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MAJOR ARTICLE

Posttraumatic *Pseudomonas aeruginosa* Osteomyelitis in Mosul and Gaza: A Retrospective Cohort Study, 2018–2022

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Background. The history of conflicts in the Middle East has resulted in a high burden of complications from conflict-related wounds like posttraumatic osteomyelitis (PTO). This is particularly challenging to manage in settings like Mosul, Iraq and Gaza, Palestine, where healthcare systems are weakened. In nonconflict settings, PTO caused by *Pseudomonas aeruginosa* (PAPTO) can lead to >20% of treatment failures. We aim to describe the clinical characteristics, outcomes, and management, in PAPTO patients admitted to Médecins Sans Frontières (MSF) facilities in Mosul and Gaza between 1 April 2018 and 31 January 2022.

Methods. We conducted a retrospective cohort study on patients with PAPTO diagnosed with culture of intraoperative bone biopsy, using routinely collected data.

Results. Among 66 PAPTO episodes from 61 enrolled patients, 37.9% had a multidrug-resistant *Pseudomonas aeruginosa*, with higher antibiotic resistance in Gaza. Polymicrobial infections were prevalent (74.2%), mainly involving *Staphylococcus aureus* (74.1%), being predominantly methicillin-resistant (95.0%). Overall, 81.7% received appropriate antibiotic treatment, with monotherapy used in 60.6% of episodes and a median treatment duration of 45.5 days. Recurrence was observed in 24.6% of episodes within a median of 195 days (interquartile range, 64–440 days). No significant differences were found in recurrence rates based on the type of antibiotic treatment (mono- or dual therapy) or episode (mono- or polymicrobial).

Conclusions. Management of PAPTO in the conflict-affected, low-resource settings of Mosul and Gaza achieved a recurrence rate aligned with global reports through appropriate and targeted antibiotic use, primarily in monotherapy, provided over a mean treatment duration of 45.5 days.

Keywords. antibiotic resistance; Gaza; Iraq; posttraumatic osteomyelitis; *Pseudomonas aeruginosa*.

The long history of conflicts in the Middle East has resulted in a high burden of complications from conflict-related wounds like osteomyelitis, an infection to the bone following trauma or surgery. Posttraumatic osteomyelitis (PTO) is especially prevalent and challenging to manage in conflict-affected settings like Mosul, Iraq and Gaza, Palestine, where healthcare systems are weakened. This leads to negative outcomes of care in affected patients, including lifelong disabilities [1].

Factors such as suboptimal infection control practices, lack of antibiotic stewardship, limited or delayed access to timely and effective microbiological and surgical interventions, and inconsistent availability of antibiotics [2, 3]—all of which are exacerbated by conflicts—complicates the management of PTO [4]. In these settings, up to 55% of conflict-related wounds, including osteomyelitis, show multidrug resistance (MDR), putting further strain on healthcare resources [5, 6].

Pseudomonas aeruginosa, a gram-negative bacterium resistant to many antibiotics, is a common pathogen identified in conflict-related wounds [6, 7], with nearly half of the strains in the Middle East showing resistance to first-line antibiotics, such as ceftazidime [6]. PTO caused by *P aeruginosa* (PAPTO) is generally associated with longer hospital stays, suboptimal clinical outcomes, higher recurrence, and increased mortality compared to other pathogens [8, 9]. In nonconflict settings, PAPTO treatment failures are around 21%, with a relapse rate twice that of other bacterial causes of osteomyelitis [10, 11].

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Despite these challenges, there is a considerable knowledge gap about the characteristics and clinical management of PAPTO patients in conflict-affected settings. Therefore, this study aims to describe the clinical characteristics, outcomes, and management including appropriateness of antibiotic treatment for PAPTO patients admitted at the Médecins Sans Frontières (MSF/Doctors Without Borders) facility in Mosul's Al Wahda tertiary orthopedic center and at Gaza's MSF-supported surgical units in Al-Awda and Naser hospitals.

METHODS

Study Design

This was a retrospective descriptive cohort study carried out using routinely collected data on patients with PAPTO admitted between 1 April 2018 and 15 September 2021 at 1 of the 3 MSF-supported-facilities in Mosul, Iraq and Gaza, Palestine. These patients were followed up till 31 January 2022.

