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Review

Conflict and catastrophe-related severe burn injuries: A challenging setting for antimicrobial decision-making

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SUMMARY

Severe burns are a major component of conflict-related injuries and can result in high rates of mortality. Conflict and disaster-related severe burn injuries present unique challenges in logistic, diagnostic and treatment options, while wider conflict is associated with driving local antimicrobial resistance. We present a targeted review of available literature over the last 10 years on the use of systemic antimicrobial antibiotics in this setting and, given limited available data, provide an expert consensus discussion. While international guidelines do not tend to recommend routine use of prophylactic systemic antibiotics, the challenges of conflict settings and potential for polytrauma are likely to have ongoing impacts on antimicrobial decision-making and use. Efforts must be made to develop a suitable evidence base in this unique setting. In the interim, a pragmatic approach to balancing selective pressures of antimicrobial use with realistic access is possible.

Background

Conflict drivers of antimicrobial resistance (AMR) are a global health risk of increasing significance.[1] While limited, reports of high-rates of multidrug resistant infections among hospital patients with combat-related wounds from Ukraine are deeply concerning, with recognition of spread throughout Europe,[1] and the recent outbreak of conflict in Gaza presents additional concerns.[2] Together, these and other crisis situations (e.g. the recent earthquakes in Turkey) demonstrate major challenges to addressing the development and spread of AMR among healthcare facilities both locally and cross-border.

Within conflict, burns are common injuries, and subsequent sepsis due to infection is a major cause of mortality.[3] Where post-burn infections occur within the first couple of days, they tend to be with Gram positive organisms with later infections driven by Gram negative organisms.[4] International guidelines, primarily intended for use in civilian/non-disaster settings, do not routinely support immediate prophylactic antibiotics for burns citing a lack of available evidence.[3,5,7] The International Society for Burns Injuries Practice

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Guidelines do however acknowledge in resource poor settings, where microbiology monitoring may be difficult, use of prophylactic antibiotics by burn specialists may see a lowered threshold given concerns for sepsis as a leading cause of death.[3] Systematic reviews used to inform these guidelines tend to draw on small numbers of studies across several decades, with practice changing considerably over the time period.[3] A 2013 Cochrane analysis likewise concluded unclear effects of early systemic antibiotic prophylaxis on burn wound infections.[8] Perhaps more relevant for disaster settings, Médecins Sans Frontières and the evidence-based review Prevention of Combat-Related Infections Guidelines likewise do not advise systemic antimicrobial therapy for isolated severe burn injuries in the absence of signs of systemic infection while highlighting the importance of early debridement, topical antibiotics and rigorous infection prevention and control.[9,10] The 2017 Guidelines for Burn Care in Austere Environments broadly recommend avoiding prophylactic antibiotics due to a lack of definitive evidence.[6] In contrast, a 2010 meta-analysis concluded a potential for beneficial effect of prophylactic antibiotics in severe burns but likewise acknowledged methodological data as weak,[11] while a large nationwide Japanese study from 2017 suggested a potential benefit in those with severe burns needing mechanical ventilation in the first 48 h.[12]

In some conflict scenarios, however, the possibility of considerable delay (≥24 h) to first debridement, co-existent polytrauma (e.g. open fracture), environmental contamination with potential for multidrug-resistant organisms, or mass-casualty limiting opportunity for detailed examinations may occur,[5] which may impact early antimicrobial decision making. While broad-spectrum antimicrobial use is a selective pressure for AMR,[13] the choice of agent in conflict and catastrophe scenarios has multiple influencers, not least logistical challenges. Disruption to diagnostic pathways, drug supply chain insecurity, increased economic cost of reserve antibiotics, delay to initial surgery, and limited remote diagnostics could all understandably increase the likelihood of early prophylactic antimicrobial prescribing and selection of a broad-spectrum agent. The development of antimicrobial resistance in conflict-related infected wounds has resulted in the need to consider novel antibiotic combinations to manage late-stage infections.[14] Given the time since the publication of guidelines and limited available evidence, we undertook a review of the recent literature for conflict and/or disaster-related use of antibiotics in severe burn injuries. We then offer expert advice on considerations to limit broad-spectrum use of early systemic antibiotics, where they may be indicated, given associated challenges.

