Prevention of Infections Associated With Combat-Related Extremity Injuries

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Abstract: During combat operations, extremities continue to be the most common sites of injury with associated high rates of infectious complications. Overall, ~15% of patients with extremity injuries develop osteomyelitis, and ~17% of those infections relapse or recur. The bacteria infecting these wounds have included multidrug-resistant bacteria such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, extended-spectrum β-lactamase-producing *Klebsiella* species and *Escherichia coli*, and methicillin-resistant *Staphylococcus aureus*. The goals of extremity injury care are to prevent infection, promote fracture healing, and restore function. In this review, we use a systematic assessment of military and civilian extremity trauma data to provide evidence-based recommendations for the varying management strategies to care for combat-related extremity injuries to decrease infection rates. We emphasize postinjury antimicrobial therapy, debridement and irrigation, and surgical wound management including addressing ongoing areas of controversy and needed research. In addition, we address adjuvants that are increasingly being examined, including local antimicrobial therapy, flap closure, oxygen therapy, negative pressure wound therapy, and wound effluent characterization. This evidence-based medicine review was produced to support the *Guidelines for the Prevention of Infections Associated With Combat-Related Injuries: 2011 Update* contained in this supplement of *Journal of Trauma*.
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Historically, the extremities have been the most common sites of injury in combat, and this has remained true during the ongoing wars in Iraq and Afghanistan (Table 1).[1–7] The rate of vascular injuries in modern combat is five times than that reported in previous wars.[8] There are approximately equal numbers of upper and lower extremity injuries; however, lower extremity injuries are more severe, with higher infection rates, especially when associated with a vascular injury (Table 2).[5,9–13] Extremity injuries are associated with major morbidity as evidenced by high complication rates and healthcare utilization. Over a 56-month period, of 5,684 casualties with major limb injuries, 423 (7.4%) underwent major limb amputation, similar to the 8.3% rate during the Vietnam War.[14] A review of 1,333 soldiers revealed that those with extremity injuries had the longest average hospital stay (17.9 days), accounting for $65.2 million total inpatient resource utilization with a projected cost of $170 million disability benefit. Extrapolation of total disability costs for these wars was ~$2 billion.[15]

The goals of extremity injury care are to prevent infection, promote fracture healing, and restore function. Our previous review of combat-related extremity injury infection prevention and management focused on wound debridement and irrigation, initial stabilization, tetanus prophylaxis, systemic antimicrobial therapy, and delayed wound closure.[16] Adjuvant treatments are increasingly being examined to improve outcomes. These include use of local antimicrobial therapy, flap closure, oxygen therapy, and characterization of wound effluent. In this updated supporting document to the guidelines for prevention of infections associated with combat-related injuries,[17] we use a systematic review of military and civilian extremity trauma data to provide evidence-based recommendations for the varying management strategies. We focus on data primarily from 2007 through 2011 to augment the previous guidelines with an emphasis on antimicrobial therapy, debridement and irrigation, and wound management highlighting ongoing areas of controversy and needed research. We include recommendations as they apply to role (echelon or level) of care: Role 1—self-aid, buddy aid, combat lifesaver, and combat medic/corpsman care at the point-of-injury; physician/physician assistant care but no patient holding capacity. Role 2—72-hour patient holding capacity, basic blood transfusion, and radiography and labo-

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TABLE 1. Review of Combat-Related Extremity Injury Infection Articles Published During the Wars in Iraq and Afghanistan

