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PEDIATRIC INFECTIOUS DISEASES (I BROOK, SECTION EDITOR)

Pediatric Infectious Diseases Encountered During Wartime Part II: Infectious Diseases Complications in the Individual Pediatric Patient

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Purpose of Review Children in many regions face the daily threat of injury from armed conflict. The direct effects of combat trauma have led to many morbidities in survivors, including a variety of infectious complications. Contemporary experiences from recent military operations have advanced combat casualty care and concurrently informed the care of civilian combat trauma. Unfortunately, there is a lack of data to correlate the impact armed conflict has on the specific risks for infection in pediatric casualties. We review modern literature and apply data from adult casualties to pediatric combat trauma features to form management considerations and identify future research needs. Children require a disproportionately high number of resources when injured, and recently developed pediatric injury severity scoring systems can be predictive of potential outcomes. Blast injuries are the most common trauma type, and children suffer unique injury patterns with subsequent risks for infections. Experience has shown that mixed injuries, including blasts, penetrating injuries, burns, and the need for massive blood transfusions, can pose unique infectious challenges such as invasive fungal infections. Antimicrobial resistance is a top health priority with combat injuries, as multidrug-resistant organisms rapidly emerge in hospitals caring for those injured in conflict. Resources to assist in the management of infectious complications of direct injury to children in armed conflict regions are provided.

Recent Findings We review the recent literature with an emphasis on publications over the past decade, apply data from adult casualties to pediatric combat trauma features to form management considerations, and identify future research needs.

Summary Children require a disproportionately high number of resources when injured, and recently developed pediatric injury severity scoring systems can be predictive of potential outcomes. Blast injuries are the most common trauma type, and children suffer unique injury patterns with subsequent risks for infections. Experience has shown that mixed injuries, including blasts, penetrating injuries, burns, and the need for massive blood transfusions, can pose unique infectious challenges such as invasive fungal infections. Antimicrobial resistance is a top health priority with combat injuries, as multidrug-resistant organisms rapidly emerge in hospitals caring for those injured in conflict. Resources are provided to assist in the management of infectious complications resulting from direct injury to children in armed conflict regions.

Keywords Armed conflict · Children · Infections · Trauma

Introduction to Part II

Armed conflict represents a clear and present threat in the daily lives of many people throughout the world. Specifically, the twenty-first century armed conflicts have been predominantly marked by asymmetric warfare, state vs non-state actors, and unconventional tactics and tools, which have brought combat activities into children's environments and increased their risk for injury and/or death. Armed conflict inflicts both direct and indirect effects on children, which can be exacerbated by infectious processes. This is the second article of a two-part series describing recent updates in the infectious complications

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encountered during armed conflict. The first article focused on the indirect effects of combat (i.e., infrastructure destruction, forced displacement, and resource scarcity), resulting in increased communicable diseases, vaccine-preventable diseases, and opportunities for the spread of emerging infectious diseases. The focus of this article is the infectious complications resulting from the direct effects of armed conflict on children.

The Burden of Injuries in Individual Children Related to Conflict

Pediatric patients account for a significant yet variable percentage of direct trauma during conflict. A recent systematic review covering the global twenty-first century armed conflict reported 34.7% of conflict-related injuries occurred in people less than 18 years old [1]. An International Committee of the Red Cross study of eight field hospitals located at a variety of countries including the Democratic Republic of the Congo (DRC), Afghanistan, Thailand, Kenya, Pakistan, and the Russian Federation, from 1988 to 2014, found that 15.4% of patients were under 15 years of age [2]. Over the first decade in Iraq and Afghanistan, 5.8% of all role 3 (combat support field hospital) admissions were children [3]; another summary using the Department of Defense Trauma Registry (DoDTR) reported 8% of patients from 2007 to 2016 were children [4]. Trauma associated with armed conflict is accompanied by significant mortality, and pediatric patients are at a higher risk of mortality than adults (4.1% vs 2.7%) [5]. It has been demonstrated in Iraq and Afghanistan that younger age is independently associated with mortality [3]. Furthermore, females were disproportionately represented among trauma victims; moreover, they experienced increased morbidity and an increased mortality rate compared to males [6].

Pediatric Trauma Injury Severity Scoring

When assessing the individual traumatically injured patient, injury severity scores are used to stratify mortality risk and determine the necessary resources. In adults, the ability of the Denver and Marshall injury severity scores to predict risk of infection following civilian trauma has been demonstrated [7]. To date, no pediatric injury scoring system has demonstrated a similar ability; however, an easily calculable pediatric severity scoring system known as the "BIG" score, using base deficit, international normalized ratio, and Glasgow Coma Scale (GCS) recently has been developed [8].