Review of the literature

Available data on outcomes in choice of antimicrobial agent for early prophylaxis of contaminated burns injuries is limited. Medline and Cochrane database searches were conducted for articles published in the last 10 years using terms 'burn' and 'conflict' or 'war' or 'combat' or 'catastrophe' or 'disaster' and 'antibiotic' or 'antimicrobial'. 1089 articles were returned (Supplementary Figure 1). Abstracts were reviewed by two independent investigators for articles that considered the use of early systemic prophylactic antibiotics in a conflict or disaster setting. Articles were excluded if they did not consider the use of prophylactic systemic antibiotics in a conflict or disaster setting. 34 articles were selected for full review by two independent investigators, and eight met the inclusion criteria (Supplementary Figure 1).[15–22]

Of the eight articles included, three reported observations of antimicrobial prophylaxis use in the context of burns following a mass casualty incident.[15–17] Two separate papers reported on the same 33 adult patients involved in an outdoor dust explosion,[15–17] and a further reported on 16 adult patients involved in a gas tanker explosion near eastern China.[17] One of these articles considered directly the benefit of prophylactic antibiotic use, showing a reduction in infection rates against time and no mortalities but was limited by a lack of control group and recommended the need for a randomised control trial in the setting of a major burn incidents.[16] All three reported potential benefits in considering early systemic prophylactic antibiotics for severe burns following a mass casualty incident, but recognise considerable limitations in sample sizes and study design.[15–17]

Parrish and Seda, summarising the special consideration of radiation burns, highlight a triage approach to burns patients that includes special consideration of early systemic prophylactic antibiotics following exposures greater than 2 Gy.[18] A summary of antimicrobial use for battlefield injuries managed in French military facilities mentions simple burns, for which they do not recommend any antimicrobial prophylaxis but do not directly comment on severe burns, although do recommend prophylaxis in cases of multiple trauma (first line intravenous amoxicillin-clavulanate).[19] The final articles represented clinical guidelines for use in combat-related injuries,[20] in military prolonged field care settings,[21] and the report of the World Health Organisation (WHO) technical working group on mass casualty burns where systemic prophylactic antibiotics were not routinely advised,[20–22] albeit with recognition of the potential for the need to provide cover for concomitant wounds (e.g. open fractures),[21,22] and with a recommendation to carry appropriate antibiotics in case of evidence of early infection.[21] The US Clinical Practice Guideline recommended only topical antimicrobials in the context of superficial, deep partial or full-thickness burns.[20] There is also guidance provided however for situations of expected delay to reach surgical care, which recommended moxifloxacin or ertapenem as first-line oral and intravenous/intramuscular options respectively.[20] In short, evidence for the benefit of systemic prophylactic antibiotics in conflict or disaster-related severe burn injuries remains limited and unclear. However, the chaotic nature of conflicts and disasters, with the potential for gross contamination and polytrauma, means that their use is likely to continue. Recognition of high rates of AMR associated with conflict in general, but over the last two years, particularly with conflict-related wounds in Ukraine,[1] is then likely to impact the antimicrobial agent of choice, with the temptation to select a broader agent. More thorough data on pre-injury carriage rates of AMR could help reassure in this situation.

In lieu of adequate evidence available now, and given the concurrent risk of conflict-related burns and evolving multi-drug resistance in Ukraine and other major conflict areas, we assembled an Expert Advisory Group to consider burns in conflict settings and discuss options in these circumstances. The assembled group was selected using snowball sampling to gather appropriate expertise in civilian medical microbiology and infectious diseases, military medical microbiology and infectious diseases, global public health (in the context of AMR), antimicrobial pharmacy, antimicrobial stewardship, humanitarian medicine, burns and plastic surgery and hold associated academic and/or national or international advisory roles. After review of the literature and expert discussions, antimicrobial agents included for discussion were selected based on available agents licensed for appropriate systemic Gram-positive antimicrobial cover in Europe (including newer agents) or supported by knowledge of current agents being employed in areas of ongoing European conflict.[20] Antimicrobials were excluded if considered prohibitively expensive for widespread use. Key points discussed included (i) common causes of early infection in severe burns, (ii) potential ideal properties of an antimicrobial agent for use in conflict settings, (iii) potential value, and limitations, of AMR surveillance repositories in these settings, (iv) potential advantages and disadvantages of available antimicrobial agents and (v) potential future work of benefit. The outcome of discussions and a summary table of considerations for potential antimicrobial agents in this scenario are presented.

Table 1
Potential antimicrobial considerations for early prophylaxis in conflict-related severe burns injuries subject to delayed initial debridement.

