

## Multidrug-Resistant Chronic Osteomyelitis Complicating War Injury in Iraqi Civilians

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**Background:** War-related orthopedic injury is frequently complicated by environmental contamination and delays in management, placing victims at increased risk for long-term infectious complications. We describe, among Iraqi civilians with war-related chronic osteomyelitis, the bacteriology of infection at the time of admission.

**Methods:** In the Médecins Sans Frontières Reconstructive Surgery Project in Amman, Jordan, we retrospectively reviewed baseline demographics and results of initial intraoperative surgical cultures among Iraqi civilians with suspected osteomyelitis.

**Results:** One hundred thirty-seven patients (90% male; median age, 35 years [interquartile range {IQR}, 28–46]; median time since initial injury, 19 months [IQR, 10–35]) were admitted with suspected chronic osteomyelitis after war-related injury. One hundred seven patients had a positive intraoperative culture. Before arrival, patients had undergone a median of 4 (IQR, 2–6) surgical procedures in Iraq. Fifty-nine (55%) of 107 patients with confirmed osteomyelitis had a multidrug-resistant (MDR) organism isolated at admission: cefepime-resistant *Enterobacteriaceae* ( $n = 40$ ), methicillin-resistant *Staphylococcus aureus* ( $n = 16$ ), and MDR *Acinetobacter baumannii* ( $n = 3$ ). An association of borderline significance existed between a history of more than two prior surgical procedures in Iraq and an MDR isolate at program entry (multivariate: odds ratio, 5.3; 95% confidence interval, 0.9–30.6;  $p = 0.064$ ).

**Conclusion:** Health care actors, including Iraqi health facilities and humanitarian medical organizations, must be aware of the link between chronic war injury and antimicrobial drug resistance in this region and should be prepared for the management challenges involved with the treatment of chronic drug-resistant osteomyelitis.

**Key Words:** Drug resistance, Iraq, Osteomyelitis, War surgery.

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War-related orthopedic injury is commonly associated with both contamination with environmental debris, soft tissue injury, and delayed medical intervention, placing the injured person at risk for long-term complications includ-

ing chronic infection. In 2006, Médecins Sans Frontières initiated a surgical project in Amman, Jordan, for Iraqi civilian victims of war, which included medical and surgical management of chronic osteomyelitis complicating war injury. We describe the bacteriology of chronic osteomyelitis among Iraqi civilians using cultures obtained in the operating room at the time of project admission. We also determined whether, as suggested in a previous report,<sup>1</sup> prior exposure to Iraqi secondary health facilities was associated with multidrug-resistant (MDR) bacterial infection.

### PATIENTS AND METHODS

We performed a retrospective analysis of the patients from Iraq with suspected war-related chronic osteomyelitis admitted to the Médecins Sans Frontières Reconstructive Surgery Project in Amman between October 1, 2006, and June 30, 2009. Upon admission, all patients underwent surgical exploration and debridement, at which time intraoperative cultures were routinely obtained. Osteomyelitis was defined by one or more positive cultures from an intraoperative bone specimen.

Standard microbiology techniques were used to process samples. Methods recommended by the Clinical and Laboratory Standards Institute and Analytical Profile Index system (bioMérieux, Durham, NC) were used for species identification. Using standard Clinical and Laboratory Standards Institute guidelines, susceptibility testing was performed using Kirby-Bauer disc diffusion and automatic methods (bioMérieux).

We defined an MDR isolate as any of the following: (1) *Enterobacteriaceae* (*Escherichia coli*, *Klebsiella* spp., *Enterobacter cloacae*, or *Proteus* spp.) with resistance to cefepime; (2) *Pseudomonas aeruginosa* with resistance to piperacillin/tazobactam, ceftazidime, imipenem, and amikacin; (3) *Acinetobacter baumannii* resistant to  $\geq 3$  classes of antimicrobial agents; and (4) methicillin-resistant *Staphylococcus aureus* (MRSA).

Multivariable logistic regression modeling was used to explore associations between baseline characteristics and presence of an MDR organism on initial culture. Covariates of interest were initially fit alone (age, gender, geographical origin, time from injury to admission, injury location, and number of prior procedures in Iraq), and those suggestive of an association ( $p < 0.1$ ) were fit in a multivariable model.

### RESULTS

Baseline characteristics are shown in Table 1. In total, 173 organisms were isolated from 107 patients. Thirty (22%)

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**TABLE 1.** Admission Characteristics of Iraqi Patients With War-Related Chronic Osteomyelitis

	Patients (N = 137)
<b>Demographics</b>	
Median age (yr) [IQR]	35 [28–46]
Men, n (%)	123 (90)
Origin within Iraq, n (%)	
Baghdad	96 (70)
Mosul	15 (11)
Kirkuk	5 (4)
Arbil	5 (4)
Najaf	3 (2)
Baqubah	3 (2)
Other	7 (7)
<b>Clinical characteristics</b>	
Median months since injury [IQR]	19 [10–35]
Months since injury, n (%)	
<12 mo	26 (30)
12–24 mo	25 (29)
>24 mo	36 (41)
Injury location, %	
Upper extremity	18 (13)
Lower extremity	119 (87)
Median prior surgical procedures in Iraq [IQR]	4 [2–6]

of 137 patients had no organism isolated and were considered not to have osteomyelitis. Gram-negative organisms represented 63% of isolates, most commonly *Escherichia coli* (20%), *Pseudomonas aeruginosa* (18%), *Klebsiella pneumoniae* (12%), *Proteus* spp (9%), *Enterobacter* spp (9%), and *Acinetobacter baumannii* (4%). *Staphylococcus aureus* was the most common individual organism, representing 21% of isolates. Fifty-nine (55%) of 107 patients were found to have an MDR organism: cefepime-resistant *Enterobacteriaceae* (n = 40), MRSA (n = 16), and MDR *Acinetobacter baumannii* (n = 3) (Table 2).