Comparative evaluations have demonstrated similar performance to well-established trauma severity illness scores utilized in industrialized western nations: **P**ediatric **RIS**k of **M**ortality (**PRISMIII**), **P**ediatric **I**ndex of **M**ortality 2 (**PIM2**), and the **PE**diatric **L**ogistic **O**rgan **D**ysfunction (**PELOD**) score [9]. Similarly, BIG performed well compared to the **N**ew **I**njury **S**everity **S**core (**NISS**), **TR**auma and **I**njury **S**everity **S**core (**TRISS**), and **P**robability of **S**urvival 20**14** (**PS14**) scores in a pediatric population from Turkey and Syria [10]. Evaluating the newer BIG score and other pediatric trauma scoring systems for their ability to predict risk of infection could extend their utility.

Epidemiology of Pediatric Trauma During Armed Conflict

During armed conflict, pediatric injuries and admissions are primarily a result of trauma or burns. The injuries caused by direct trauma are typically categorized as blunt force, blast, or penetrating injuries. Children are more commonly injured by blast or blunt force mechanisms, with extremity trauma being a dominant injury pattern. Figure 1 graphically demonstrates the frequency of the different injury types as described by studies from various regions [2, 3, 11–15]. Additionally, a prospective study at Camp Bastion, Afghanistan, provided detailed descriptions of pediatric trauma patients, and demonstrated over 75% of traumatic injuries were distributed to the extremities and head and neck regions [11]. Furthermore, over a 4-year period in Afghanistan, the French military combat hospital identified penetrating trauma as the main injury mechanism, with blast injuries being more common than those due to firearms [16].

Blast Injury Patterns in Children

Distinctive blast injury patterns influence outcomes for children, and often require longer hospitalizations, increased operative workloads, and an overall larger resource burden. In 2019, a mixed-methods narrative review characterized the distinct pediatric blast patterns in detail; Fig. 2 demonstrates the frequency of specific blast injury patterns reported [17]. Seven years of British military experience in Afghanistan describing pediatric blast injuries suggested that severe head, face, and neck injuries are more likely in children than adults [18]. Blasts are often complicated by severe skin and soft tissue injuries including burns. There is an association between prolonged intensive care unit (ICU) length-of-stay and children with burns or other superficial skin injuries suffered during traumatic blasts [19]. In addition to the direct result of active armed conflict, the discovery of unexploded ordinances such as landmines is more likely to impact children versus adults. Children injured by these devices were more likely to have injuries to their arms, upper body, and head than adults [20].

