TACTICAL COMBAT CASUALTY CARE: TRANSITIONING BATTLEFIELD LESSONS LEARNED TO OTHER AUSTERE ENVIRONMENTS

Field Wound Care: Prophylactic Antibiotics

Clinton K. Murray, MD

From the Army Medical Department Center and School, Health Readiness Center of Excellence, Medical Corps Office, JBSA-Fort Sam Houston, TX.

Adequate management of wounds requires numerous interventions, one of which is the appropriate use of antimicrobials to attempt to minimize the risk of excess morbidity or mortality without increasing toxicity or multidrug resistant bacterial acquisition. There are numerous recommendations and opinions for not only the use of systemic prophylactic antimicrobials, but also the agent, dose, route, and duration. To best address the implementation of systemic antimicrobials in a field scenario, one must weigh the factors that go into that decision and then determine the best agents possible. The epidemiologic triangle (ie, the host, the agent, and the environment) forms the basis for selecting the correct prophylactic antibiotic for field wound care. Extreme conditions can be encountered in both military and nonmilitary systems, requiring a unique selection process to make the right antibiotic choice. A modifiable weighted matrix, recommended previously for point of injury combat casualty care, assists in selecting the best oral and intravenous/intramuscular agent based on the epidemiologic risk determination.

Keywords: ertapenem, fluoroquinolones, trauma, remote

Introduction

A cornerstone of infectious disease is the epidemiologic triangle, which consists of the interactions between the host (the who), the agent (the what), and the environment (the where) (Figure). Host factors are intrinsic risk factors that include the individual's exposure, susceptibility, and response to the causative agent. Factors such as hygiene, nutritional or immunologic status, anatomic structure, presence of disease, and medication all play roles. The agent includes the microorganism that is not only present but also causes disease. The virulence and pathogenicity of the microorganism, along with inoculum, influence the infection rate. The environment includes extrinsic factors such as climate, sanitation, supplies, and availability of health services. The interaction of elements in the epidemiologic triangle provides a framework to assess the myriad issues that ultimately stratify a wound's potential for infection, the identity of the microorganism, and

potential outcomes. Understanding these interactions enables one to determine the best management options for field wound care to optimize outcomes.

Many of the fundamentals of wound management as described in Homer's *The Iliad* (~900 BC) are still used today: Mechanically debride with removal of arrow, irrigate with water or wine, cover wound with bandage soaked in wine, apply analgesic, and apply styptic herbal drugs.¹

Clinical practice guidelines have been provided by the Infectious Disease Society of America (IDSA), the Wilderness Medical Society (WMS), the National Park Service (NPS), the International Committee of the Red Cross (ICRC), World Health Organization (WHO), and combat-related injury infections and tactical combat casualty care military committees (CoTCCC).^{2–9} Interventions recommended include wound irrigation and debridement, immunization for rabies and tetanus, wound preparation and closure, bandaging, stabilization, prophylactic topical or systemic antimicrobial therapy, and close clinical monitoring for signs or symptoms of infection. At the core of wound care during field conditions are the challenges associated with the extremes of the epidemiologic triangle, including poor hygiene, lack of supplies, and prolonged field care,

Corresponding author: Clinton K. Murray, MD; e-mail: clinton.k.murray.mil@mail.mil.

Presented at the Tactical Combat Casualty Care: Transitioning Battlefield Lessons Learned to Other Austere Environments Preconference to the Seventh World Congress of Mountain & Wilderness Medicine, Telluride, Colorado, July 30–31, 2016.

Figure. Epidemiologic triangle of the host, agent, and environment that leads to wound infection.⁸⁹

among other extremes at the host, agent, or environment level.

This review will provide an overview of the incidence of traumatic wounds and infection rates, followed by examples of the epidemiologic triangle that influence wound infections. Antimicrobial options will then be provided, proposing a modifiable weighted matrix approach to assist determination of the ideal prophylactic antibiotic for field wounds. Overall emphasis is placed on extremity wounds and Food and Drug Administration (FDA)-approved antibiotics.

Traumatic wounds

Understanding the rates of traumatic wounds in austere settings is important in determining the ultimate need of field wound care and antimicrobial selection. During the spring climbing season of Mount Everest between 2003 and 2012, physicians in the clinical treatment area treated 2941 patients with 3569 diagnoses, of which

500 (14%) were trauma.¹⁰ Lacerations comprised 21% of the trauma cases, with cellulitis in 21 cases and abscesses in 25 cases, but only 2 tibial/fibular fractures and 1 pelvic fracture. Search and rescue for 239 persons in the Adirondack Park in New York had soft tissue and skeletal systems as the most commonly reported traumatic injuries, with 98 (49%) and 56 (28%) reported, respectively.¹¹ Of 100,000 outdoor recreational injuries, 14.8% were lacerations.¹² Another study noted 4% of wilderness or outdoor activities were injuries to the skin or infection, with infection rates of 0.02–0.04 per 1000 participant days.¹³ During a 10-day adventure race, there were 286 presentations for skin and soft tissue issues, of which avulsions/lacerations occurred in 2% of cases (n=9).¹⁴ Differences in rates of trauma were also reported for urban versus rural expeditions, earthquakes, tsunamis, deserts, and flood-associated environments.^{15–21} Overall, wound infection rates vary but typically are reported at the 1% to 10% rate, based upon many factors.²² Specific infections such

as abscesses, necrotizing fasciitis, bacteremia, and endocarditis are rare but are reported, especially based upon mechanism of injury.²³

Among traumatic wounds to the extremities, open fractures are recognized as having a high potential for soft tissue infections and ultimately osteomyelitis. Gustilo and Anderson classified open fractures into 3 types with associated infection rates.²⁴ Type I fractures are defined as those with a laceration of less than 1 cm with minimal soft tissue damage and no gross contamination (0–2% infection rate). Type II fractures have lacerations of greater than 1 cm with moderate soft tissue damage (2–5% infection rate). Type III fractures are high-energy injuries, typically with bone comminution or loss. Type III fractures have 3 subtypes: IIIa, characterized by extensive soft tissue injury but with adequate soft tissue coverage (5–10% infection rate); IIIb, which includes extensive soft tissue injury along with bone exposure requiring soft tissue coverage (10–50% infection rate); and IIIc, which has extensive soft tissue damage and the need for arterial repair (25–50% infection rate).^{25,26} Twice as many tibia injuries appear to result in infection compared with other extremities. Other extremity injuries such as human bites or animal bites to the hand also have high infection potential.^{3,27}