Setting

Mosul, a large city in northern Iraq, has faced political and social instability since the early 1990s. The most recent significant conflict was in 2017 with the battle to retake Mosul from the Islamic State Group. To respond to the needs resulting from this conflict, MSF opened a tertiary orthopedic center at Al Wahda hospital in east Mosul in 2018, consisting of 40 single inpatient rooms.

Gaza strip, a densely populated territory in Palestine, and under Israeli blockade since 2006, has experienced frequent violent conflicts and wars [12], severely straining the healthcare system. Most recently, the war on Gaza, which began on 7 October 2023, has further exacerbated the humanitarian crisis, depleting medical resources and infrastructure and leading to an unprecedented increase in war-affected wounds and surgical needs [13, 14]. Prior to this, Gaza was profoundly impacted by the Great March of Return in 2018, which resulted in >35 000 injuries among Palestinians [15]. In response, MSF started supporting surgical orthopedic departments in Al-Awda and Naser hospitals, with 26 and 21 beds, respectively.

Clinical Management of Osteomyelitis

The 3 facilities provide comprehensive multidisciplinary reconstructive surgery care including medical, diagnostic, surgical, psychological, physiotherapy, and health education services. Standard osteomyelitis care includes debridement, with an intraoperative collection of 3 to 5 deep tissue and bone samples for pathogen identification and antimicrobial susceptibility testing (AST). These samples are collected after the patient has been off antibiotics for at least 7 days. Sample collection follows standard procedures, ensuring proper identification and immediate sterile transportation to the laboratory. AST is conducted in an MSF-validated external microbiology laboratory in Erbil (for Mosul) and an MSF microbiology laboratory in Gaza.

No empirical treatment is provided, rather, targeted antibiotic treatment following culture results. However, patients showing signs of instability or severity (eg, sepsis, neurological symptoms, or necrotizing fasciitis) are immediately started on antibiotics while awaiting their blood culture results. Clinical guidelines follow the MSF's pathogen-specific treatment guideline [16], which previously favored a dual antibiotic treatment for PAPTO treatment, then shifted to a single-regimen therapy in 2019. PAPTO treatment typically includes at least 1 week of intravenous antibiotics, followed by oral fluoroquinolones when appropriate, for a total duration of 6 weeks. Antibiotics with an intermediate result on their AST are considered last-resort options when no other susceptible antibiotics are available, maintaining the recommended duration for intravenous and oral antibiotics. In case of a relapse, treatment includes at least 2 weeks of intravenous antibiotics followed by oral therapy where appropriate, for a total treatment duration of 12 weeks.

In these facilities we have restrictive and regularly monitored antimicrobial stewardship (AMS) and infection prevention and control (IPC) programs in place. Those include multidisciplinary AMS and IPC committees, the implementation of transmission-based precautions, placement of patients with multidrug-resistant infections, and ongoing monitoring of AMS and IPC indicators such as antibiotic use through point-prevalence surveys, weekly antibiotic rounds, hand hygiene, and surgical site infections reporting among others, throughout the year.

Follow-up visits every 1–3 months are scheduled at outpatient level to assess infection recurrence. Patients are discharged and declared cured only if no clinical, biochemical, or radiological signs of infection are evident up to 24 months post–treatment completion. Therefore, X-rays were systematically done to all patients at 24 months of follow-up.

Study Population

All patients diagnosed with PAPTO confirmed by intraoperative bone biopsy cultures at MSF study facilities between 1 April 2018 and 15 September 2021, followed until 31 January 2022, were included in the study.

Patients with only tissue biopsy results showing possible contamination have been excluded. In Gaza, patients treated at both MSF sites were counted only once.

Study and Outcome Definitions

Supplementary Table 1 presents the detailed definitions used in this study, including infection outcomes, antibiotic appropriateness, MDR osteomyelitis, and polymicrobial episode.

Contamination was defined as a positive bone biopsy that also contains the following pathogens classified as possible contaminants: coagulase-negative staphylococci, *Corynebacterium* spp, and *Bacillus* sp, interpreted along the clinical assessment of the patient.

An MDR infection was defined as an infection with a drug-resistant bacterium that has an acquired nonsusceptibility to at least 1 agent in 3 or more antimicrobial categories as per the corresponding antibiogram [17].