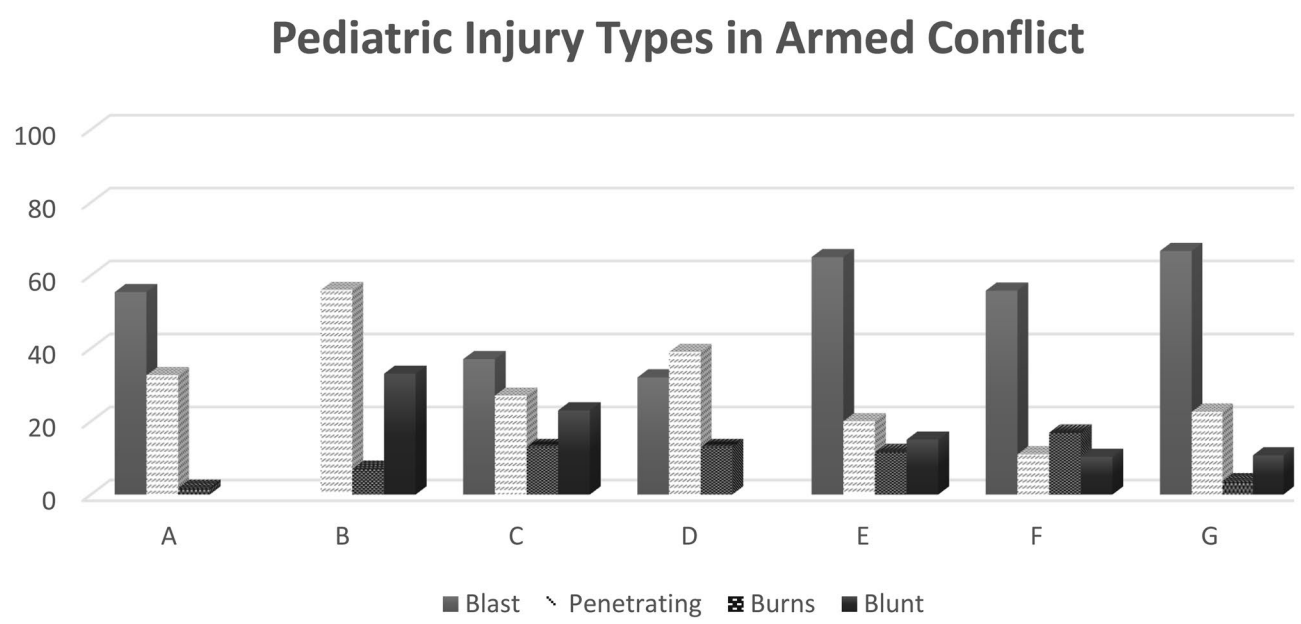

Fig. 1 (**A**) International Committee of the Red Cross reported injury types from pediatric patients at hospitals throughout the world had burns 1.8%, gunshot wounds (penetrating injury) 32.6%, and blast injuries 55.4% [8]. (**B**) Pediatric patients in Afghanistan from 2008 to 2014 had penetrating injuries 56%, blunt injuries 33%, and burns 7% [15]. (**C**) Experience from 10 years of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF): blast injuries 37%, penetrating injuries 27%, blunt injuries 23%, and burns 13% [3]. (**D**) The first 2000 pediatric admissions during OIF and OEF had 39% penetrating injuries, 32% blast injuries, and 13% burns [13]. (**E**) The British military field hospital in Camp Bastion, Afghanistan, reported 15% blunt injuries, 65% blast injuries, 20% gunshot wounds, and 11.6% burns [14]. (**F**) During another time period, the British military field hospital in Camp Bastion, Afghanistan, managed 55% blast injuries, 11% penetrating injuries, 10% blunt trauma, and 16.9% burns [11]. (**G**) Of Syrian children in 2013, the following patterns were seen: 66.7% blast injuries, 22.6% penetrating injuries, 10.7% blunt force injuries, and 3.6% burns [12]

Infectious Complications of Combat Trauma

To our knowledge, there are no recent published studies regarding the pediatric specific infectious complications related to direct injury during armed conflict. Drawing from the available adult literature, the bulk of which has been published based on the recent US military experience, however, we can attempt to extrapolate infectious complications to similar pediatric traumatic injuries. It should be noted that there are some major limitations to this type of comparison. In addition to the physiological differences, children have a very different hospitalization experience than combatants. As US and North Atlantic Treaty Organization (NATO) service members are typically quickly evacuated, local pediatric casualties can remain in theater hospitals for longer duration. Such extended stays may present an additional a risk factor that may confound our comparative assessment.

Infections complicate combat trauma and can be a major driver of mortality in those who survive initial injury. Adult combat-related extremity wound infections are independently associated with traumatic amputations, improvised explosive device (IED) blast injuries, polytrauma, shock index, and blood transfusions [21]. From 2003 to 2009, 5.5% of adult US military casualties in OIF and OEF developed an infection involving the skin, wound sites, lung, or blood, most caused by Gram-negative organisms. Furthermore, a high injury severity score (ISS) was the primary risk factor associated with infection [22]. Combat-associated abdominal injuries frequently require exploratory laparotomies and are at risk for developing subsequent surgical site infections. A descriptive study of pediatric combat casualties found laparotomies were twice as common compared to adult US military casualties [23]. 14.4% of adult US military combat casualties requiring a combat-related exploratory laparotomy developed a surgical site infection [24]. Following multivariable assessment, risk factors independently associated with skin and soft tissue infection development included colorectal injury, duodenal injury, and history of prior infection. Interestingly, blast injury was associated with lower likelihood (RR 0.13) of infection compared to penetrating injuries [25]. Pediatric civilian trauma center data demonstrate similar rates of infectious sequelae. A single-center trauma center analysis of damage control laparotomies experienced 18% surgical site infections [26]. Additionally, a National Trauma Data Bank based study, examining pediatric damage control laparotomies in non-combat trauma reported surgical site infections, pneumonia, and sepsis as the most common infectious complications at 13.3%, 12.5%, and 4%, respectively[27].