In addition to extremity injuries, other traumatic injuries are associated with infectious complications that were reviewed by a panel of civilian and military experts to determine posttrauma antimicrobial prophylaxis.^{7,28} The rate of posttraumatic empyema after chest injuries varies from 2% to 25%, with recent series having an incidence less than 5%.²⁹ Postinjury infection following penetrating abdominal injury ranges from 4% to 31%.²⁹

Civilian and military literature has reported varying rates of infections after central nervous system injury, with a military study describing 408 patients with closed or penetrating head trauma evaluated and managed at Walter Reed Army Medical Center or National Naval Medical Center in Bethesda, MD.^{30,31} There was a 9% rate of meningitis, with a rate of 26% in patients who had concomitant cerebrospinal fluid leakage from nose, ear, or wound. A recent meta-analysis of eye, maxillo-facial, and neck injuries described combat injury incidences of 8% to 20% for the face, 2% to 11% for the neck, and 0.5% to 13% for the eye and periocular structures, with variable infection rates.³²

Burns comprised approximately 5% of injuries, especially early during the Iraq War, with infections being the primary cause of mortality.³³ Although combat-related injuries are the extremes of injury patterns, they allow for risk stratification of types of wounds that might benefit from early empiric antimicrobial therapy. Within combat, infections are a major issue with many

lessons learned, but one must be cautious in making generalizations with the knowledge that military trauma has extremes of injury mechanism combined with higher rates of penetrating trauma.³⁴

The host

Injury patterns and individual patient risk factors are associated with infections. Among 3957 patients with lacerations in community and urban teaching hospitals, the infection rate did not differ.³⁵ Comorbid conditions such as diabetes mellitus are associated with increased rates of infection.³⁵ Massive trauma and large-volume blood transfusions are increasingly being recognized as markers of relative immunosuppression.^{36,37}

Wound characteristics themselves are also associated with infectious complications. For example, lacerations to the lower extremities, grossly contaminated lacerations, and lacerations greater than 5 cm are more likely to become infected.^{35,38} Degrees of fracture as described above are risk factors for infection, along with hollow organ-penetrating injury. Contamination can occur through not only hollow organ penetration or rupture but also through host skin colonization and the environment. Methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* (MSSA and MRSA, respectively) colonize humans approximately 25% and 3% of the time, respectively.³⁹ In addition, there have been increasing reports of skin and gastrointestinal tract colonization by gram-negative bacteria in healthy individuals. These include multidrug-resistant species, especially extended-spectrum, beta-lactamase-producing Enterobacteriaceae such as *Escherichia coli* and *Klebsiella* species.^{40,41}

The agent

The complex interplay between the virulence and pathogenicity of a microorganism plays a central role in its ability to colonize and infect a wound. This interplay must be understood because it influences the selection of antimicrobials. The microorganisms most frequently associated with wound infections, regardless of the mechanism of injury and the environment, are the common skin pathogens *S aureus* and *Streptococcus pyogenes*.

However, other pathogens are also encountered based upon a number of parameters, so risk factors for their isolation should be sought by the clinician. For example, during World War I and World War II in Europe, wounds that were heavily contaminated with fertile soil and associated with prolonged evacuation times saw increased recovery of *Clostridium* species, *Streptococcus* species, *Staphylococci* species, and coliform bacilli.^{1,5}

Of note, many wound-associated pathogens during the wars in Iraq and Afghanistan saw a shift from *Acinetobacter* to other gram-negative rods with multidrug-resistance to Enterobacteriaceae (eg, *E coli*, *Klebsiella* species) with extended-spectrum beta-lactamase production and *Enterococcus*.^{36,42} Evidence supports *Acinetobacter* as a nosocomial pathogen, rather than inoculation at the time of injury in Iraq.

Cultures from fresh wounds at the time of injury from Vietnam revealed an even mix of gram-positive and gram-negative bacteria, including coagulase negative staphylococci (CNS), *Bacillus subtilis*, and *Enterobacter* group.⁴³ After 5 days of therapy and antimicrobials, 84% of wounds grew gram-negative bacteria, primarily *Pseudomonas aeruginosa*. As is often the issue with many of these studies, initial anaerobic and fungal cultures were not obtained. In Iraq, a study of 61 fresh wounds revealed 32 CNS, 4 *S aureus* (2 of those MRSA), as well as *Pseudomonas stutzeri*, *C meningosepticum*, and *E coli*, but no multidrug-resistant gram-negative bacteria.⁴⁴ In a study of 14 mangled extremity wounds in Afghanistan, immediate culture revealed colonization with low-virulence, environmental, gram-negative bacteria, reflecting wound contamination. These isolates were not associated with subsequent infection.⁴⁵

A study of 213 open tibia injuries revealed that 27% were complicated by a deep infection. Of 145 surveillance cultures, *Acinetobacter* was recovered 61% of the time; *Enterobacter cloacae* 18%; and *K pneumoniae*, *E faecium*, and *P aeruginosa* each at 14%.⁴⁶ Of those tibias that became infected, *S aureus* was isolated in 35%, with *Acinetobacter* and CNS in 20%, *K pneumoniae* in 12%, and *E faecium* in 8%.

It is still important to know that nosocomial infection greatly influences these pathogens. Other pathogens associated with wound infections include obligate anaerobes, which were common during World War II but rarely seen during the wars in Iraq and Afghanistan. This is likely reflective of improvements in wound care, including early surgical intervention, delayed primary closure, differences in soil pathogens from Europe vs desert or mountainous regions, and possibly antimicrobial coverage.⁴⁷ Tetanus is rarely seen now for similar reasons.³⁴ Low-virulence pathogens like mycobacteria and fungi have rarely been described.^{48–50} Although *Clostridium* species and *S pyogenes* were seen less commonly during in Iraq and Afghanistan compared with prior wars, there was the trend toward increasing resistance, likely reflective of nosocomial infections.

Other unique exposures that affect the microbiology of wound infections should be noted. Dog and cat bites are associated not only with the typical pathogens of

Streptococcus and *Staphylococcus* species but also gram-negative bacteria (to a lesser degree) and some unique, and potentially invasive, organisms, including *Pasteurella multocida*, *Capnocytophaga canimorsus*, and *Weeksella zoohelcum*.²⁷ Anaerobic bacteria include *Fusobacterium*, *Bacteroides*, *Porphyromonas*, and *Prevotella* species. Human bites and closed fist injuries are typically contaminated with *Eikenella corrodens*, *S aureus*, *S pyogenes*, and anaerobic bacteria.⁵¹ Burn wounds experience a transition in bacteria over time, reflective initially of skin colonization and eventually the nosocomial environment, as shown with *Acinetobacter*.⁵²

Although very complicated and incompletely understood, pathogenesis, virulence, antimicrobial resistance, and inoculum effect are important aspects in the establishment of infection and therapy.^{53–55} This is likely reflective of why *S aureus* is commonly associated with infections, especially osteomyelitis, and why heavily contaminated wounds have higher rates of infection, especially with delayed therapy.