Baseline characteristics were evaluated for an association with the presence of an MDR organism at entry. An association was found between a history of more than two prior surgical procedures in Iraq and the presence of an MDR isolate in both univariate and multivariate analysis (multivariate: odds ratio, 5.3; 95% confidence interval, 0.9–30.6; p = 0.064), which was of borderline significance.

### DISCUSSION

The pathogens most commonly isolated from deep cultures among Iraqi civilians with war-related osteomyelitis were highly drug-resistant *Enterobacteriaceae* (*Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus* spp.) and MRSA. The management of chronic osteomyelitis involving these organisms will pose difficult management challenges for Iraqi health facilities compromised by conflict.<sup>2</sup> Other health care actors in the region, including humanitarian relief organiza-

**TABLE 2.** Antimicrobial Susceptibility of Frequently Isolated Pathogens Among Iraqi Patients With War-Related Chronic Osteomyelitis

Organism	<i>Staphylococcus aureus</i>		Coagulase-Negative <i>Staphylococcus</i>		<i>Escherichia coli</i>		<i>Klebsiella pneumoniae</i>		<i>Pseudomonas aeruginosa</i>		<i>Acinetobacter baumannii</i>	
	N = 33	Resistant (%)	N = 22	Resistant (%)	N = 30	Resistant (%)	N = 15	Resistant (%)	N = 27	Resistant (%)	N = 6	Resistant (%)
Amikacin					29	17	15	20	25	0	6	17
Ampicillin					28	96	15	100	8	N/A	4	N/A
Amoxicillin-clavulanate					21	100	13	100	7	N/A	2	100
Cefotaxime					28	93	15	87	13	N/A	3	100
Ceftriaxone					28	93	15	87	23	N/A	6	100
Cefepime					28	93	15	93	12	67	4	75
Cefixime					26	100					2	100
Ciprofloxacin					21	29	11	36	16	38	4	75
TMP/SMX					15	60	11	82	16	100	4	75
Gentamicin					19	74	7	86	17	77	6	67
Piperacillin/tazobactam					21	10	13	39	22	14	5	60
Imipenem					29	0	15	0	25	0	6	50
Penicillin	25	96	13	92								
Oxacillin	25	84	13	31								
Clindamycin	22	32	11	18								
Gentamicin	22	50	13	54								
Rifampin	14	43	N/A	N/A								
Fusidic acid	10	0	5	60								
TMP SMX	8	38	8	50								
Ciprofloxacin	22	23	12	0								
Vancomycin	27	0	17	0								

tions, must be aware of the link between chronic war injury and antimicrobial drug resistance.

Historically, gram-negative bacteria, including *Enterobacteriaceae* (such as *Escherichia coli*, *Klebsiella* spp., and *Enterobacter* spp.) and *Pseudomonas aeruginosa*, have been isolated from war injuries in World War II, the Korean War, the Vietnam War, and the 1973 October War.<sup>3-6</sup> Resistant gram-negative organisms have also been reported as pathogens among Iraqis in US military facilities treated acutely.<sup>1</sup> However, the long-term complications of war injury among civilians, including chronic infection, have been a neglected subject of research attention. Infection with highly resistant organisms as a long-term complication of war injury adds an additional concern.

The time point before admission to our program at which patients became infected with MDR organisms is unclear. However, a potential association emerged in our study between the presence of MDR bacteria at the time of program entry and a higher level of exposure to Iraqi hospitals before admission. This suggests a possible link between Iraqi health care structures and acquisition of MDR organisms. If this is the case, nosocomial spread of drug-resistant bacteria in Iraqi medical facilities could have resulted from inadequate current infection control practices and suboptimal management and control of antibiotics in the inpatient and outpatient sectors in Iraq. Importantly, we cannot exclude reverse causation: that before presentation at our project, patients with existing drug-resistant infections were more likely to have required additional procedures in Iraqi facilities.

The most difficult management challenges were posed by patients with infections associated with highly resistant *Enterobacteriaceae*. Only carbapenems and amikacin were found to be consistently active against these commonly isolated gram-negative organisms. Although we did not have access to specific testing for the production of extended-spectrum  $\beta$ -lactamases (ESBLs), given the high rate of resistance observed against cefepime (an extended-spectrum cephalosporin) and the geographical context of the project, it is likely that a significant proportion of *Enterobacteriaceae* isolates from patients in our project were ESBL producers. A high prevalence of ESBL production among *E. coli* and *Klebsiella* spp. has been documented in the Middle East region both in hospitals and the community.<sup>7-9</sup>

*Enterobacteriaceae*, particularly suspected ESBL-producing strains of *Enterobacteriaceae*, significantly increased project costs in two ways<sup>1</sup>: the isolation of these organisms required the introduction of additional parenteral

antibiotics, notably imipenem/cilastatin and amikacin, and<sup>2</sup> patients with osteomyelitis caused by highly resistant *Enterobacteriaceae*, for whom active oral antibiotic options were lacking, generally required a prolonged hospitalization for long-term intravenous antibiotics.

In conclusion, we report a high prevalence of drug-resistant *Enterobacteriaceae* and MRSA among Iraqi patients with war-related osteomyelitis with very limited effective antibiotic options. The presence of MDR organisms from deep surgical cultures may be associated with prior contact with Iraqi health facilities. The high prevalence of drug-resistant organisms noted here could portend a worrisome growing synergy between conflict and bacterial resistance in the Middle East. This development could present significant management challenges for health care systems in the region, particularly those whose function has been compromised by conflict.

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