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Antimicrobial Drug-Resistant Bacteria Isolated from Syrian War-Injured Patients, August 2011-March 2013

To the Editor: Soft-tissue injuries sustained during wars are subject to environmental contamination and, thus, to a high risk for infection. Efforts to describe the epidemiology of war-associated infections are complicated by difficult access to patients, limited availability of microbiology support, and widespread empirical antimicrobial drug use. Nevertheless, identifying the relevant pathogens is critical because war-associated injuries commonly become infected and antimicrobial drug-resistant bacteria are well-described in these injuries, including those in the Middle East (1-3).

The Médecins Sans Frontières (MSF) surgical project in Amman, Jordan, was initially developed for war-injured Iraqis needing surgical reconstruction or management of chronic osteomyelitis. Infection management is based on organism-directed antimicrobial agents and wide surgical resection of involved tissue. The proximity of this project to the Syrian conflict provided an opportunity to describe microbiologic features of infections caused by war-associated injuries in Syrians, who may be at increased risk for infection-associated complications because of exclusion from care in official health systems. We describe a cross-sectional series of 61 Syrian orthopedic patients who had suspected infections, as determined on the basis of surgical samples obtained intraoperatively.

Syrian patients admitted to the MSF clinic underwent initial surgical exploration of wounds; if infection was suspected, ≥ 3 intraoperative samples (bone, fibrous tissue,

fluid) were obtained for culture and transported (at 4°-8°C) within 2 h to the laboratory at Ibn al-Haytham Hospital in Amman. Patients who were treated with antimicrobial drugs within 2 weeks before admission were excluded from analysis.

We retrospectively reviewed data for patients admitted during August 1, 2011-March 31, 2013. Data were collected from databases and individual charts in Amman and analyzed by using Stata 12 (<http://www.stata.com/stata12/>). This study was deemed exempt from additional ethical approval by the MSF review board because it involved routinely collected data.

We defined a multidrug-resistant (MDR) isolate as 1) extended-spectrum β -lactamase-expressing *Enterobacteriaceae*; 2) *Pseudomonas aeruginosa* and *Acinetobacter baumannii* isolates resistant to at least 1 agent in 3 antimicrobial categories typically used for treatment; or 3) methicillin-resistant *Staphylococcus aureus* (MRSA). Pathogen identification was conducted by using conventional methods and the API system (bio-Mérieux, Durham, NC, USA). Antimicrobial drug susceptibility testing was conducted by using the MicroScan Walk-Away System (Dade Behring, West Sacramento, CA, USA).

During the study period, 870 patient consultations were conducted, of which 345 (40%) were for patients from Syria. At the initial operating room evaluation, infection was suspected in 61 (18%) Syrians. These patients had a median age of 26 years (interquartile range 22-34); 98% were male. The median time from injury to admission was 5 months (interquartile range 1.2-8.1), but for 27 (44%) patients, the time from injury to admission was >6 months. The 2 most common injuries were gunshot wounds (32 patients [52%]) and wounds from explosions (20 patients [33%]). The dominant injury was located in an upper extremity in 14 (23%) patients and a lower extremity in 47 (77%) patients.

For the 61 patients, a total of 67 bacterial isolates were identified from cultures of surgical specimens. Overall, 45 (74%) patients had at least 1 positive culture, and 6 (13%) patients had polymicrobial results. Gram-negative organisms represented 24 (56%) of 43 isolates; 10 (23%) were *P. aeruginosa*, 8 (19%) were *E. coli*, and 6 (14%) were *A. baumannii*. Gram-positive bacteria, including MRSA, represented 19 (44%) of 43 isolates (Table). Overall, 31 (69%) of 45 patients with confirmed infection were positive for MDR organisms. Within this group, MRSA represented 8 (42%) of 19 staphylococcal isolates.

Patients who had experienced delayed definitive management were frequently positive for MDR organisms, especially gram-negative pathogens and MRSA. For a humanitarian surgical project, infection with MDR organisms leads to formidable diagnostic, treatment, and control challenges. For example, treatment of MDR infections requires ongoing access to high-quality clinical microbiology support; late-generation antimicrobial drugs, which are typically given parenterally for up to 6 weeks; trained personnel; and sufficient hospital space to isolate patients with resistant strains. Our findings

support the previously reported linkage between war-associated injuries and infection with antimicrobial drug-resistant organisms (1–4) and the implications for patient management.

The source of antimicrobial drug-resistant organisms in war-associated injuries remains uncertain; possibilities include nosocomial transmission (5), particularly through prior contact with severely compromised health systems (6). Another possibility is fecal colonization with extended-spectrum β -lactamase-producing gram-negative bacteria. (7,8). Another likely contributor in Syria is the wide availability of antimicrobial drugs without a prescription (9).