Reference	Time Frame	Evacuation Time	Antimicrobials	Focus of Study	Subjects	Infectious Information	Bacteria
Helgeson et al.[125]	2001–2006	N/A	N/A	Calcium sulfate carrier for antimicrobials and bone graft substitute	15 patients (17 fractures)	Postoperatively 4 of 18 grafting procedures showed clinical infection, with 13 of 17 having positive intraoperative bacteria 22% rate of osteomyelitis	Intraoperative cultures: 11 *Acinetobacter*, 5 *Staphylococcus*, 2 *Klebsiella*, 2 *Pseudomonas*, 1 each with *Bacteroides*, *Bacillus*, and *Corynebacterium*
Lin et al.[274]	2001–2003	7.9 d	Cefazolin plus gentamicin for dirty wounds	Extremity injuries	52 (15 with traumatic amputations)	No infections in fracture only group; two infections among amputee patients	*Pseudomonas*, MRSA, and *Acinetobacter*
Yun et al.[10]	2003–2006	None listed	Variable include early vancomycin	Orthopedic injuries with osteomyelitis	2,854 admission with 664 admitted to orthopedics; 103 with osteomyelitis 2:1 ratio of lower to upper extremities injuries with osteomyelitis	84 (83%) of these patients did not relapse during a follow-up that ranged from 2 to 36 wk	*A. baumannii*, *K. pneumoniae*, and *P. aeruginosa* isolated during an original episode Gram-positive organisms were more likely during recurrences; *S. aureus* (13% vs. 53%)
Enad and Headrick[2]	2003	N/A	Broad spectrum that included gram-negative coverage	Orthopedic injuries	58 total service member, 30 fractures, and 14 total with battle injury	No perioperative infections	None listed
Hinsley et al.[275]	2003	Rapid, but not detailed	Benzyl penicillin before arrival to hospital	90% Iraqi	39 patients with 50 ballistic fractures (17 upper and 33 lower extremity)	43 evaluable wounds: 13 of 43 became infected, with 5 of 43 deep infections Infection occurred significantly more often with gunshot fractures, wound closed primarily, and intra-articular fractures	None listed
Petersen et al.[74]	2003	4.2 d	Variable	Evacuation to US naval hospital ship	211 patients (179 Iraqi)	44 of 56 extremities injuries developed infection; no fracture data	Most common bacteria— *Acinetobacter*, *E. coli*, *Pseudomonas*, and *Enterobacter* species
Johnson et al.[20]	2003–2006	7.4 d	Variable	Type III tibial fractures	62 open tibial fractures with 40 Type III (35 with data)	27 with at least 1 organism (deep wound culture) None of the initially recovered gram-negative bacteria cultured again after being treated for a deep infection or osteomyelitis 5 of 35 patients ultimately required limb amputation with infectious complications cited as the reason in 4	*Acinetobacter* species, *Enterobacter* species, and *P. aeruginosa* were the most commonly recovered bacteria initially Staphylococcal organisms were found in every wound at the time of repeat operation, along with *P. aeruginosa* in 3 samples

TABLE 1. Review of Combat-Related Extremity Injury Infection Articles Published During the Wars in Iraq and Afghanistan (continued)

Reference	Time Frame	Evacuation Time	Antimicrobials	Focus of Study	Subjects	Infectious Information	Bacteria
Mack et al.[276]	2003–2007	N/A	N/A	Open periarticular shoulder	44 (33 Type IIIa, 1 Type IIIb, and 10 Type IIIc)	31 of 44 initially cultured of which 22 were positive 1 or more year of follow-up; 5 of 35 became infected (4 IIIa and 1 IIIc)	Of 22 initial cultures, 14 were *A. baumannii*
Possley et al.[206]	2003–2007	N/A	N/A	Safety of external fixation	55 Type III tibia fractures	No cases of pin tract osteomyelitis 8 cases of osteomyelitis at fracture site An additional 22 tibias were clinically diagnosed and treated for osteomyelitis at the fracture site without a positive bone culture Two soft tissue infections	Not listed
Geiger et al.[1]	2003–2005	N/A	Not stated but initially meropenem added until wounds closed	Plastic surgery care	42 patients with lower extremity injury, 20 with upper extremity, and 10 with both	15 of 62 developed acute osteomyelitis, and 1 of 62 developed chronic osteomyelitis	9 *A. baumannii*, 5 *Enterobacter*, 4 coagulase negative *Staphylococcus*, 3 *Enterococcus*, 2 MRSA, 1 *Bacillus*, and 1 *Klebsiella*
Brown et al.[21]	2003–2008	92% within 12 h	Majority penicillin/ floxacilin plus anaerobic coverage	Mangled extremity	84 casualties (85 extremities)	24% developed infection with 6% developed osteomyelitis Fasciotomy, antimicrobials during air evacuation, and *P. aeruginosa* were significantly associated with infectious complications	*S. aureus* were recovered later in casualties' clinical course in contrast to early recovery of *Acinetobacter*
Brown et al.[11]	2003–2008	Less than 6 h 95%	N/A	Vascular injury	37 total (29 with fractures)	20 of 29 limbs with a fracture developed superficial infection and 2 of 8 limbs without a fracture developed a superficial infection 3 of 29 with fracture developed deep infection	None listed
Clasper and Phillips[209]	2003	N/A	N/A	External fixation use	15 external devices (14 patients)	3 fixators developed pin track infections and failed despite antimicrobials	None listed
Mody et al.[19]	2003–2007	N/A	N/A	Damage control orthopedics	58 patients—34 Type IIIa, 9 Type IIIb, and 3 Type IIIc	Fracture site infection 40% and suspected osteomyelitis 17%	Surgical Site infections (23): polymicrobial 44%, gram-negative 65%, and gram-positive 44% Early infections (13)—9 gram-positive and 5 gram-negative Late infection (9)—5 gram-positive and 6 gram-negative