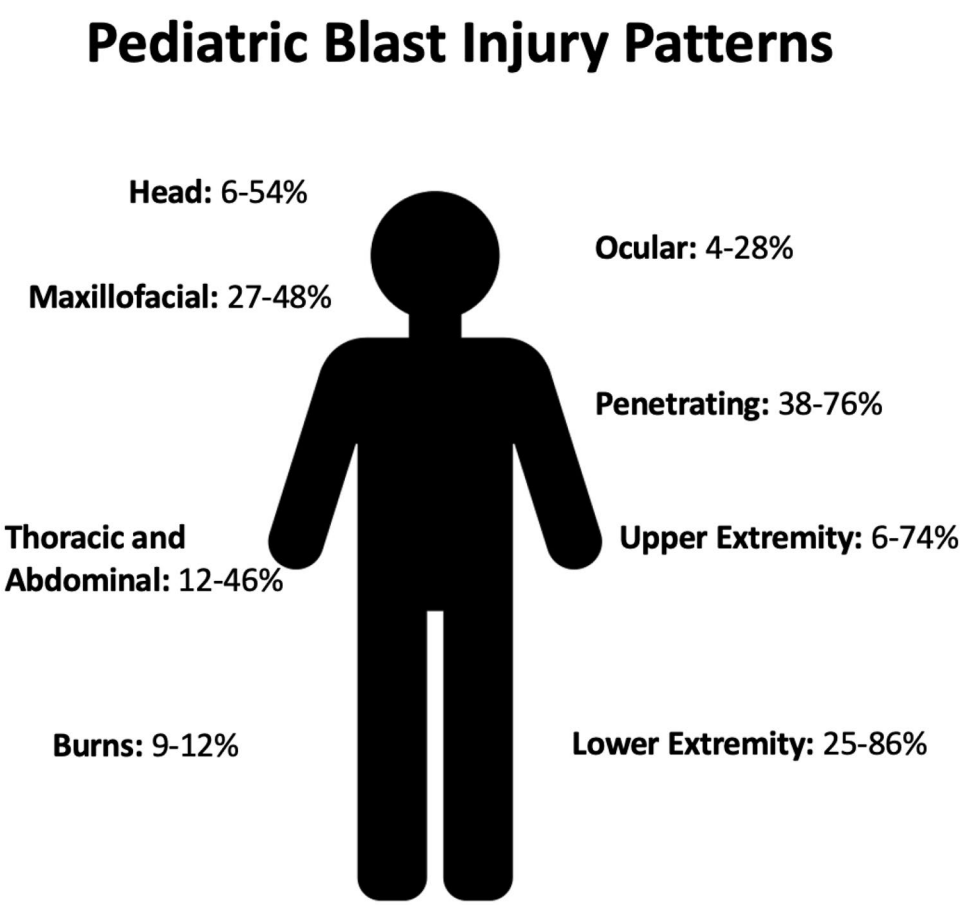

Fig. 2 Descriptive representation of the blast injury patterns and their frequency in children [17]

Importantly, recommendations provided by the US Joint Trauma System (JTS) "Prevention of Combat-Related Infections Guidelines Panel" have been published to deliver specific scenario and injury pattern guidance. In 2011, the Infectious Diseases Society of America and the Surgical Infection Society endorsed updated guidelines for prevention of infections associated with combat-related injuries [28]. An effort to lower infection incidence following war-related wounds resulted in the Tactical Combat Casualty Care (TCCC) guidelines, recommending that prehospital antibiotics be given for all open combat wounds [29]. Adults are to receive moxifloxacin or ertapenem at the point of injury if unable to be evacuated to a medical facility within 3 h; however, the TCCC guidelines do not specifically address the pediatric population weighing fewer than 40 kg (where these antibiotics are less commonly utilized). To our knowledge, the only report to date evaluating prehospital antimicrobial administration in children found a wide range of antibiotics given, with cephalosporins, cefazolin, and ceftriaxone being the most commonly administered. This was attributed to medication availability and logistical issues complicating pediatric care at the point of injury [30]. Furthermore, because the preferred oral agent in adult casualties, moxifloxacin, is not FDA-approved in children, the JTS is unable to formally recommend its use in children under 18 years of age. Newer data, however, demonstrates moxifloxacin's tolerability in children for prolonged periods of time [31] [32, 33]. The American Academy of Pediatrics has recommended the use of fluoroquinolones in various infections [34]. Additionally, a current meta-analysis showed fluoroquinolones, when compared to other antibiotics, have no differential effect on adverse events of the musculoskeletal system [35]. We believe the benefits of early antibiotic administration at the point of injury would outweigh the minimal risk of adverse drug effect due to short-term moxifloxacin administration until reaching a medical facility, in all patients ≥ 40 kg, and could be considered in younger children. The ability to provide appropriate point-of-injury antibiotics would be increased with pediatric-tailored tools and availability of pediatric medication doses. In the following paragraphs of this section, we highlight the JTS recommendations, describe recommended empiric antimicrobials for different anatomic patterns of penetrating injuries in Fig. 3, and provide pediatric-specific dosing for suggested antimicrobials in Table 1.

Extremity Injuries

The most common injury site for children is the extremities. Injuries to the extremities occur more frequently in younger, previously healthy patients such as military service