This study has limitations. Although measures were taken to ensure that positive cultures represented clinical infection rather than colonization, we cannot exclude colonization as a possible source of some recovered organisms. In neglected war-associated injuries, multiple pathogens are potentially present, but every strain is not necessarily clinically relevant (10). Furthermore, complete patient histories are difficult to obtain in crisis settings, limiting our ability to describe all prior interventions. Study strengths included

partnership with a high-quality culture laboratory, which is uncommon in programs treating war injuries; systemic sampling of patients with suspected infection; and use of intraoperative samples for culture. Further research needed in this neglected area includes prospective studies to determine the effect of MDR isolates on patient outcomes and randomized clinical trials of antimicrobial drug strategies to inform treatment protocols.

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Table. Antimicrobial drug resistance among frequently isolated bacterial isolates from Syrian patients with war-associated wound infections, August 2011–March 2013*

Antimicrobial drug	No. MDR-resistant isolates/no. total (%)			
	<i>Staphylococcus aureus</i> , n = 19	<i>Pseudomonas aeruginosa</i> , n = 10	<i>Escherichia coli</i> , n = 8	<i>Acinetobacter baumannii</i> , n = 6
Amikacin		1/11 (9)	1/7 (14)	6/6 (100)
Ampicillin			5/5 (100)	
Amoxicillin/clavulanic acid			6/6 (100)	
Cefotaxime			6/8 (75)	
Ceftriaxone			5/8 (62)	
Ceftazidime		3/9 (33)	5/8 (62)	4/4 (100)
Cefepime			5/8 (62)	5/5 (100)
Cefixime			5/8 (62)	5/5 (100)
Ciprofloxacin	7/17 (41)	5/8 (62)	2/7 (28)	5/5 (100)
Colistin		NA	NA	0/5
Trimethoprim/sulfamethoxazole	3/14 (21)		3/5 (60)	
Gentamicin	10/18 (55)	4/9 (44)	4/8 (50)	6/6 (100)
Piperacillin/tazobactam		2/9 (22)	3/7 (42)	NA
Imipenem		0/9	1/7 (14)	4/5 (80)
Penicillin	9/10 (90)			
Oxacillin	7/17 (41)			
Clindamycin	9/17 (52)			
Rifampin	6/15 (40)			
Fusidic acid	10/15 (66)			

*Blank cells indicate that testing was not done.

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Multidrug-Resistant IncA/C Plasmid in *Vibrio cholerae* from Haiti

To the Editor: The agents of epidemic cholera are *Vibrio cholerae* toxigenic serogroups O1 and O139. Cholera symptoms include watery diarrhea and severe dehydration, which can rapidly result in death unless rehydration therapy is prompt (1). Antimicrobial agents may reduce the severity and duration of disease (1); commonly used are tetracyclines, fluoroquinolones, macrolides, and trimethoprim/sulfamethoxazole (1). However, *V. cholerae* resistance to antimicrobial drugs is increasing because of the accumulation of genetic mutations and the acquisition of resistance genes, which are usually transferred on mobile genetic elements such as integrating conjugative elements (ICEs) (1).

As of March 12, 2014, the ongoing cholera outbreak that began in Haiti in October 2010 had caused 700,796 cases and 8,548 deaths (2). To characterize infections, the National Public Health Laboratory in Haiti and the US Centers for Disease Control and Prevention (CDC) collaborated to perform standard microbiological and antimicrobial-drug susceptibility testing on isolates from case-patients.

Since October 2010, the National Public Health Laboratory has identified 465 isolates, which were then forwarded to CDC for determination of MICs for 15 antimicrobial agents by broth microdilution (Sensititer; Trek Diagnostics Systems, Cleveland, OH, USA) according to manufacturer's recommendations (Table). Resistance was defined by the Clinical and Laboratory Standards Institute interpretive standards, when available (3). The typical outbreak strain (2010EL-1786) displayed resistance to streptomycin, sulfisoxazole, trimethoprim/sulfamethoxazole, and nalidixic acid, and decreased susceptibility to ciprofloxacin and chloramphenicol (4). Resistance was caused by mutations in the QRDR regions of the *gyrA* and *parC* genes and presence of ICE Vch Hait1 containing the *dfxA1*, *floR*, *strAB*, and *sul2* resistance genes (4).

In April of 2012, the 2 agencies began sentinel laboratory-based surveillance for acute diarrheal disease at 4 hospitals in Haiti (5). As part of this surveillance, fecal specimens were sent to the National Public Health Laboratory for organism isolation, identification, antimicrobial-drug testing, and subsequently to CDC for expanded antimicrobial-drug testing and molecular characterization. One isolate, 2012EL-2176, showed the typical resistance phenotype of the outbreak strain but additional resistance to ampicillin, amoxicillin/clavulanic acid, cefoxitin, ceftriaxone, ceftiofur; the tetracycline MIC was intermediate (Table).

Analysis of this isolate by serotype, pulsed-field gel electrophoresis, multilocus variable number–tandem repeat analysis, and whole-genome sequencing confirmed that the isolate was similar to outbreak isolates (data not shown) (6). PCR and whole-genome sequencing analysis by use of ResFinder (<http://www.genomicepidemiology.org/>) identified the original outbreak resistance determinants (*aac(3)-IIa*, *bla*_{CMY-2}, *bla*_{CTX-M-2}, *bla*_{TEM-1P}, *dfxA15*,