The environment

The environment influences many aspects of wound field care, including type of pathogens inoculated into the wound, care available based upon remote conditions, prolonged evacuation times, and supply limitations. Although the infecting pathogens are most commonly from the patient's own skin flora being inoculated into the wounds, one must not minimize the importance of microorganisms in the environment.

Injuries associated with water exposure have increased rates of gram-negative pathogens, as evidenced by the tsunami in 2004. Most wounds were polymicrobial, including *Aeromonas* species, *E coli*, *K pneumoniae*, *S aureus*, *Proteus vulgaris*, and *P aeruginosa*. Anaerobic cultures were rarely performed to determine their role, but they were not associated with established infection on further monitoring.^{38,56} Most infections occurred 2–3 days after injury. Antimicrobial therapy within 1 day of the tsunami appeared to be protective. Higher rates of *S aureus*, *Acinetobacter*, and *Enterococcus* were reported after an earthquake in 2008 in China. These differences could reflect nosocomial or regional differences in host colonization or inoculation from the environment.¹⁶ After the tsunami, other atypical infections were noted, including rapidly growing mycobacteria late after injury (3–11 months) along with other atypical pathogens that were noted early during initial wound management near the time of injury, such as *Burkholderia pseudomallei* and *Cladophilaphora bantiana*.⁵⁷

In addition to the above reports, marine and freshwater pathogens that have been described include *Vibrio* species, *Aeromonas hydrophila*, and other atypical

pathogens like *Plesiomonas* species, *Mycobacterium marinum*, and *Erysipelothrix rhusiopathiae*.⁵⁸ Of note, other injuries have similar microbiology, including those sustained in boating accidents; propeller-related injuries; shark bites; and injuries related to alligators, crocodiles, barracuda, and moray eels. In addition, regional differences have been reported: *V. vulnificus* in the Gulf of Mexico, *Chromobacterium violacei* in the Western Pacific, and *Shewanella* species infections in the Mediterranean and Western Pacific.¹⁹

Other distinct pathogens include environmental molds, which have been reported in natural disasters including tornadoes, hurricanes, earthquakes, and volcano eruptions and are reported to be associated with high mortality.⁵⁹ Invasive mold infections show the overlapping influence of the host, pathogen, and environment. During the war in Afghanistan, mold infections were associated with dismounted complex blast injuries in Helmand and Kandahar Provinces with high-level amputations and perineal injuries in patients requiring massive blood product support.^{49,60} In addition to geography, seasonality can also affect pathogen isolation.¹ During the Korean War, *Clostridium*, *Streptococci*, and *Staphylococci* were most commonly isolated in the winter months, compared with fecal coliforms in the summer.¹

Because the environment and access to care can affect timing of interventions, this can affect infection rates. Ongoing debate surrounds time to closure, with a report comparing closure before or after 12 hours showing no statistically different infection rate.³⁵ In addition, use of antibiotics along with aggressive debridement with primary suture appeared successful in many cases, but clinical follow-up of patient outcomes is unclear.^{38,61}

Another issue is related to timing of antimicrobial administration, especially as it relates to early versus delayed surgical care. The combat-related injury working groups extensively reviewed this in their publications in 2008 and 2011.^{25,26} Studies supporting the protective role of antimicrobials within 3 hours of injury include the 1973 October War in Israel, the Falklands Campaign in 1982, the British military experience in Afghanistan, and civilian studies. A study examining the efficacy of point of injury antimicrobials by the US Army Rangers did not show decreased rates of infection, but reassuringly also did not show increased rates of multidrug-resistant colonization.⁶² However, the study was limited by the low use of point-of-injury antimicrobials, likely reflective of inadequate training.

Two recent orthopedic surgery articles of severe open fractures reported conflicting outcomes of the effect of early antibiotics on rates of infection.^{63,64} Open fracture

models in animals indicate the combination of early surgery and antimicrobials (within 2 hours for both) is key for preventing infection.⁶⁵ If antimicrobials are given within 2 hours and surgery is delayed 6 hours, there is an increased rate of infection; however, if surgery occurs within 2 hours but antimicrobials are delayed 6 hours, even higher rates of infection are noted. In animal models, other data indicate that although wounds take 3 days to develop clinical evidence of infection, therapy is ineffective if delayed 6 hours.⁶⁶ Overall inoculum effect (ie, dose of bacteria) is also able to override the impact of antimicrobials. Other animal models using weapons of various calibers revealed similar findings: Earlier antimicrobial exposure (1–2 hours compared with 6 hours postinjury) is associated with decreased infection rates.⁶⁷ Similar studies also revealed that penicillin was associated with less devitalized tissue in the wound, with an effect that may last 12 hours or more.^{68,69} As such, antimicrobial therapy is likely useful if surgery is delayed, but it is not a substitute for surgery, and increased bacterial load can possibly override the beneficial effect of antimicrobials, especially if blood flow to an area is limited by severity of injury or shock.

Antimicrobial weighted matrix

Foundational to therapy is determining when benefits of systemic antimicrobials outweigh the associated risks: potential antimicrobial-resistance pressure, *C difficile*-associated diarrhea; allergic reactions; drug-specific toxicities, including cardiac, hepatic, renal, and hematopoietic; and drug interactions. It also must be understood that timely irrigation and debridement is paramount to successful wound management. Appropriate closure of open wounds, bandaging, and close follow-up are also key.

It has been recognized repeatedly over time that reliance on antimicrobial therapy instead of good wound debridement and irrigation leads to excess morbidity and mortality. During World War I, Alexander Fleming stated, “All the great success of primary wound treatment have been due to efficient surgery, and it seems a pity that the surgeon should wish to share his glory with a chemical antiseptic of more than doubtful utility.”⁷⁰ During World War II, topical sulfanilamide became part of the standard of care after a lecture series about its success was attended by a team of Army and Navy medical personnel stationed in Hawaii just 36 hours before the attack on Pearl Harbor. However, this reliance on sulfanilamide powder replaced appropriate debridement, which had to be corrected after increased rates of infection were noted.⁷¹ During the Yom Kippur

Table 1. Recommended antimicrobials for field care and combat-related or disaster-associated extremity wounds that could be delivered at the point of injury or during care with increased medical assets