Recurrent infection was defined as a relapse with the same strain or a new infection with a different pathogen (non–*P aeruginosa*). Only recurrence that happened during the study period was reported. A cure was declared if no recurrence was noted 24 months post–antibiotic treatment course. Therefore, cure was only captured and reported for patients who had completed a 24-month follow-up within the study period.

Antibiotic appropriateness was assessed against the MSF 2019 guideline [16], with deviations assessed by an expert panel on a case-by-case basis. Review of antibiotics provided for surgical prophylaxis was not included.

Data Sources

Patient data included sociodemographic, clinical (including injury characteristics, symptoms, clinical treatment), microbiological (such as bacterial species, sample-related data), and radiological (nonunion/malunion, periosteal reaction, sequestrum, bone lucency, cortical irregularity, and bone abscess) information, as well as antibiotic treatment. Data were collected from various databases used routinely across the facilities, with some data retrospectively retrieved from patients' medical files and/or pharmacy prescriptions. Eligible patients were identified based on their microbiological information encoded in the WHONET database, used routinely at project level.

Microbiological Procedures

The antibiotic susceptibility test was done using disk diffusion method for most antibiotics (Kirby-Bauer method), the minimum inhibitory concentration test strips method for vancomycin and tigecycline, and broth microdilution method for colistin, adhering to the Clinical and Laboratory Standards Institute guidelines or the European Committee for Antimicrobial Susceptibility Testing, adapted as per the regular corresponding updates.

Data Analysis

Data were analyzed at patient and episode levels. The prevalence of polymicrobial, monomicrobial, MDR and non-MDR isolates, and resistance patterns in *P aeruginosa* isolates were calculated. Bacteria were classified as not susceptible to an antibiotic if they showed corresponding intermediate or resistant results. Outcomes were calculated at clinical episode level for all PAPTO with 24 months of follow-up post-completion of the antibiotic treatment for osteomyelitis as a cutoff.

Appropriateness of antibiotic use was calculated at patient level, considering a patient treated inappropriately if any of their PAPTO episodes was treated with at least 1 antibiotic not according to the protocol. One patient was excluded from this analysis as they were referred out before receiving antibiotics. The reasons of choosing inappropriate antibiotics were collected. In calculating type of therapy proportions (monotherapy or dual therapy) among PAPTO episodes, those without complete antibiotic data or those receiving >2 antibiotics were excluded.

Differences in main study characteristics and endpoints, including clinical episode outcomes, type of therapy, and antibiotic resistance, were compared between Gaza and Mosul using Pearson χ^2 or Fisher exact tests for categorical variables, and unpaired *t* tests or Wilcoxon-Mann-Whitney tests for continuous variables, as appropriate. Variables with >5% missing values were excluded. A *P* value <.05 was considered significant. Analyses were performed using Stata version 14.0 software.

RESULTS

Population Demographics

The study included 61 PAPTO patients: 20 (32.8%) from Mosul and 41 (67.2%) from Gaza, with a median age of 25 years (interquartile range [IQR], 21–34 years), 93.4% (57/61) male, and 83.6% (51/61) without preexisting chronic comorbidities. Gaza patients had significantly higher prevalence of violent trauma (92.7% [38/41]) and multifragmentary fractures (100%) than those in Mosul (20.0% [4/20] and 21.0% [4/19], respectively) ($P < .001$; Table 1).

PAPTO Episodes

Characteristics

Of 79 PTO episodes among the 61 enrolled patients, 66 were PAPTO with 31.8% (12/66) in Mosul and 68.2% (45/66) in Gaza. The median hospital stay was 42 days (IQR, 24–53 days), with a median of 2 surgeries per episode (IQR, 1–5), and longer median follow-up in Gaza compared to Mosul ($P = .01$; Table 2).

Resistance and AST

Multidrug-resistant *P aeruginosa* was identified in 37.9% (25/66) of PAPTO cases, with 46.7% (21/45) in Gaza compared to 19% (4/21) in Mosul; however, the difference was not statistically significant ($P = .06$; Table 2). Polymicrobial infections were present in 74.2% (49/66) of episodes, with 55.1% (27/49) including non–*P aeruginosa* MDR isolates: predominantly *Staphylococcus aureus* (74.1% [20/27]), with 95.0% (19/20) being methicillin-resistant (MRSA); *Escherichia coli* was isolated in 14.8% (4/27), with 100% being extended-spectrum β-lactamase; and 33.3% (1/3) of the *Enterobacter cloacae* isolates were carbapenem resistant (Table 3).