TABLE 1. Review of Combat-Related Extremity Injury Infection Articles Published During the Wars in Iraq and Afghanistan (continued)

Reference	Time Frame	Evacuation Time	Antimicrobials	Focus of Study	Subjects	Infectious Information	Bacteria
Orr et al.[277]	2003–2008	N/A	N/A	Sural artery flap foot and ankle	10 Type IIIb	3 deep wound infections with osteomyelitis	MDR *Klebsiella* and *Acinetobacter*
Keeling et al.[229]	2004–2007	N/A	Cefazolin plus meropenem plus vancomycin beads	Ring external fixation	67 Type III tibial shaft fractures with 45 tibia fixations with 36 cases reviewable	Standardized treatment protocol—3 of 38 tibia infected and all treated successfully with debridement and antimicrobials without frame removal	None listed
Leininger et al.[136]	2004–2005	Within 24 h of injury	N/A	Negative pressure wound therapy study	Soft tissue infections—20 upper and 38 lower extremity	No fracture data present No infections described with standard debridement and use of negative pressure wound therapy	None listed
Kumar et al.[13]	2004–2007	N/A	N/A	Upper extremity flaps	23 patients with 26 upper extremity injuries	46% of wound colonized at admission 2 flaps early postop infections with no sequelae	75% *A. baumannii*
Kumar et al.[12]	2004–2007	12 open fractures (75%) nailing within 72 h	N/A	Lower extremity flap reconstruction	43 patients all with Type IIIb and Type IIIc fractures—22% upper extremity, 52% tibia/fibula, and 22% ankle/foot	50% of wounds colonized at admission 8 flaps early infection with no sequelae	57% *A. baumannii*
Keeney et al.[278]	2005–2006	N/A	First-generation cephalosporin plus fluoroquinolone until 48 h after wound closure	Immediate nailing or staged treatment of closed femoral fracture	22 patients (23 femoral fractures) with 16 Type IIIa open fractures	Follow-up 2 mo for 8 and 6 mo for 5 No infections	None listed
Stinner et al.[207]	2001–2008	N/A	N/A	Outcome of in the combat zone internally fixed fractures	47 patients with 50 fractures (14 hip, 14 forearm, and 14 ankle)	1 infection	MRSA
Burns et al.[279]	2003–2007	N/A	N/A	Does large zone of injury impact flap coverage	67 Type IIIB tibia fractures	None described	

N/A, not available.

TABLE 2. Gustilo Fracture Classification System and Associated Infection Rates*

Gustilo Fracture Type	Characteristics	Rates of Infection[32,169,191–193]
Type I	Puncture wound <1 cm Minimal contamination Minimal soft tissue damage	0–2%
Type II	Laceration >1 cm but <10 cm Moderate soft tissue damage Adequate bone coverage Minimal comminution	2–5%
Type IIIA	Laceration >10 cm Extensive soft tissue damage Adequate bone coverage, segmental/ severely comminuted fractures, or heavily contaminated wounds	5–10%
Type IIIB	As a Gustilo Type IIIA injury, but with periosteal stripping and bone exposure	10–50%
Type IIIC	Any open fracture with vascular injury requiring repair	25–50%

* Tibial fractures are associated with twice the infection rate of other bone.

ratory support; may be supplemented with surgical assets (Level IIb). Role 3—combat support hospital (CSH, US Army), Air Force theater hospital (AFTH, US Air Force), or casualty receiving ships (US Navy); full inpatient capacity with intensive care units and operating rooms. Role 4— regional hospital (Landstuhl Regional Medical Center, Germany) or USNS hospital ships (US Navy), typically outside of the combat zone; general and specialized inpatient medical and surgical care. Role 5—care facilities within United States, typically tertiary care medical centers.

METHODS

A MEDLINE search using PubMed from the US National Library of Medicine National Institutes of Health was performed using the key words "extremity," "orthopaedics," "military," "combat," "infection," "prevention," "osteomyelitis," "negative pressure wound therapy," "fixation," "irrigation," "debridement," "antimicrobial," "oxygen," "culture," "bacterial," "fungal," and "wound infection" with an emphasis on June 2007 through January 1, 2011. We also cross-referenced published bibliographies for additional manuscripts. In addition, we analyzed ongoing research projects with data published in abstract form or preliminary draft manuscripts for inclusion in the guidelines.