<i>Recommender</i>	<i>Antimicrobial^a</i>	<i>Indications</i>
National Park Service ⁴	Cefazolin 1 g IV q 8 hours	Severe wounds (deep, crushed, exposed tendon, heavy contamination, or open fracture) with expected time from injury to definitive care > 3 hours Do not give cefazolin in the following circumstances: burns, shallow wounds (ie, not through all layers of the skin), wounds where the expected transport to definitive care is < 1 hour
Wilderness Medical Society ³	Levofloxacin Amoxicillin/clavulanate, second choice moxifloxacin	Analgesia/oral antibiotics: administer pill pack, levofloxacin Treatment with systemic antibiotics is indicated in the presence of open fractures, human bites, and mammalian bites of the hand but not in burn wounds. Second choice for those allergic to penicillin or with aquatic exposures, have higher likelihood of gram-negative organisms
Committee on Tactical Combat Casualty Care ⁹	Moxifloxacin 400 mg po daily Cefotetan 1 g q12h IV push over 3–5 minutes or ertapenem 1 g IV/IM daily	If the patient can swallow For shock, unconscious
International Committee for the Red Cross ⁵	Penicillin-V tablets 500 mg po QID for 5 days Penicillin-G 5 mIU IV QID for 48 hours followed by Penicillin-V 500 mg po QID until DPC	Minor soft-tissue wounds, uncomplicated grade 1 Compound fractures, traumatic amputations, major soft-tissue wounds (grades 2 and 3). Continue penicillin-V for 5 days if closure is performed with a split skin graft. If redebridement is performed instead of DPC: stop antibiotic unless there are signs of systemic infection or active local inflammation—in latter case, add metronidazole
Combat-related injury infections ^{7,73}	Penicillin-G 5 mIU IV q6 h + metronidazole q8 h for 48 hours followed by Penicillin-V tablet 500 mg po QID and metronidazole 500 mg po TID until DPC Cefazolin 2 g IV q6–8 h for 1–3 days, alternate clindamycin (300–450 mg po TID or 600 mg IV q8h)	Compound fractures or major soft-tissue wounds with delay of more than 72 hours Antipersonnel landmine injuries to limbs, whatever the delay
World Health Organization ⁶	Penicillin-G IV 8–12 mIU once. Metronidazole IV, 500 mg once (infused over 30 min)	Skin, soft tissue, open fractures, exposed bone, or open joints unless POI and then follow CoTCCC. Redose antimicrobials if large-volume blood loss resuscitation Antibiotic prophylaxis is indicated in situations or wounds at high risk for infection, such as contaminated wounds, penetrating wounds, abdominal trauma, compound fractures, lacerations greater than 5 cm, wounds with devitalized tissue, high risk anatomical sites such as hand or foot, etc. These indications apply for injuries that may or may not require surgical intervention. For injuries requiring surgical intervention, antibiotic prophylaxis is also indicated and should be administered before surgery, within the 2-hour period before the skin is cut. Recommended prophylaxis consists of penicillin G and metronidazole given once (more than once if the surgical procedure is > 6 hours).

Table 1 (continued)

Recommender	Antimicrobial ^a	Indications
Israeli Defense Force	Moxifloxacin 400 mg IV once per day Moxifloxacin 400 mg po once per day Ceftriaxone 2 mg IV once per day + metronidazole 500 mg IV q8 h	Penetrating injury, with evacuation delayed more than 1 hour, trunk injury Penetrating injury, with evacuation delayed more than 1 hour, extremity injury Penetrating injury, with evacuation delayed more than 1 hour, head injury

IV, intravenous; po, by mouth; q, every; IM, intramuscularly; QID, 4 times a day; DPC, delayed primary closure; TID, 3 times a day; CoTCCC, Committee on Tactical Combat Casualty Care.

^a If no dose or interval provided then it was not provided in the recommendation.

War, the overemphasis on antimicrobials led authors to state that “this leads towards the temptation to ‘sterilize’ the wound with massive doses of antibiotics and favors a false security with less reliance on good surgical technique.”⁷² The ICRC states that “the best antibiotic is good surgery.”⁵ As such, it is paramount to risk stratify the wound’s potential for infection based on parameters addressed by the epidemiologic triangle, along with access to appropriate wound care and surgical intervention, if need be.

Recommendations regarding antimicrobials include those by the IDSA, ICRC, WMS, NPS, CoTCCC, WHO, and combat-related injury infection prevention guidelines (Table 1).⁷³ In comparison, Israelis reportedly use moxifloxacin, ceftriaxone, cephalexin, and/or metronidazole, while the British recommend penicillin or amoxicillin/clavulanate for cases that include abdominal injuries.^{74–77} These recommendations are based on factors reflected within the epidemiologic triangle. The differences in choices are based on availability of supplies, evacuation chains, severity of injury, site of injury, and so on. As such, there is a difference between the benefits of point-of-injury antimicrobials for a severe open injury with prolonged evacuation to care and a minor injury with surgical care available in 20 minutes. Risk stratification for field care or point-of-injury antimicrobials must take into account many factors, including if the care is provided by a physician, a medic, or the person himself or herself; severity of the injury; and timely access to appropriate wound care.

The key to the right antimicrobial in field care is simplicity of use, ease of transport and storage, reconstitution, administration, safety, duration of activity, spectrum of activity, and cost for the field environment (Table 2). This is typically maximized by an oral agent. The NPS and the CoTCCC recommend an oral fluoroquinolone for initial injury as part of a pill pack carried by the patients themselves. The NPS and the CoTCCC do not outline the indications for the antimicrobials. The combat-related injury infection guideline committee recommended in their 2008 and 2011 publications to provide point-of-injury antimicrobials if evacuation is delayed or not expected for more than 3 hours.^{7,78} The difference between the the TCCC and combat-related injury infection guidelines are recommendations for levofloxacin and moxifloxacin. Levofloxacin has better activity for gram-negative bacteria including *P. aeruginosa* and water pathogens, while moxifloxacin has no *P. aeruginosa* activity.^{78–81} Although moxifloxacin has more anaerobic activity than levofloxacin, it is associated with increasing rates of resistance to concerning intraabdominal bacteria, notably *Bacteroides* species. Both antimicrobials have adequate

Table 2. Characterization of prophylactic antimicrobial agents for field wound care