Of the 66 *P aeruginosa* strains, sensitivities to ceftazidime and carbapenem (imipenem and meropenem) were tested in 63 (95.4%). Of these, 36.5% (23/63) were ceftazidime-resistant and 22.2% (14/63) were resistant to imipenem or meropenem.

Table 1. Characteristics of Patients With Posttraumatic Osteomyelitis Caused by *Pseudomonas aeruginosa*, April 2018 to September 2021, Médecins Sans Frontières–Supported Facilities in Mosul (Iraq) and Gaza (Palestine)

Characteristic	Total Cohort[a] (n = 61)	Mosul (n = 20)	Gaza (n = 41)	*P* Value[b]
Sociodemographic and general characteristics				
Age, y, median (IQR)	25 (21–34)	26 (13–45)	25 (22–31)	.96
Sex				
Male	57 (93.4)	17 (85.0)	40 (97.6)	.10
Female	4 (6.6)	3 (15.0)	1 (2.4)	
Preexisting comorbidity at admission[c]				
No	51 (83.6)	16 (80.0)	35 (85.4)	.72
Yes	10 (16.4)	4 (20.0)	6 (14.6)	
Status of patients at end of study period				
Under follow-up in the program	39 (63.9)	8 (40.0)	31 (75.6)	.01
Lost to follow-up[d]	17 (27.9)	11 (55.0)	6 (14.6)	
Referred	5 (8.2)	1 (5.0)	4 (9.8)	
Injury-related characteristics				
Year of injury				
≤2018	33 (54.1)	11 (55.0)	22 (53.7)	.77
>2018	28 (45.9)	9 (45.0)	19 (46.3)	
Mechanism of injury[e]				
Violent trauma	42 (68.8)	4 (20.0)	38 (92.7)	<.001
Nonviolent trauma	19 (31.1)	16 (80.0)	3 (7.3)	
Bone fractures				
1	31 (50.8)	12 (60)	19 (46.3)	.32
≥2	30 (49.2)	8 (40)	22 (53.7)	
Site of injury				
Tibia	35 (57.4)	8 (40.0)	27 (65.9)	.06
Fibula	23 (37.7)	5 (25.0)	18 (43.9)	.15
Femur	11 (18.0)	3 (15.0)	8 (19.5)	.67
Foot	10 (16.4)	5 (25.0)	5 (12.2)	.20
Type of fracture				
Multifragmentary	44 (74.6)	4 (21.0)	40 (100)	<.001
Simple or wedge	15 (25.4)	15 (78.9)	0 (0)	
Infection-related characteristics				
PTO episodes				
1	47 (77.0)	18 (90.0)	29 (70.7)	.12
≥2	14 (23.0)	2 (10.0)	12 (29.3)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: IQR interquartile range; PTO, posttraumatic osteomyelitis.

[a]Patients admitted at different points in time for 2 different fracture locations (n = 1) were included once.

[b]$P < .05$ is statistically significant.

[c]Patients with at least 1 chronic comorbidity including diabetes, cardiovascular diseases, psychiatric illnesses, and others.

[d]Patients who have missed their last 3 appointments or had >6 months elapsing without any follow-up visit.

[e]Violent trauma includes war-related trauma (explosives, gunshot, and mines); nonviolent trauma includes but is not limited to road traffic accidents, burns, and surgical pathologies.

Resistance to ciprofloxacin and gentamycin was significantly higher in Gaza (45.0% [18/40] and 51.2% [21/41], respectively), compared to Mosul (16.7% [3/18], and 23.8% [5/21], respectively) ($P = .04$; Table 3).

Type of Therapy

Among 66 PAPTO episodes, 61 (92.4%) had complete antibiotic data and were given ≤2 antibiotics. Monotherapy was used in 60.6% (37/61) and dual therapy in 39.3% (24/61), showing no statistically significant country variation. Ceftazidime with ciprofloxacin (intravenous or oral) was the predominant combination in dual therapy (33.3% [8/24]). Mean treatment duration was comparable between monotherapy (45.7 days [standard deviation {SD}, 18.0 days]) and dual therapy (45.4 days [SD, 11.7 days]). Oral therapy was used in 47.5% (29/61) of cases.