Agent	Spectrum						Route	Dosing	AMS	Cost	Advantages	Limitations of use	
Drug	Pathogens			Commensal*			*IV (intravenous); B (bolus) or I (infusion) / IM (intramuscular) / PO (oral)*	*Frequency of dosing*	*Risk of selective pressure on multi-drug resistant Gram negative pathogens*	*£(< €20/d) / ££ (€20-40d) / £££(> €40/d)*	*NS (narrow spectrum), WA (widely available), LA (long acting)*	*AMR (selective pressure on G negative resistance), MDD (multiple daily dosing)*	*WHO AWaRe category*
	MSSA	*MRSA*	*Group A Strep*	*Pseudomonas sp.*	*Acinetobacter sp.*	*Enterobacterales*							
Cefazolin	+	-	+	-	-	±	IV(B&I) / IM	8 hourly	Moderate	£	NS, WA	MDD	Access
Ceftaroline fosamil	+	+	+	-	-	+	IV (B&I)	12 hourly	Moderate - high	£££	Anti-MRSA	Limited availability, AMR (ESBL and CRO risk)	Reserve
Ceftriaxone	+	-	+	-	-	+	IV(B&I) / IM	24 hourly	Moderate – high	£	WA, LA	AMR (ESBL and CRO risk)	Watch
Dalbavancin	+	+	+	-	-	-	IV infusion	Stat / weekly	Low	£££	NS, anti-MRSA, LA	Infusion only, limited availability	Reserve
Daptomycin	+	+	+	-	-	-	IV (B&I)	24 hourly	Low	£££	Anti-MRSA, NS, LA	Fridge storage only	Reserve
Delafloxacin	+	+	+	+	-	+	IV (I) / PO	12 hourly	Moderate	£££	Oral administration	Limited availability	Watch
Ertapenem	+	-	+	-	-	+	IV (I) / IM	24 hourly	Moderate - high	££	WA, LA	AMR risk for CRO	Watch
Flucloxacillin	+	-	+	-	-	-	IV(B&I) / IM / PO	6 hourly	Low	£	NS, WA,	MDD	Access
Linezolid	+	+	+	-	-	-	IV (I) / oral	12 hourly	Low	£	Anti-MRSA, NS, oral administration	Prescribing cautions with concomitant medications Potential for driving resistance in tuberculosis	Reserve
Levofloxacin	+	+	+	+	-	+	PO / IV(I)	12-24 hourly	Moderate	£	Oral administration	Potential for driving resistance in tuberculosis	Watch
Moxifloxacin	+	+	+	-	-	+	PO / IV(I)	24 hourly	Moderate	£ (PO)-£££ (IV)	Oral administration, LA	Limited availability of IV Potential for driving resistance in tuberculosis	Watch
Teicoplanin	+	+	+	-	-	-	IV(B&I) / IM	12-24 hourly	Low	£	NS, anti-MRSA, LA	Weight-based dosing	Watch
Tigecycline	+	+	+	-	+	+	IV(I)	12 hourly	Moderate	££	Anti-MRSA, LA	Broad-spectrum, nausea common, infusion only	Reserve

*CRO = carbapenem resistant organism, AMR = antimicrobial resistance, ESBL = extended spectrum beta lactamase, MRSA = methicillin-resistant S. aureus, MSSA = methicillin-susceptible S. aureus. *In the context of early causes of infection following a severe burn, Gram-negative organisms are commonly found but less likely to be the cause of infection. Potential antimicrobial options to cover common skin and soft-tissue pathogens in early infection of severe burns are listed, and characteristics for use in conflict or natural disaster scenarios are considered. Individual countries provide licensing for the use of antimicrobial agents in different infection scenarios. As an example, listed antimicrobials are approved by the European Medicines Agency for use in (i) skin and soft tissue AND bone and joint infection (ceftriaxone, teicoplanin), (ii) skin and soft tissue but NOT bone and joint infection (ceftaroline, dalbavancin, daptomycin, delafloxacin, tigecycline, tedizolid) or (iii) neither (ertapenem, except in the context of diabetic foot infections). For the remaining, the UK Medicines Health Research Authority have licensed flucloxacillin for use in bone and joint infections, moxifloxacin and levofloxacin for use in complicated skin and soft-tissue infections, and cefazolin for use in skin and soft tissue AND bone and joint infections. World Health Organisation Access, Watch, Reserve classification is provided as per the latest 2023 guidelines.*[28] Further information, including references for product information, is available in Supplementary data, Table 1.