<i>Antimicrobial agent</i>	<i>Dose</i>	<i>IV/IM</i>	<i>Dosing interval</i>	<i>Wholes in coverage</i>	<i>Adverse event</i>	<i>Mixture- IV (IM dosing)</i>	<i>IV infusion time (min)</i>	<i>Stability (temperature)</i>	<i>\$/dose</i>
Cefotetan	2 g	Both	12 h	<i>Bacteroides</i> species, <i>Pseudomoans aeruginosa</i> , <i>Enterococcus</i>	Minimal	2 g in 10–20 mL (2 g in 3 mL)	3–5	< 72 °F	33.85
Cefoxitin	1–2 g	Both	8 h	<i>Bacteroides</i> species, <i>Pseudomoans aeruginosa</i> , <i>Enterococcus</i>	Minimal	1 g in 10 mL (1 g in 2 mL water)	3–5	36–77 °F (appears stable to 122 °F)	16.14
Ertapenem	1 g	Both	24 h	<i>Pseudomoans aeruginosa</i> , <i>Enterococcus</i>	Minimal	1 g in 50 mL (1 g in 3.2 mL 1% lidocaine)	30 (data for 5 minutes)	< 77 °F, stable up to 104+ °F	42.40
Fluoroquinolone Levofloxacin	750 mg	IV only	24 h	<i>Bacteroides</i> species, Moxifloxacin (no <i>Pseudomonas</i> activity)	Small %, major events	Single use vials for dilution (750 mg in 30 mL)	60–90	59–86 °F	10.29
Moxifloxacin	400 mg					Premix single = use flexible containers (750 mg in 150 mL)			9.84
Ceftriaxone	1–2 g	Both	24 h	<i>Bacteroides</i> species, <i>Pseudomoans aeruginosa</i> , <i>Enterococcus</i>	Minimal	1 g in 10 mL (1 g in 3.6 mL diluent)	30	< 77 °F	2.36
Ampicillin/Sulbactam	3 g	Both	6 h	<i>Pseudomoans aeruginosa</i>	Minimal	3 g in 50 mL (3 g in 6.4 mL)	15–30	< 86 °F	7.12

Oral levofloxacin 750 mg po per day \$0.275/day, moxifloxacin 400 mg po per day \$2.23/day, amoxicillin/clavulanate 875 mg BID \$0.264/day.

IV ampicillin/sulbactam coverage is the same as po amoxicillin/clavulanate.

DoD costs as of June 15, 2016.

IV, intravenous; IM, intramuscular; po, by mouth; BID, twice a day; DoD, Department of Defense.

Streptococci and MSSA activity with some MRSA activity. Recently, the FDA has recommended against the use of even short-course fluoroquinolones, especially for sinusitis, bronchitis, and uncomplicated urinary tract infections, which have other treatment options. This is due to disabling and potentially permanent, serious side effects that can occur together. These adverse events can involve the tendons, muscles, joints, nerves, and central nervous system. Other oral agents such as penicillin, doxycycline, amoxicillin/clavulanate, ciprofloxacin, and cephalosporins have either inadequate coverage, are administered multiple times a day, or have adverse event profiles that limit their utility. Increasing multidrug-resistant bacteria present through environmental contamination and host colonization might increase the future need for broader coverage, but this is not the case with perioperative antibiotics yet.

The NPS recommends intravenous (IV) cefazolin for severe wounds (deep, crush, exposed tendon, heavy contamination, or open fracture) with an expected time from injury to definitive care of >3 hours, unless the injury is a burn, a shallow wound (ie, not through all layers of the skin), or wounds where the expected transport to definitive care is <1 hour (Table 1). The CoTCCC currently recommends intravenous/intramuscular (IV/IM) therapy with cefotetan or ertapenem for shock and for unconscious patients, with previous indications including abdominal injury for point-of-injury care. Other agents are recommended by various organizations for intraabdominal, chest, and central nervous system injury in addition to extremity wound injuries when the patient reaches definitive care (Table 1).^{4-6,9} A single dose of IV antibiotics, benzylpenicillin, to be given only if evacuation is going to be delayed, such that surgical intervention is not possible within 4 hours, is recommended by British Military experts in the field.¹⁷ This is to minimize the risk of multidrug-resistant bacteria while still covering the pathogens of

historical concern, including *Streptococcus* species and *Clostridium non-difficile* species.

Based on the Ranger point-of-injury antimicrobial data and results of the Trauma Infectious Disease Outcome Study that indicated no difference between rates of subsequent isolation of resistant-bacteria after broad- versus narrow-spectrum antimicrobial coverage at the time of injury, it is unclear that short-duration antimicrobial selection pressure leads to collateral prolonged damage within the trauma population (unpublished data).⁶² It is important to note that the current regimens appear to modify the commonly encountered infections with *Streptococcus* species and *Clostridium* species that have directed field wound antimicrobials in the past. However, other factors may be involved, including differences in the environment of injury or host colonization, in contrast to other wars.⁸² Gas gangrene resulted in 3 of 15 deaths among warfare-related limb injury in the Chinese military.⁸³ The Chinese also reported cases associated with Wenchuan earthquake victims.⁸⁴ A modifiable weighted matrix was previously published for the indications of various IV/IM medication, including ertapenem, for point-of-injury care in tactical combat casualty care to augment the CoTCCC recommendation of cefotetan (Table 3).⁸⁵ Since that publication, data support that ertapenem can be delivered with a 5-minute infusion.⁸⁶ Also, intraosseous and IM delivery of ertapenem appear to be adequate.²⁶ Use of ertapenem and cefotetan in colorectal surgeries has been compared, with better outcomes with ertapenem.⁸⁷ Overall, activity of ertapenem is enhanced in comparison to cefotetan for streptococcal, MSSA, gram-negative bacteria, and anaerobic bacteria. Although ertapenem has limited activity against *P aeruginosa*, versus none with cefotetan, ertapenem is not an agent recommended for *P aeruginosa* because of high resistance rates.

A study in Iraq of the role of antimicrobials and irrigation, which included 53 wounds, noted the lowest infection rates (2.6%) with the combination of antibiotics and irrigation. Wounds that received no antimicrobial but

Table 3. Modifiable weighted matrix system for determining ideal field care antibiotics (higher score is better) utilizing the risk by host, agent, and environment to modify the weighted item and importance

Weighted items	4	3	2	1
\$/day (1)	<5	5–10	10–25	>25
Mixture (2)	Vial, <50 mL reconstitute	Vial, >50 mL reconstitute	Premix <50 mL	Premix >50 mL
Infusion time (2)	≤5 min	>5 ≤30 min	>30 ≤60 min	>60 min
Stability (2)	Extremes	Limited	Not tested	
Adverse events (3)	Minor, small %	Minor, large %	Major, small %	Major, large %
Dosing (3)	Daily	BID	TID	QID
IV/IM (3)	Both	IV only	IM only	
Coverage (4) ^a	Appropriate	Excessive	Inadequate	None

BID, twice a day; TID, three times a day; QID, four times a day; IV, intravenous; IM, intramuscular.

^a Dictated by expected potential pathogen bacteria based upon type of exposure.

were irrigated had a 17% infection rate. Those with antimicrobials and no irrigation had a 40% infection rate, and neither therapy resulted in a 70% infection rate.⁸⁸ The agents used were parenteral ceftriaxone and/or oral fluoroquinolones predominantly, followed by second-generation cephalosporins or amoxicillin/clavulanate. Antibiotic course duration ranged from 7 to 10 days. One has to be cautious in the application of this study results given the use of 10 days of antimicrobials because it implies ongoing infection and not wound colonization, as well as the small numbers evaluated. However, the findings are intriguing given the field nature of care.