Appropriateness of Antibiotic Use

Of 60 patients with complete data, 49 (81.7%) received appropriate antibiotics, with statistically significant higher rates in Gaza (90.0% [36/40]) than Mosul (65.0% [13/20]) ($P = .03$).

Inappropriate use was due to incorrect antibiotic choice (54.5% [6/11]), underdosing (27.3% [3/11]), nonadherence to guidelines (1 case), and inadequate source control of the

Table 2. Characteristics of All *Pseudomonas aeruginosa* Posttraumatic Osteomyelitis Episodes Followed up, April 2018 to January 2022, Médecins Sans Frontières–Supported Facilities in Mosul (Iraq) and Gaza (Palestine)

Characteristic per PAPTO Episode	Total Episodes (n = 66)	Mosul (n = 21)	Gaza (n = 45)	*P* Value[a]
Hospitalization and clinical characteristics				
Length of stay, d, median (IQR)	42 (24–53)	30 (21–48)	43 (24–60)	.30
Surgical interventions, median (IQR)	2 (1–5)	4 (1–6)	1 (1–5)	.05
Clinical signs of infection at admission				
Yes	62 (93.9)	21 (100.0)	41 (91.1)	.30
No	4 (6.1)	0 (0.0)	4 (8.9)	
Months of follow-up during study period				
≤6 mo	28 (46.7)	13 (68.4)	15 (36.6)	.02
>6 mo	32 (53.3)	6 (31.6)	26 (63.4)	
Days completed under follow-up, median (IQR)	203 (72–443)	86 (24–213)	294 (111–475)	.01
Time from injury to first biopsy, d, median (IQR)	357 (37–698)	394 (20–1153)	324 (45–635)	.27
Biopsy-related characteristics				
Bone samples collected per episode, median (IQR)	5 (4–5)	4 (3–5)	5 (4–5)	.01
Time from sample collection to biopsy results, d, median (IQR)	5 (4–7)	4 (3–4)	6 (4–8)	<.001
Length of treatment, d, mean (SD)	45.5 (15.6)	39.4 (9.6)	48.4 (17.1)	.032
Infection-related characteristics				
Polymicrobial				
Yes	49 (74.2)	12 (57.1)	37 (82.2)	.03
No	17 (25.8)	9 (42.9)	8 (17.8)	
Multidrug-resistant PTO[b]				
Yes	43 (65.1)	12 (57.1)	31 (68.9)	.35
No	23 (34.8)	9 (42.9)	14 (31.1)	
Multidrug-resistant PAPTO				
Yes	25 (37.9)	4 (19.0)	21 (46.7)	.06
No	41 (62.1)	17 (81.0)	24 (53.3)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: IQR, interquartile range; PAPTO, posttraumatic osteomyelitis caused by *Pseudomonas aeruginosa*; PTO, posttraumatic osteomyelitis; SD, standard deviation.

[a]$P < .05$ is statistically significant.

[b]Calculated among recurrent infections including non-PAPTO (new infections isolated from PAPTO patients, caused by bacteria other than *P aeruginosa*).

Table 3. Proportion of Resistance to Key Antibiotics of *Pseudomonas aeruginosa* Isolates Among All Posttraumatic Osteomyelitis Cases Seen in Médecins Sans Frontières–Supported Facilities in Mosul (Iraq) and Gaza (Palestine), April 2018 to September 2021

	Total (n = 66)		Mosul (n = 21)		Gaza (n = 45)		
Antibiotic	No.	Resistant, No. (%)	No.	Resistant, No. (%)	No.	Resistant, No. (%)	*P* Value[a]
Amikacin	62 (93.9)	26 (41.9)	21	4 (19.0)	42	13 (30.9)	.38
Cefepime	38 (57.6)	14 (36.8)	0	0	38	14 (36.8)	NA
Ceftazidime	63 (95.4)	23 (36.5)	21	5 (23.8)	42	18 (42.9)	.14
Ciprofloxacin	58 (87.9)	21 (36.2)	18	3 (16.7)	40	18 (45.0)	.04
Gentamycin	63 (95.4)	17 (27.0)	21	5 (23.8)	41	21 (51.2)	.04
Carbapenem[b]	63 (95.4)	14 (22.2)	21	3 (14.3)	42	11 (26.2)	.35
Piperacillin-tazobactam	62 (93.9)	11 (17.7)	21	3 (14.3)	41	8 (19.5)	.73

Abbreviation: NA, not applicable.