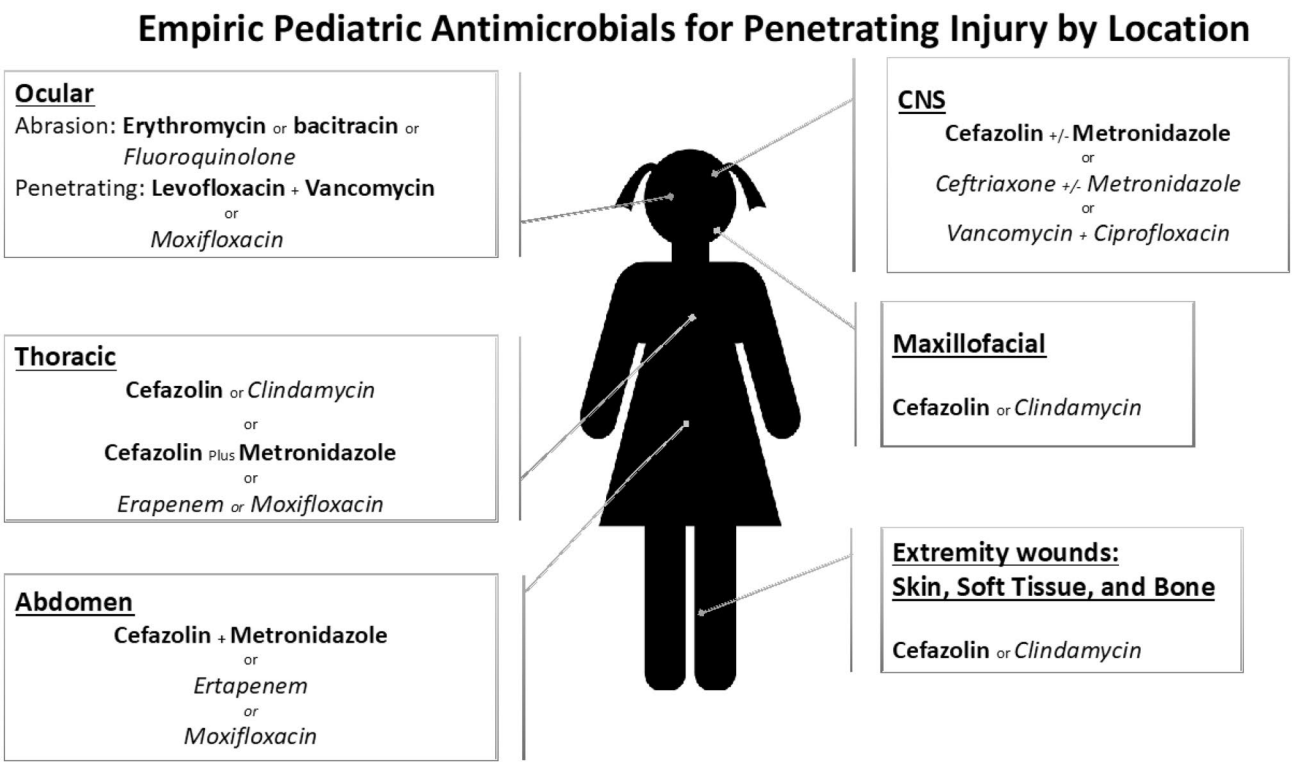

Fig. 3 Recommendations adapted from JTS infection prevention in combat-related injuries clinical practice guidelines. Alternative agent is italicized [42]

members. Subsequently, these injuries can become infected. Due to the mechanism of injury, osteomyelitis and soft tissue infections occur frequently. *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, extended-spectrum ß-lactamase (ESBL) producing *Klebsiella* species (spp.), and *Escherichia coli*, as well as methicillin-resistant *Staphylococcus aureus* (MRSA), have been frequently isolated. For open traumatic injuries during combat, early antibiotic administration is recommended and should be continued for at least 5 days after injury. Consideration of antibiotic options should include a first-generation cephalosporin, with thought of utilizing a second agent to provide enhanced Gram-negative coverage. Higher doses are recommended to optimize antimicrobial pharmacodynamics and pharmacokinetics. Prompt and effective debridement with irrigation is necessary to combat the gross contamination of these wounds [36].

Head and Neck Injuries

Head and neck injuries related to trauma occur frequently and are more common in pediatric casualties. Pathogens previously described in maxillofacial infections included *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas* spp., *Klebsiella* spp., and fungi such as *Candida*. Post-injury antibiotics are recommended, with cefazolin being the agent of choice for injuries in the maxillofacial regions, levofloxacin for penetrating eye injuries, and topical erythromycin ophthalmic ointment for eye injuries such as burns or abrasions [37]. In patients with serious head injuries, infections of the central nervous system (CNS) such as meningitis, osteomyelitis of the skull, and abscess formation have been commonly described. A 9.1% rate of meningitis was reported in Iraq and Afghanistan service members with penetrating injury [38]. *Acinetobacter baumanni*, *Staphylococcus epidermidis*, *Cutibacterium acnes*, *Enterobacter cloacae*, *Enterococcus faecalis*, *Candida* spp., *Staphylococcus capitis*, *Corynebacterium jeikeium*, and *Escherichia coli* have been isolated. Dermal organisms, such as Coagulase-Negative *Staphylococcus* are associated with later wound colonization/infections, while Gram-negative facultative aerobes and *Staphylococcus aureus* are predominant in intracranial infections [39]. Early antimicrobial options to attempt and prevent infection following CNS-penetrating injury include cefazolin or ceftriaxone, in combination with intravenous metronidazole, with continuation of antibiotics beyond the initial course of the longer duration of 5 days, or until cerebrospinal fluid (CSF) leak is closed should be tailored to culture results and susceptibilities.