An examination of the use of early cephalexin and metronidazole in 2001–2003 in Gaza City is reported for 109 patients who received initial oral antibiotics and wound management soon after injury (29±11 minutes, maximum 60 minutes) with strict exclusion criteria.⁷⁴ Eleven had an infection, although the type of bacteria was not reported. Of those 11, 2 had purulence requiring debridement.

Conclusions

Ongoing analysis of point-of-injury antimicrobials on outcomes from Iraq and Afghanistan is needed, along with randomized studies to adequately address the pros and cons of the ideal field antimicrobial, indications, and duration. Until this is done, it is ideal to combine the epidemiologic triangle, reflecting the risk of the patient, and selection of the right antimicrobial for the field care scenario under consideration. Leading agents might include oral levofloxacin and IV/IM ertapenem, based on many variables within the epidemiologic triangle, before surgical intervention, especially for severe injuries with prolonged evacuation time.

Disclaimer: The views expressed are those of the author and do not necessarily reflect the official views of the US Army Office of the Surgeon General, the Department of Defense, or the Departments of the Army. Mention of trade names, commercial products, or organization does not imply endorsement by the US government.

Financial/Material Support: None.

Disclosures: None.

References

- Murray CK, Hinkle MK, Yun HC. History of infections associated with combat-related injuries. *J Trauma*. 2008; 64:S221–S231.
- Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 updated by the Infectious Disease Society of America. *Clin Infect Dis*. 2014;59: 147–159.
- Quinn RH, Wedmore I, Johnson EL, et al. Wilderness Medical Society practice guidelines for basic wound management in the austere environment: 2014 update. *Wilderness Environ Med*. 2014;25:295–310.
- National Park Service. *Emergency Medical Service Protocols and Procedures: Field Manual 51* Washington, DC: NPS; 2010.
- Glannou C, Baldan M, (eds). *War Surgery: Working with Limited Resources in Armed Conflict and Other Situations of Violence*. Geneva, Switzerland: International Committee of the Red Cross; 2010.
- World Health Organization, Department of Violence and Injury Prevention and Disability. Prevention and management of wound infection. Available at: http://www.who.int/hac/techguidance/tools/guidelines_prevention_and_management_wound_infection.pdf. Accessed April 21, 2017.
- Hospenthal DR, Murray CK, Andersen RC, et al. Executive summary: guidelines for the prevention of infections associated with combat-related injuries: 2011 update: endorsed by the Infectious Diseases Society of America and the Surgical Infection Society. *J Trauma*. 2011; 71(2 suppl 2):S202–S209.
- O'Connor K, Butler F. Antibiotics in tactical combat casualty care 2002. *Mil Med*. 2003;168:911–914.
- Butler FK, Holcomb JB, Giebner SD, McSwain NE, Baglan J. Tactical combat casualty care 2007: evolving concepts and battlefield experience. *Mil Med*. 2007;172: 1–19.
- Nemethy M, Pressman AB, Freer L, McIntosh SE. Mt Everest base camp medical clinic “Everest ER”: epidemiology of medical events during first 10 years of operation. *Wilderness Environ Med*. 2015;26:4–10.
- Sadeghi R, Konwinski JC, Cydulka RK. Adirondack Park incidents: a retrospective review of search and rescue reports from 2008 and 2009. *Wilderness Environ Med*. 2015;26:159–163.
- Flores AH, Haileyesus T, Greenspan AI. National estimates of outdoor recreational injuries treated in emergency departments, United States, 2004–2005. *Wilderness Environ Med*. 2008;19:91–98.
- McIntosh SE, Leemon D, Visitacion J, Schimelpfenig T, Fosnocht D. Medical incidents and evacuations on wilderness expeditions. *Wilderness Environ Med*. 2007;18: 298–304.
- McLaughlin KA, Townes DA, Wedmore IS, Billingsley RT, Listrom CD, Iverson LD. Pattern of injury and illness during expedition-length adventure races. *Wilderness Environ Med*. 2006;17:158–161.
- Diaz JH. Superficial and invasive infections following flooding disasters. *Am J Disaster Med*. 2014;9:171–181.
- Tao C, Kang M, Chen Z, et al. Microbiologic study of the pathogens isolated from wound culture among Wenchuan earthquake survivors. *Diagn Microbiol Infect Dis*. 2009; 63:268–270.
- Eardley WGP, Brown KV, Bonner TJ, Green AD, Clasper JC. Infection in conflict wounded. *Philos Trans R Soc Lond B Biol Sci*. 2011;366:204–218.