[a]$P < .05$ is statistically significant.

[b]Includes those tested/resistant to imipenem or meropenem.

infection (1 case). In Mosul, 66.7% (4/6) of incorrect prescriptions were due to drug shortages.

PTO Episodes

Recurrence. Of the 79 PTO episodes, 87.3% (69/79) had outcomes recorded without completing 24-month follow-up. Recurrence occurred in 24.6% (17/69) within a median of 195 days (IQR, 64–440 days), primarily as new infections (76.5% [13/17]). Recurrence among PAPTO episodes was not affected by antibiotic treatment used (mono- or dual therapy), episode type (mono- or polymicrobial), or length of treatment (Table 4).

Table 4. Recurrence of *Pseudomonas aeruginosa* Posttraumatic Osteomyelitis Episodes by Antibiotic Therapy, Episode Type, and Length of Treatment, April 2018 to January 2022, Médecins Sans Frontières–Supported Facilities in Mosul (Iraq) and Gaza (Palestine)

Characteristic	Total	Recurrent	Nonrecurrent	*P* Value
Antibiotic therapy[a], No. (%)				
Monotherapy	36 (62.1)	7 (53.8)	29 (64.4)	.49
Dual therapy	22 (37.9)	6 (46.1)	16 (35.6)	
Episode type[b], No. (%)				
Monomicrobial	14 (23.7)	1 (7.1)	13 (28.9)	.15
Polymicrobial	45 (76.3)	13 (92.8)	32 (71.1)	
Length of treatment[b], mean (SD)	47.5 (15.9)	47.5 (15.1)	45.2 (16.3)	.63

Abbreviation: SD standard deviation.

[a]Fifty-eight episodes out of 66 posttraumatic osteomyelitis caused by *Pseudomonas aeruginosa* (PAPTO) with complete data on recurrence (13 recurred and 45 did not recur) and antibiotic therapy were included.

[b]Fifty-nine episodes out of 66 PAPTO with complete data on recurrence (14 recurred and 45 did not recur) and type of episode were included.

Two episodes had completed 24 months of follow-up. One was declared as cured with a fully united bone, while the other episode showed radiological signs of infection.

DISCUSSION

This is the first study to report on PAPTO cases from conflict-affected settings of Palestine (Gaza) and Iraq (Mosul). We show that the majority of cases occurred in young, healthy males, with violent trauma and complex injuries more predominantly in Gaza. More than one-third of episodes were MDR and predominantly polymicrobial. Most patients received appropriate antibiotic treatment, largely through monotherapy. Recurrence occurred in almost 25% within 195 days, mainly as new infections.

The recurrence rates in our cohort are in line with the 7%–30% reported range mainly in high-resource settings for PAPTO and general bone and joints infections caused by *P aeruginosa* [9, 10, 18–20]. This occurred despite the high prevalence of polymicrobial PAPTO in our cohort, a risk factor previously associated with an increased recurrence rate and resulting in up to 80% of unfavorable outcomes [21, 22]. This potentially highlights an effective surgical and antimicrobial treatment within our hospital, reflected by 81.7% of patients receiving appropriate antibiotics. However, the recurrence rate in our cohort may be underestimated, as cases that recurred after the study period ended would not have been captured in our study.

In Gaza, the higher appropriateness of antibiotic use compared to Mosul may be due to frequent shortages of common antibiotics in Mosul that force healthcare providers to resort to available drugs. Appropriate targeted antibiotic treatment and proper surgical debridement have been shown to be essential factors for successful outcomes in musculoskeletal infections, including osteomyelitis [4]. We showed that our approach, aligned with MSF guidelines [16], favoring targeted over empirical antibiotic use and monotherapy initiated within 5 days post–bone sample collection, can lead to positive outcomes even under low-resource and conflict constraints. Although a recent systematic review suggested that non–single antibiotic treatment might improve outcomes in chronic osteomyelitis [23], the largest PAPTO study in France recommended monotherapy with a shorter treatment duration (mean of 45.5 days, similar to our study) [10]. Similarly, we believe there is no strong case in favor of prolonged use of dual therapy combinations for extended periods, as was previously suggested.

