However, due to the increasing emergence of carbapenem-resistant and tigecycline-resistant strains of *Acinetobacter*, the treatment options available are diminished, and colistin, an old revived compound known for its toxicity, is increasingly being utilized in the treatment of MDR *Acinetobacter* (Karageorgopoulos and Falagas 2008; Durante-Mangoni et al. 2013). Additionally, rising carbapenem resistance is being seen in Enterobacteriaceae such as *Klebsiella* and *E. coli*. In the treatment of MRSA osteomyelitis, vancomycin is the antimicrobial of choice (Liu et al. 2011; Darley 2004). However, vancomycin is potentially toxic and requires therapeutic drug monitoring of serum drug levels (Kitzis and Goldstein 2006). Alternatives to vancomycin include teicoplanin and daptomycin, which have shown efficacy in the treatment of MRSA osteomyelitis; linezolid, which is a relatively new antibiotic associated with good outcomes in soft tissue infections, is also an option for treatment. However, its use is limited due to the high cost and possible side effects associated with prolonged use (Lalani et al. 2007; Rao and Hamilton 2007).

Prevention remains of essential value in dealing with combat injuries. Wound irrigation, especially of open wounds and fractures, and wound care are crucial (Eardley et al. 2011). Post-injury antimicrobials should be initiated early to prevent or delay the onset of infection, within the first 3 hours if feasible (Hospenthal et al. 2011). As per an update of guidelines for the prevention of infections associated with combat-related injuries, cefazolin 2 grams intravenously every 6–8 hours for 1–3 days is the antimicrobial of choice in extremity combat injuries, with clindamycin as an alternative (Viehman, Nguyen, and Doi 2014). Gram-negative coverage was advised against in prevention due to the lack of clear data regarding its benefit and concerns that it would favour the selection of nosocomial MDR pathogens (Eardley et al. 2011). Antibiotics should only be continued for confirmed infection and not based on screening cultures. Temporary external fixation should be applied for femoral and tibial fractures allowing easier observation of wounds and a reduced rate of infection (Eardley et al. 2011). Infection control practices such as hand hygiene, isolation precautions, and cohorting should be utilized (Eardley et al. 2011). In their study titled 'Infection in Conflict Wounded', Eardley et al. reported that in the

USA and the UK there is agreement on discouraging the use of enhanced, routine Gram-negative cover in acute osteomyelitis; however, our data suggest otherwise which prompts a review of the use of international guidelines in our region given the predominance of Gram negatives in acute-phase osteomyelitis (Eardley et al. 2011).

Limitations

There are several limitations to this review; the most important is the scarcity of the available data published concerning the microbiology of osteomyelitis in war wounds from the MENA region. The paucity of data is mainly observed at the acute stage of war injury where care providers are unable to obtain the necessary information through laboratory tests and microbiological specimens (Sahli, Bizri, and Abu-Sittah 2016). Most of the reliable microbiological data stem from chronic osteomyelitis and patients with subacute and chronic wound infections. The fact that regions affected by war have lost a substantial part of their medical infrastructure results in the export of best practice in the treatment of the injured. To our knowledge, this is the first report from the MENA region that includes all published data on the microbiology of osteomyelitis, in a region that is well known for its repeated conflicts.

Conclusion

Osteomyelitis associated with war injuries is a highly morbid condition that is further complicated by acquiring MDR pathogens. The increasing number of cases of MDR pathogens compels the use of expensive and potentially toxic antibiotics. In acute osteomyelitis in settings where war injuries occur, empiric antimicrobial coverage when needed should cover mainly for *Acinetobacter*, which is difficult to treat because of its multi-resistant profile, where colistin has become the mainstay of treatment. In chronic osteomyelitis, empirical therapy should be directed against Gram-negative and Gram-positive bacteria mainly *Staphylococcus*, *E. coli*, *Acinetobacter* and *Pseudomonas*. This implies either the use of glycopeptide antibiotics including vancomycin and teicoplanin or the more expensive newer anti-staphylococcal agents. In critically ill patients, whether acute or chronic osteomyelitis, broad-spectrum coverage targeting Gram-positive and Gram-negative MDRs should be considered initially.

There is a dire need to establish local guidelines in the clinical management of war-related osteomyelitis taking into account the evolving microbiology, the nature of the injury, and the availability of effective antimicrobial therapy. Since drug resistance is a major issue, the use of strict infection control practices is essential to prevent its emergence and halt its spread.

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