18. Neblett Fanfair R, Benedict K, Bos J, et al. Necrotizing cutaneous mucormycosis after a tornado in Joplin Missouri, in 2011. *N Engl J Med*. 2012;367:2214–2225.
19. Diaz JH. Skin and soft tissue infections following marine injuries and exposures in travelers. *J Travel Med*. 2014; 21:207–213.
20. Sherry NL, Padiglioine AA, Spelman DW, Cleland H. Microbiology of wildfire victims differs significantly from routine burns patients: data from an Australian wildfire disaster. *Burns*. 2013;39:331–334.
21. Tonna JE, Lewin MR, Hahn IH, Platts-Mills TF, Norell MA. A prospective, multi-year analysis of illness and injury during summer travel to arid environments. *Wilderness Environ Med*. 2009;20:107–112.
22. Abubaker AO. Use of prophylactic antibiotics in preventing infection of traumatic injuries. *Dent Clin North Am*. 2009;53:707–715.
23. Brook I, Frazier EH. Aerobic and anaerobic microbiology of infection after trauma. *Am J Emerg Med*. 1998;16:585–591.
24. Gustilo RB, Anderson JT. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones: retrospective and prospective analyses. *J Bone Joint Surg Am*. 1976;58:453–458.
25. Murray CK, Hsu JR, Solomkin JS, et al. Prevention and management of infections associated with combat-related extremity injuries. *J Trauma*. 2008;64:S239–S251.
26. Murray CK, Obremskey WT, Hsu JR, et al. Prevention of infections associated with combat-related extremity injuries. *J Trauma*. 2011;71:S235–S257.
27. Talan DA, Citron DM, Abrahamian FM, Moran GJ, Goldstein EJC, for the Emergency Medical Animal Bite Infection Study Group. Bacteriologic analysis of infected dog and cat bites. *N Engl J Med*. 1999;340: 85–92.
28. Hospenthal DR, Murray CK, Andersen RC, et al. Guidelines for the prevention of infections associated with combat-related injuries: 2011 update: endorsed by the Infectious Diseases Society of America and the Surgical Infection Society. *J Trauma*. 2011;71(2 suppl 2): S210–S234.
29. Martin G, Cho JM, Dunne JR, Solomkin JS; the Prevention of Combat-related Infectious Guidelines Panel. Prevention of infections associated with combat-related thoracic and abdominal cavity injuries. *J Trauma*. 2011;71(2 suppl 2):S270–S281.
30. Forgione MA, Moores LE, Wortmann GW, the Prevention of Combat-related Infectious Guidelines Panel. Prevention of infections associated with combat-related central nervous system injuries. *J Trauma*. 2011;71(2 suppl 2): S258–S263.
31. Bell RS, Vo AH, Neal C, et al. Military traumatic brain and spinal column injury: a 5-year study of the impact blast and other military grade weaponry on the central nervous system. *J Trauma*. 2009;66(suppl 4):S104–S111.
32. Petersen K, Colyer MH, Hayes DK, Hale RG, Bell RB; the Prevention of Combat-related Infectious Guidelines Panel. Prevention of infections associated with combat-related eye, maxillofacial and neck injuries. *J Trauma*. 2011; 71(2 suppl 2):S264–S269.
33. D'Avignon LC, Chung KK, Saffle JR, Renz EM, Cancio LC. the Prevention of Combat-related Infectious Guidelines Panel. Prevention of infections associated with combat-related burn injuries. *J Trauma*. 2011;71(2 suppl 2): S282–S289.
34. Blyth DM, Yun HC, Tribble DR, Murray CK. Lessons of war: combat-related injury infections during the Vietnam War and Operation Iraqi and Enduring Freedom. *J Trauma Acute Care Surg*. 2015;79(4 suppl 2):S227–S235.
35. Quinn JV, Polevoi SK, Kohn MA. Traumatic lacerations: what are the risks for infection and has the “golden period” of laceration care disappeared. *Emerg Med J*. 2014;31:96–100.
36. Tribble DR, Li P, Warkentien TE, Lloyd BA, et al. Impact of operational theater on combat and noncombat trauma-related infections. *Mil Med*. 2016;181:1258–1268.
37. Binkowska AM, Michalak G, Slotwinski R. Current views on the mechanisms of immune response to trauma and infection. *Cent Eur J Immunol*. 2015;40:206–216.
38. Doung-ngern P, Vatanaprasan T, Chungpaibulpatana J, et al. Infections and treatment of wounds in survivors of the 2004 tsunami in Thailand. *Int Wound J*. 2009;6:347–354.
39. Ellis MW, Hospenthal DR, Dooley DP, Gray PJ, Murray CK. Natural history of community-acquired methicillin resistant *Staphylococcus aureus* colonization and infection in soldiers. *Clin Infect Dis*. 2004;39:971–979.
40. Vento TJ, Cole DW, Mende K, et al. Multidrug-resistant gram-negative bacteria colonization of healthy US military personnel in the US and Afghanistan. *BMC Infect Dis*. 2013;13:68.
41. Vetter R, Murray CK, Mende K, et al. The use of PCR/electron spray ionization-time-of-flight-mass spectrometry (PCR/ESI-TOF-MS) to detect bacterial and fungal colonization in healthy military service members. *BMC Infect Dis*. 2016;16:338.
42. Yun HC, Murray CK. Infection prevention in the deployed environment. *US Army Med Dep J*. 2016;2:114–118.
43. Tong MJ. Septic complications of war wounds. *JAMA*. 1972;21:1044–1047.
44. Murray CK, Roop SA, Hospenthal DR, et al. Bacteriology of war wounds at the time of injury. *Mil Med*. 2006; 171:826–829.
45. Wallum TE, Yun HC, Rini EA, et al. Pathogens present in acute mangled extremities from Afghanistan and subsequent pathogen recovery. *Mil Med*. 2015;180:97–103.
46. Burns TC, Stinner DJ, Mack AW, et al. Microbiology and injury characteristics in severe open tibia fractures from combat. *J Trauma Acute Care Surg*. 2012;72: 1062–1067.
47. White BK, Mende K, Weintrob AC, et al. Epidemiology and antimicrobial susceptibilities of wound isolates of obligate anaerobes from combat casualties. *Diagn Microbiol Infect Dis*. 2016;84:144–150.
48. Fiske LC, Homeyer DC, Zapor M, et al. Isolation of rapidly growing nontuberculous mycobacteria in wounds following combat-related injury. *Mil Med*. 2016;181:530–536.