Despite typically poor prognoses associated with PAPTO [11], our 24.6% recurrence rate, which is close to that in high-resource settings, could potentially be explained by the younger and healthier population, as higher PTO risk has been associated with older patients with comorbidities [19, 24]. While this result could also be due to effective debridement [20], we cannot confirm this from our study results as we did not specifically assess debridement practices. It is possible that our recurrence rate might be underestimated, as many patients were still under follow-up at the end of the study period.

However, considering that the literature suggests that 78% of posttrauma osteomyelitis recurrences occur within 6 months and >90% recur within 1–2 years of follow-up [11, 25], and with our median follow-up period of 203 days (IQR, 72–443 days)—equivalent to around 7 months—we believe a biggest majority of recurrences in our cohort were likely captured.

In Gaza, the higher recurrence could be influenced by longer follow-up (>3 times longer than Mosul) or more aggressive MDR and polymicrobial infections, or other unassessed factors that could differ between the included facilities like inadequate initial debridement or the impact of the repurposing of Mosul hospital during the coronavirus disease 2019 pandemic. This highlights the importance of the development of context-adapted contingency plans, and prioritization of surgical activities in health systems affected by conflicts, to ensure minimum follow-up of chronic infections during emergencies, given the high proportion of MDR *P aeruginosa* in our cohort. MDR *P aeruginosa* observed in our settings was higher compared to

that in regional conflict–associated wounds, where 30% MDR *P aeruginosa* was reported among war-wounded civilians in Syria and Iraq who were admitted from 2016 to 2019 to the tertiary traumatology center of the International Committee of the Red Cross (ICRC) in Lebanon [26]. Differences in resistance could be partly due to the varying study populations and regional differences in antimicrobial resistance epidemiology. Additionally, the journey and potentially more complex therapeutic trajectory of patients traveling from the region to the ICRC traumatology center in Lebanon could have contributed to variations in the prevalence of resistance seen across the various centers. Additionally, our study showed high MDR rates in non–*P aeruginosa* bacteria such as *S aureus* and Enterobacterales compared to regional studies. MRSA prevalence was 95%, significantly higher than in war-wounded PTO from Syria, Iraq, and Yemen (60.5%) [6], from an MSF-supported hospital in Yemen (72.6%) [27], and among PTO patients in Brazil (12.3%) [9].

Resistance to third-generation cephalosporins in our Enterobacterales isolates reached 100% for *E coli*, compared to 44.6% in skin, soft tissues, and bone isolates among war-wounded patients from Syria and Iraq [26]. This reflects the severe antimicrobial resistance challenges in conflict-affected settings and highlights the critical need for context-adapted antibiotic stewardship strategies. For instance, in MSF, we review our antibiogram yearly and accordingly adapt the clinical guidelines as per the changes in the epidemiology of antimicrobial resistance (AMR) among our catchment population. We also take into consideration any change in the supply and shortages of antibiotics. We also ensure difficult-to-treat cases are discussed by the AMS committee and referred to AMS experts to identify the most appropriate antibiotic treatment. Ciprofloxacin resistance was observed in more than a third of our PAPTO strains, with rates higher in Gaza than Mosul. This resistance level, which is between 30% and 50% in PAPTO osteomyelitis in war-wounded persons from low-resource settings [6, 26], and up to 3 times higher than in higher-resource settings [10, 28], highlights the disproportionate impact of AMR in low-resource settings and challenges the efficacy of oral fluoroquinolones, such as ciprofloxacin, a primary antibiotic for transitioning to oral therapy in PAPTO [29]. In our study, nearly half of the Gaza strains tested showed resistance to ciprofloxacin, complicating and limiting the switch to oral monotherapy, particularly with the emergence and transmission of resistance globally [30]. Inability to switch to oral monotherapy meant prolonged intravenous treatment and extended hospital stays. Consequently, assessing alternative treatment strategies and models of care, like outpatient parenteral antimicrobial therapy, is essential in such settings to reduce healthcare-associated infection risks, improve bed availability, and accelerate earlier patient home return. However, the implementation of such modalities in these settings is often challenging due to shortage of resources, infrastructure limitations, and security concerns, limiting the feasibility of outpatient care models.