Table 1 Table of common antimicrobials with pediatric dosing and helpful notes for the clinician

Medication	Route	Dose (mg/kg/dose unless specified)	Frequency	Max daily	Notes
Antibacterials					
Amoxicillin-clavulanate	PO	14:1 formulation 40–45 mg/kg 7:1 formulation 15–25 mg/kg 4:1 formulation 10–15 mg/kg	14:1 and 7:1–Q 12 h 4:1–Q 8 h	4 g	Dosed on amoxicillin component
Piperacillin-tazobactam	IV	80–100 mg/kg	Q 6–8 h	16 g	Dosed on piperacillin component
Cefazolin	IV	20–30 mg/kg (SSTI) 100 mg/kg/day (bone and joint)	Q 6–8 h Q 6 h	12 g	
Cephalexin	PO	15–25 mg/kg (SSTI) 100 mg/kg/day for (bone and joint)	Q 6–8 h Q 6 h	4 g	
Ceftriaxone	IV, IM	50–100 mg/kg	Q 24 h	4 g	
Ertapenem	IV, IM	15–20 mg/kg	Q 12 h	6 g	Poor activity against *Pseudomonas* and *Acinetobacter* spp.
Meropenem	IV	20 mg/kg 40 mg/kg (meningitis)	Q 8 h	6 g	
Levofloxacin	IV, PO	8 mg/kg ≥ 50 kg–500 mg	Q 12 h Q 24 h	500 mg	
Ciprofloxacin	IV, PO	10–15 mg/kg	Q 12 h	1.5 g	
Moxifloxacin	IV, PO	10 mg/kg ≥ 40 kg–400 mg	Q 24 h	400 mg	Not FDA-approved for pediatric patients
Clindamycin	IV, PO, IM	10–13 mg/kg	Q 8 h	1.8 g	
Doxycycline	IV, PO	1.1–2.2 mg/kg	Q 12 h	200 mg	Appropriate to use for short (< 14 days) duration due to concerns of tooth staining
Trimethoprim-sulfamethoxazole	IV, PO	4–5 mg/kg	Q 12 h	320 mg	Dosed per Trimethoprim component
Metronidazole	IV, PO	7.5–10 mg/kg	Q 6 h	4 g	
Vancomycin	IV	15–20 mg/kg	Q 6–8 h	2 g per dose	Loading dose of 20–25 mg/kg should be considered
Antifungals					
Amphotericin B	IV	Deoxycholate 1–1.5 mg/kg/day Lipid 3–5 mg/kg/day	Q 24 h	1.5 mg/kg 10 mg/kg	Does not cover *Aspergillus terreus*, *Scedosporium apiospermum*, or *Scedosporium prolificans*. Renally cleared with good CSF penetration
Voriconazole	IV, PO	< 50 kg: 9 mg/kg twice daily on day 1, then 8 mg/kg twice daily ≥ 50 kg or ≥ 15 years old: 6 mg/kg twice daily on day 1, then 4 mg/kg (or 200 mg) twice daily	Twice daily	600 mg	Does not cover *Mucor*, *Rhizopus*, *Aspergillus calidoustus*, or *Candida glabrata*. Hepatically cleared with good CSF penetration. QTc prolonging. Limited safety and efficacy in < 12 years old
Posaconazole	IV, PO	< 34 kg: 18–24 mg/kg/day ≥ 34 kg: 800 mg/kg/day	Divided four times daily		Does not cover *Aspergillus calidoustus*. Good for *Mucor*, *Rhisopus*, and *Scedosporium*. Minimal CNS penetration. QTc prolonging. Non-FDA approved for < 18 years old

Adapted from AAP Red Book 2018 [47]