49. Tribble DR, Rodriguez CJ, Weintrob AC, et al. Environmental factors related to fungal wound contamination following combat trauma in Afghanistan (2009–2011). *Emerg Infect Dis*. 2015;21:1759–1769.
50. Blyth DM, Mende K, Weintrob AC, et al. Resistance patterns and clinical significance of candida colonization and infection in combat-related injured patients from Iraq and Afghanistan. *Open Forum Infect Dis*. 2014;1: ofu109.
51. Kennedy SA, Stoll LE, Lauder AS. Human and other mammalian bite injuries of the hand: evaluation and management. *J Am Acad Orthop Surg*. 2015;23:47–57.
52. Keen EF, Robinson BJ, Hospenthal DR, et al. Incidence and bacteriology of burn infections at a military burn center. *Burns*. 2010;36:461–468.
53. Rosenstein R, Gotz F. What distinguishes highly pathogenic *Staphylococci* from medium- and non-pathogenic? *Curr Top Microbiol Immunol*. 2013;356:33–89.
54. Dautzenberg MJD, Haverkate MR, Bonten MJM, Bootsma MCJ. Epidemic potential of *Escherichia coli* ST131 and *Klebsiella pneumoniae* ST258: a systemic review and meta-analysis. *BMJ Open*. 2016;6:e009971.
55. Hess DJ, Henry-Stanley MJ, Wells CL. Interplay of antibiotics and bacterial inoculum on suture-associated biofilms. *J Surg Res*. 2012;177:334–340.
56. Hiransuthikul N, Tantisiriwat W, Lertutsahakul K, Vighagool A, Boonma P. Skin and soft-tissue infections among tsunami survivors in Southern Thailand. *Clin Infect Dis*. 2005;41:393–396.
57. Appelgren P, Farnebo F, Dotevall L, Studahl M, Jonsson B, Petrini B. Late-onset posttraumatic skin and soft-tissue infections caused by rapid-growing mycobacteria in tsunami survivors. *Clin Infect Dis*. 2008;47:e11–e16.
58. Noonburg GE. Management of extremity trauma and related infections occurring in the aquatic environment. *J Am Acad Orthop Surg*. 2005;13:243–253.
59. Benedict K, Park BJ. Invasive fungal infections after natural disasters. *Emerg Infect Dis*. 2014;20:349–355.
60. Lewandowski LR, Weintrob AC, Tribble DR, et al. Early complications and outcomes in combat injury related invasive fungal wound infections: a case-control analysis. *J Orthop Trauma*. 2016;30:e93–e99.
61. Sirijatuphat R, Siritongtaworn P, Sripojtham V, Boonyasiri A, Thamlikitkul V. Bacterial contamination of fresh trauma pl at trauma center, Siriraj Hospital, Bangkok, Thailand. *J Med Assoc Thai*. 2014;97(suppl 3):S20–S25.
62. Murray CK, Hospenthal DR, Kotwal RS, Butler FK. Efficacy of point-of-injury combat antimicrobials. *J Trauma*. 2011;71(suppl 2):S307–S313.
63. Weber D, Dulai SK, Bergman J, Buckley R, Beaupre LA. Time to initial operative treatment following open fracture does not impact development of deep infection: a prospective cohort study of 736 subjects. *J Orthop Trauma*. 2014;28:613–619.
64. Lack WD, Karunakar MA, Angerame MR, et al. Type III open tibia fractures: immediate antibiotic prophylaxis minimizes infection. *J Orthop Trauma*. 2015;29:1–6.
65. Penn-Barwell JG, Murray CK, Wenke JC. Early antibiotics and debridement independently reduce infection in an open fracture model. *J Bone Joint Surg Br*. 2012;94:107–112.
66. Mellor SG, Cooper GJ, Bowyer GW. Efficacy of delayed administration of benzylpenicillin in the control of infection in penetrating soft tissue injuries in war. *J Trauma*. 1996;40(suppl 3):S128–S134.
67. Tikka S. The contamination of missile wounds with special reference to early antimicrobial therapy. *Acta Chir Scand Suppl*. 1982;508:281–287.
68. Dahlgren B, Almskog B, Berlin R, et al. Local effects of antibacterial therapy (benzyl-penicillin) on missile wound infection rate and tissue devitalization when debridement is delayed for twelve hours. *Acta Chir Scand Suppl*. 1982;508:271–279.
69. Almskog BA, Haljamae H, Norastrom G, Seeman T. Effects of penicillin G on local metabolic changes in skeletal muscle following high velocity missile injury. *Eur Surg Res*. 1984;16:194–200.
70. Fleming A. The action of chemical and physiological antiseptics in a septic wound. *Br J Surg*. 1919;7:99–129.
71. Klein RS, Berger SA, Yekutieli P. Wound infection during the Yom Kippur War: observations concerning antibiotic prophylaxis and therapy. *Ann Surg*. 1975;182:15–21.
72. Hardaway RM. 200 years of military surgery. *Injury*. 1999;30:387–397.
73. Hospenthal DR, Murray CK, Andersen RC, et al. Guidelines for the prevention of infection following combat-related injuries. *J Trauma*. 2008;64(suppl 3):S211–S220.
74. Hamouda HM, Witso E, Moghani NK, Shahwan A, Nygaard OP. Soft tissue infection after missile injuries to the extremities—a non-randomized, prospective study in Gaza City. *Prehosp Disaster Med*. 2007;22:106–108.
75. Brown KV, Murray CK, Clasper JC. Infectious complications of combat-related mangled extremity injuries in the British military. *J Trauma*. 2010;69(suppl 1):S109–S115.
76. Parker PJ. Pre-hospital antibiotic administration. *J R Army Med Corps*. 2008;154:5–6. discussion 6–9.
77. Hutley EJ, Green AD. Infection in wounds of conflict—old lessons and new challenges. *J R Army Med Corps*. 2009;155:315–319.
78. Grillon A, Schramm F, Kleinberg M, Jehl F. Comparative activity of ciprofloxacin, levofloxacin, and moxifloxacin against *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia* assessed by minimum inhibitory concentrations and time-kill studies. *PLoS One*. 2016;11:e0156690.
79. Ng LS, Kwang LL, Rao S, Tan TY. Anaerobic bacteremia revisited: species and susceptibilities. *Ann Acad Med Singapore*. 2014;44:13–18.
80. Farrell DJ, Liverman LC, Biedenbach DJ, Flamm RK, Jones RN. Surveillance of JNJ-Q2 activity tested against *Staphylococcus aureus* and beta-hemolytic streptococci as a component of the 2010 sentry antimicrobial surveillance program. *Diagn Microbiol Infect Dis*. 2011;71: 415–410.
81. Wexler HM, Molitoris E, Molitoris D, Finegold SM. In vitro activity of levofloxacin against a selected group of anaerobic

- bacteria isolated from skin and soft tissue infections. *Antimicrob Agents Chemother*. 1998;42:984–986.
82. Stevens DL, Aldape MJ, Bryant AE. Life-threatening clostridial infections. *Anaerobe*. 2012;18:254–259.
 83. Cheng CZ, Zhao DH, Li QY, Qu HY, Chen BC, Lin ZD. Causes of inpatient death for patients with warfare-related limb trauma and logistic regression analysis of the risk factors. *Eur J Trauma Emerg Surg*. 2012;38:107–112.
 84. Chen E, Deng L, Liu Z, Zhu X, Chen X, Tang H. Management of gas gangrene in Wenchuan earthquake victims. *J Huazhong Univ Sci Technol*. 2011;31: 83–87.
 85. Murray CK, Hospenthal DR, Holcomb JB. Antibiotics use and selection at the point of injury in tactical combat casualty care for casualties with penetrating abdominal injury, shock or unable to tolerate an oral agent. *J Special Op Med*. 2005;5:56–61.
 86. Wiskirchen DE, Housman ST, Quintiliani R, Nicolau DP, Kuti JL. Comparative pharmacokinetics, pharmacodynamics and tolerability of ertapenem 1 gram/day administered as a rapid 5-minute infusion versus the standard 30-minute infusion in healthy adult volunteers. *Pharmacotherapy*. 2013;33:266–274.
 87. Goldstein EJC, Ciltron DM, Merriam CV, Abramson MA. Infection after elective colorectal surgery: bacteriological analysis of failures in a randomized trial of cefotetan vs ertapenem prophylaxis. *Surg Infect*. 2009;10:111–118.
 88. Gerhardt RT, Matthews JM, Sullivan SG. The effect of systemic antibiotic prophylaxis and wound irrigation on penetrating combat wounds in a return-to-duty population. *Prehosp Emerg Care*. 2009;13:500–504.
 89. Emmerson M. A microbiologist's view of factors contributing to infection. *New Horiz*. 1998;6(suppl 2): S3–S10.