Despite geographical proximity and similarities in community behaviors related to AMR [31], the resistance patterns observed in Gaza highlight the unique resistance epidemiological patterns driven by local factors like prolonged conflicts and consecutive wars that lead to a potential higher emergence and spread of AMR infections [32]. Our study showed almost similar resistance to carbapenem compared to other studies conducted among *P aeruginosa* osteomyelitis cases from conflict-associated wounds, where resistance was 15% to imipenem and 24% to meropenem in war-wounds treated between 2016 and 2019 [26]. Given the increasing trend of carbapenem-resistant, gram-negative bacteria in the Middle East [33], it is crucial to strengthen surveillance of MDR infections and antibiotic stewardship programs and reinforce IPC measures.

Our study is the largest in the Middle East in terms of cohort size focusing on PAPTO [9, 26] and comparable to the only known study from a high-resource setting conducted over a 15-year period [10]. Despite that, it lacked the power to assess recurrence risk factors of PAPTO. While providing new insights into managing PAPTO in low-resource settings like Gaza and Mosul, our findings are not broadly generalizable, and thus, recommendations for wider PAPTO treatment remain limited. The observed outcomes, based only on targeted therapy, should be interpreted cautiously given the lack of a comparative group and incomplete assessment of common factors that could affect outcomes such as debridement and infection control measures. The multicountry nature of the study, conducted in 3 different facilities, introduced context specificities that could have influenced the results despite the use of uniform antibiotic treatment guidelines, surgical standards, and optimal IPC measures. Therefore, more comprehensive and prospective research is needed to evaluate the effectiveness of various osteomyelitis treatment options on long-term patient outcomes and the role of surgical management and multidisciplinary approaches in PAPTO management in such settings. Despite the 3-year study period, the chronic nature of PAPTO meant many patients were still under follow-up with no definitive outcome at the end of the study period, possibly underestimating recurrence. Furthermore, X-ray results, which would allow the identification of clinically asymptomatic but radiological recurrences, are not systematically integrated as part of patients' follow-ups. They are only conducted at 24 months of follow-up to confirm radiological cure. However, the predominance of osteomyelitis recurrence within the first year posttreatment, and our median follow-up of 7 months, suggests that our findings align closely with expected results. Our study served in building evidence and complementing the scarce existent literature around PAPTO in conflict-affected settings,

informing future research and promoting tailored antibiotic stewardship.

CONCLUSIONS

Our study showed that, despite the high resistance and polymicrobial nature of posttraumatic *P aeruginosa* osteomyelitis in the low-resource, conflict-affected settings of Mosul, Iraq and Gaza, Palestine, we were still able to achieve good outcomes of care, with recurrence rates comparable to global reports. This was possible through appropriate and targeted use of antibiotics, primarily in monotherapy, provided over a mean treatment duration of 45.5 days, through a multidisciplinary approach that included surgical management, IPC, and access to a microbiology laboratory. To optimize treatment strategies in such contexts, further large-scale and adequately powered prospective studies with long-enough follow-up periods are needed to report on risk factors associated with PAPTO poor clinical outcomes and to assess the efficacy and safety of antibiotic treatment in monotherapy and dual therapies, as well as the impact of multidisciplinary approach on the case management of PAPTO in conflict-affected settings.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Author contributions. The authors contributed as follows: A. Q. M. T., C. W., K. M., and M. K. contributed to the study conception. Data collection was conducted by A. Q. M. T., F. G. G., M. R., R. A., and M. A. and supervised by K. M., who was also responsible for data curation. Data analysis was performed by A. Q. M. T. and K. M., with the technical support of all co-authors, and supervised by K. M. Drafting of the original manuscript was performed by A. Q. M. T., with the support of K. M. and M. K. The work was supervised by K. M. and M. K. All authors contributed to the study design, the interpretation and review of the results, and the approval of the final version of the article.

Patient consent. The research was approved by MSF Ethics Review Board protocol number 2165 (28/3/2022) and by the Ministry of Health and Environment of the Nineveh Health Directorate, Iraq (protocol number 10830; 27 March 2022) as well as the Helsinki committee in Gaza (protocol number PHRC/HC/1026/22; 7 February 2022). Written consent from patients was waived by the MSF and local ethics committees following the nature of the study design.

Data availability. Data are available upon request to the corresponding author.

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