Thoracic and Abdominal Cavity Injuries

Thoracic and abdominal cavity injuries are common and present unique infectious risks. Thoracic wounds can lead to empyema and other infectious complications. Timely tube thoracostomy for hemothorax limits the retention of blood products, which can be a nidus for infection and development of empyema. Cefazolin, for up to 24 h, has been recommended for prophylaxis to reduce pneumonia in thoracic trauma. Abdominal wounds are more commonly caused by blast injuries, as opposed to gunshot or penetrating injuries. Up to 30% of abdominal injuries will develop an infection, with even higher risk for those with hollow-viscus perforation. Unsurprisingly, the organisms most responsible are Gram-negative enteric organisms such as *Escherichia coli*, other *Enterobacterales*, as well as *Bacteroides* spp., *Klebsiella* spp., and fungi, *Candida* spp. [40]. Post-injury antibiotic prophylaxis is recommended. A combination of cefazolin and metronidazole is recommended, while ertapenem or moxifloxacin could be considered for additional Gram-negative bacterial coverage. As previously discussed for pediatric patients, the use of a fluoroquinolone has not been endorsed due to lack of US Food and Drug Administration (FDA) approval and risk of side effects, and they should only be used with caution. Another infectious consideration is severe abdominal injury involving the spleen. In this case, a splenectomy might be necessary. If so, heightened awareness for overwhelming post-splenectomy infections and specific immunizations should be considered as indicated, to prevent future invasive infection by encapsulated organisms. The JTS recommends a vaccine naïve patient receive *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type b vaccinations at the first available opportunity in the immediate post-operative period, but not later than 14 days following splenectomy[41].

Special Consideration–Fungal Infections

Invasive fungal infections (IFI) from combat trauma commonly present within 1 week and can occur as frequently as in 10–12% of high-risk patients; identified risk factors include dismounted blast injuries (injured while ambulatory), traumatic transfemoral amputations, extensive perianal, genitourinary, or rectal injury, and massive blood transfusions [43]. The continued necrosis in debrided wounds is a hallmark of blast injuries complicated by fungal infection. *Mucorales* order fungi, *Aspergillus* spp., and *Fusarium* spp. are implicated in the overwhelming majority of IFI [44]. Often, fungal infections due to combat injuries are polymicrobial, with multiple molds and/or bacterial pathogens present. Early application of 0.025% Dakin's antifungal topical solution should be used to irrigate high-risk wounds, in addition to frequent insistent debridement. For wounds with continued tissue necrosis and concern for fungal infection, empiric systemic antifungal treatment should include dual antifungal therapy with both amphotericin B and an intravenous triazole [45]. Risk stratification tools for invasive fungal wound infections can help optimize management decisions, such as https://www.sc2i.org/tools/ [44]. Additionally, a recently described decision support tool has been developed to predict IFI risk, using available information at two key locations: initial care and tertiary care settings. The model has been externally validated as a clinical decision support tool for use at the point of injury to identify high risk individuals for early antifungal therapy. This model utilizes a calculation of the blood requirement during initial resuscitation, need for colostomy, pelvic injury, rectal injury, genitourinary injury, transfemoral amputation, base deficit, and shock index to predict risk [46]. Future research is needed to determine the feasibility of these newly described risk stratification tools to predict IFI in pediatric populations. In addition to IFI, risk factors such as prolonged hospitalizations, invasive devices, and frequent antimicrobial exposure place pediatric combat trauma patients at risk for *Candida* spp. and additional fungal pathogens.

Impact of Blood Transfusions

Comorbidities associated with battlefield injuries can increase rates of complications, infections, and death. One important example is blood transfusion, which commonly occurs in trauma patients. Blood product administration has been shown to cause immune system dysfunction, which can exacerbate the inflammatory immunologic response to trauma [48]. In adults of military age, blood transfusions have been associated with increased infection rates attributable to the immunomodulatory effects they exert on the recipient [49]. The majority of pediatric patients admitted to the intensive care unit received packed red blood cell transfusions [50]. Blood product administration was associated with a prolonged admission, as well as a significant increase in ISS and mortality, if massive transfusion was provided [51]. Pediatric patients with at least 60% total body surface area burns and inhalation injury are more likely to develop sepsis if given high amounts of blood products [52]. Nosocomial infections are also increased with blood transfusions [53].

Burn Injuries

Pediatric burns pose distinctive and difficult challenges. War-related burn injuries can be a result of blast injuries and pose a risk for infection, which are a leading cause of mortality in burn victims. Domestic burns sustained in the household, however, account for most of the burns in pediatric patients cared for in combat zones. The most frequent early infectious complication in pediatric burns is cellulitis, and its risk is not decreased by antibiotic prophylaxis. Early infectious organisms colonizing combat burns include Gram-positive skin flora and Gram-negative endogenous gastrointestinal organisms. Multi-drug-resistant organisms (MDRO) as well as yeasts and fungi are becoming more of a concern. Systemic prophylactic antibiotics can be considered, but have not been proven to be effective, and the International Society for Burn Injury (ISBI) as well as the US Army Institute of Surgical Research (USAISR) Burn Center do not recommend their use. Additionally, a meta-analysis published in 2019 provided more evidence for the lack of efficacy of prophylactic antibiotics in pediatric patients [54]. Care should focus on topical antimicrobials, meticulous wound care, and prompt excision and grafting [55]. Using the experience from Iraq and Afghanistan with the DoDTR, external abbreviated injury scale (AIS) and international normalized ratio (INR) were two independently associated variables for mortality due to burns in pediatric patients in the largest published study to date [56]. The ISBI and USAISR have published guidelines for burn care, and we encourage the reader to refer to these for specific management guidance.