Expert consensus

Severe burn injuries are associated with longer hospital stays, higher rates of antimicrobial exposure and severe sepsis that can be difficult to distinguish from burns pro-inflammatory pathophysiology in the early phase.[4] Review of casualties from modern conflicts highlights a rising incidence of burn injuries, in both military and civilian populations.[23] Mortality rates are associated, among other factors, with total body surface area (TBSA) burned, with 24% mortality rates in those with > 30% TBSA involvement seen in Ukraine even prior to the outbreak of conflict.[24] After initial resuscitation, sepsis is considered the leading cause of death.[25] Early causes of infection are typically with Gram positive organisms such as *Staphylococcus aureus,* with Gram negative organisms colonising the wound within the first 5–7 days and often being responsible for later episodes of infection.[26] If used, therefore, early antimicrobials must be optimised while acknowledging the challenges above to provide suitable cover against common Gram-positive organisms while reducing antimicrobial selective pressure on late (often Gram negative) infections as much as possible. This is particularly important in the context of extensive, conflict-related injuries with severe burns that often require a protracted course of healing.

Where a decision is made to prescribe an antimicrobial for patients who have experienced severe burn injuries in conflict settings, desirable properties may include agents that (i) are deliverable via intravenous bolus (rather than infusion) and/or intramuscular injection (or ideally a highly bioavailable oral agent), (ii) have a long half-life requiring minimal daily (or less frequent) dosing, (iii) have a good spectrum of Gram-positive organism activity, (iv) are cost-effective and (v) have a reliable drug supply chain without the need for cold chain storage (Table 1).

Pre-conflict antimicrobial surveillance data may help guide the initial selection of prophylactic agents. However, often, due to the concurrent conflict there is significant disruption to these surveillance systems, therefore limiting their ability to guide these selections. Current data sets should however be interpreted with caution, with recognition of considerable variability across surveillance repositories for key organisms, including *Staphylococcus aureus*, evident over recent years.[27] Moreover, key international observatories, such as the World Health Organization's Global Antimicrobial Use and Surveillance System, tend to derive data from countries in conflict from a limited number of hospital samples, making generalisation to a population at the point-of-wounding inappropriate.[28] Data for Ukraine for example, held in the Central Asian and European Antimicrobial Surveillance repository pre-conflict, suggests 30.1% of (n = 176, 2021) invasive *Staphylococcus aureus* samples were reported as methicillin resistant.[28] Despite this, there have been reports from Ukraine of good outcomes with ceftriaxone at the point-of-wounding,[29] suggesting caution must be applied in interpreting these limited data among the general population.

Several potential agents exist that may provide appropriate options for early systemic prophylaxis and treatment of infection in those who have also experienced severe burn injuries while limiting AMR selective pressures. Where delays or multiple injuries may occur, Table 1 describes potential options for pre-debridement antimicrobial prophylaxis in severe conflict-associated burn injuries, being cognizant of the location of the patient in the evacuation pathway, the severity and location of burn, time to initial debridement, potential concurrent injuries and considering posological aspects of the different agents in this setting. When selecting an antibiotic, it is also worth noting WHO AWaRe (access, watch, reserve) classifications that consider individual agent's potential impact on antimicrobial resistance as well as current safety notices (Table 1).[30] Fluoroquinolones for example, may be associated with selecting out porin producing *Pseudomonas aeruginosa,* impacting a range of antimicrobial classes and have been the focus of safety notices aimed at restricting their use.[31,32] These may be relevant considerations if treatment courses beyond a single dose were considered.

While conflict presents challenges to all levels of antimicrobial stewardship, efforts must be made to balance broad selective antimicrobial pressures against appropriate antimicrobial access. Without such, we risk increasing levels of AMR associated with nosocomial infections and further limiting options for late-stage treatment of infected patients. Reporting of data on outcomes, including early microbiological results and incidence of post-injury blood-stream infection underpinned by reliable diagnostics and the impact of IPC programmes in different settings (e.g. field hospitals vs urban hospitals) will be paramount in helping build a suitable evidence base for antimicrobial decision making in the context of conflict or catastrophe-related severe burn injuries.

Author contributions

All authors contributed significantly to pre-draft discussions for this work. SJCP, RM, SH and LSPM drafted the initial manuscript. SJCP, ZL, and SDW conducted the literature search. SH prepared the manuscript table. RM prepared the Supplementary data file. All authors contributed significantly to revisions and preparation of the final draft.

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Declaration of Competing Interest

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106224.

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