Antimicrobial Resistance in Conflict

Antimicrobial resistance poses a major threat to global health and development and, as such, is a WHO top health priority. Just recently, the first review specifically addressing the antimicrobial resistance evidence gaps in the Middle East was published. Not surprisingly, the authors found no data available for children from conflict-affect settings [57]. Common infections worldwide are becoming more difficult to treat; however, children injured during armed conflict are also inevitably at risk for acquiring MDRO. The high risk for MDRO carriage and infection in children has been shown in Syrian children who were wounded or ill during the ongoing civil war. In this report, 83% of children were colonized with at least one MDRO, and wounded children had more frequent MDRO infections than children hospitalized for other illnesses. ESBLs were most common, followed by carbapenem-resistant *Enterobacterales*, and multi-drug resistant *Acinetobacter baumanni*, with 5% or less being MRSA or vancomycin-resistant *Enterococcus* [58]. The specific carriage rates and type of MDRO present are variable and dependent on regional and local epidemiology. For example, *Klebsiella pneumoniae*

Table 2 Recommended list of useful resources for providing care to children in regions of armed conflict

Organization	Title	Location/source	Notes
World Health Organization	Pocket Book of Hospital Care for Children	https://www.ichrc.org/pocketbook-online-second-edition	Compilation of WHO guidelines for managing inpatient pediatric patients.
Médecins Sans Frontiéres	Clinical Guidelines	https://medicalguidelines.msf.org/	English, French, Spanish, Arabic versions. Lessons learned from extensive accumulated field experience throughout the world. Has app for both Apple and Google Play
United States Army Medical Department	Pediatric Surgery and Medicine for Hostile Environments	https://medcoe.army.mil/borden-tb-pediatric-surgery	Current and concise source for providing pediatric medical, surgical, and critical care in austere environment
Centers for Disease Control and Prevention	CDC Yellow Book	https://wwwnc.cdc.gov/travel/page/yellowbook-home	Primary resource for travel-related information and country-specific details
Oxford University Press	Oxford Handbook of Tropical Medicine	https://oxfordmedicine.com	Excellent resource for diagnosing and managing disease in tropical environment
The Johns Hopkins Hospital	The Harriet Lane Handbook	https://www.us.elsevierhealth.com/the-harriet-lane-handbook-9780323674072.html	Premier point-of-care clinical information for pediatrics. Includes a formulary; updated every three years
American Public Health Association	Control of Communicable Diseases Manual	https://www.apha.org/ccdm	Field sized reference that provides in-depth detailed information regarding specific diseases

carbapenemase (KPC) family is the most extensively distributed and widespread in South and Central America in comparison to the burden of New Delhi Metallo-ß-lactamases (NDM) predominately in Asia [59]. Additional information comes from the Eastern part of the DRC, where antibiotic-resistant *Mycobacterium tuberculosis* and *Salmonella typhi* identification, isolation, and control have been obstructed by war and conflict [60]. Frequently, post-traumatic osteomyelitis in civilian casualties results from first-line antibiotic-resistant bacteria [61]. The most useful tool in combating MDRO in austere environments is the emphasis on basic infection prevention and control measures. Another useful process is cohorting local national populations together to limit the spread of MDRO established in a host-nation reservoir. Antimicrobial stewardship is an important tool in preventing MDRO, and every effort should be made to limit antibiotic duration while using narrow spectrum coverage.

Conclusion

In conclusion, physicians who find themselves providing medical care in regions of armed conflict must be familiar with pediatric trauma and its complications. A list of resources provided in Table 2 are recommended for in-depth material on managing specific individual infectious diseases in austere and resource-limited environments as well as region-specific details prior to operational activity. We have seen the impact infections can have following combat injuries, and we hope the reader has an increased understanding of the impact that armed conflict has on injuries inflicted on children. Unfortunately, the ability to make definitive and specific recommendations is hindered by a lack of data and research in pediatric patients. In order to meet the goals of the AAP policy statement on "The Effects of Armed Conflict on Children" [62], and to provide optimal care to the most vulnerable casualties of combat, future studies are needed to thoroughly characterize the infectious complications of injuries sustained by children during armed conflict.

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Declarations

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Conflict of Interest/Competing Interests Martin Ottolini and Michael Rajnik are both retired from the US Air Force, Medical Corps, and currently are faculty members at the Uniformed Services University of the Health Sciences, Blake Cirks is a current Pediatric Infectious Diseases Fellow at the National Capital Consortium. Kathleen B. Madden is a civilian faculty member at the Uniformed Services University of the Health Sciences. The authors declare no conflicts of interest or competing interests

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