EPIDEMIOLOGY/MICROBIOLOGY OF WOUND COLONIZATION AND INFECTION

The primary complication associated with combat-related extremity injuries is infection. Approximately 15% of patients develop osteomyelitis, and ~17% of those infections relapse or recur.[10] Many of the traditional host factors associated with increased risk of extremity injury infections are not present in young, healthy military personnel.[18] Therefore,

infections are likely to be related to the mechanism of injury, presence of orthopedic devices, fracture severity (Type), site of injury, antimicrobial agents received, infection prevention strategies employed, surgical care, environmental contamination, and infecting pathogens, especially those that are resistant to antimicrobials.[10,19–22] The bacteria infecting these wounds have included multidrug-resistant (MDR) bacteria such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, extended-spectrum β-lactamase-producing *Klebsiella* species and *Escherichia coli*, and methicillin-resistant *Staphylococcus aureus* (MRSA).[10,19,20] Although initial infections are often complicated by gram-negative pathogens, many of the late relapses are gram-positive bacteria, commonly methicillin-sensitive *S. aureus* and MRSA.[10,19,20]

POSTINJURY ANTIMICROBIALS

The nature of combat-related extremity injuries results in gross contamination of the wound along with anatomic and physiologic derangement of the local tissue. In addition, there are likely systemic immune alterations from the severe trauma complicating the patient's ability to control infection. Therefore, antimicrobial activity through systemic, and possibly local, delivery is required to prevent subsequent infections.

Timing of Antimicrobials

The current recommendation by the United States for tactical combat casualty care (TCCC) committee is rapid delivery of oral or intravenous antimicrobial therapy at the point-of-injury. This is primarily based upon expert opinion with limited supporting military data (Table 3).[23–27] Delivery of antimicrobials within a 3-hour window for limb soft tissue injuries was associated with fewer infections in comparison with those who received antimicrobials after 3 hours during the Falklands Campaign in 1982.[28] During the 1973 October War in Israel, the low rates of infections were attributed to casualties on the battlefield receiving antimicrobials within 30 minutes to 60 minutes of injury.[29] During the war in Afghanistan, the British military did not reveal that the timing of antimicrobials was related to infection prevention, but all antimicrobials were delivered soon after injury.[21]

Guidelines have recommended initiation of antimicrobials as soon as possible.[16,30] Retrospective civilian studies have not shown substantial differences in rates of infection based upon timing of the delivery of antimicrobial agents, but timing is typically defined by 3 hours and 6 hours, which might not correlate with the casualty taking the antimicrobial themselves or being provided by a medic near the time of injury.[31] One civilian study noted a higher infection rate (7.4%, 49 of 661 patients) if antimicrobials were given after 3 hours versus a lower infection rate (4.7%, 17 of 364) when antimicrobials were given within 3 hours.[32] However, this was not confirmed in other large studies, and care must be taken in general when comparing civilian and military trauma as the mechanism of injury can vary dramatically (i.e., motor vehicle crashes vs. blast injuries).[33–35] In addition, one of these studies was limited by lack of follow-up because many patients with Type IIIb and IIIc fractures being transferred to tertiary care hospitals for definitive management.[33]

TABLE 3. Relationship Between Timing of Postinjury Antimicrobial Delivery and Subsequent Infection Rate

Author	Year	Study Type	No. of Patients	Time to Antimicrobial Initiation	Infection Rates of Early vs. Late Antimicrobial Timing	Significant Difference
Patzakis and Wilkins[32]	1989	Civilian, retrospective	1,104 (fractures)	≤3 h	4.7% (17 wounds of 364 open fractures) vs. 7.4% (49 wounds in 661 open fractures)	Yes
Al-Arabi et al.[33]	2007	Civilian, prospective	133	<2, <4, and <6 h	<2 h (9.2%) (6 of 65 patients) <4 h (2.2%) (1 of 45 patients) <6 h (0%) (0 of 14 patients) >12 h (100%) (2 of 2 patients)- surgery and antimicrobials delayed past 24 h	No, $P = 0.26$
Dellinger et al.[34]	1988	Civilian, prospective	240	≤3 h	16% (29 of 183 patients) vs. 17% (8 of 47 patients	No
Jackson[28]	1984	Military, retrospective soft tissue extremity injuries	49	≤3 h	0% (0 of 17 patients) vs. 28% (9 of 32 patients); 2 of 11 treated between 4 and 6 h became infected and 4 of 7 treated between 7 and 9 h became infected	None provided

Animal studies have shown that the earlier antimicrobials are provided, the more effective they are at preventing infections, especially in the first couple of hours after injury.[36–41] (Joseph C. Wenke, personal communication).

Antimicrobial Agents of Choice

The choice of antimicrobials was selected based upon a review of prospective and retrospective clinical trials taking into consideration the bacteria likely associated with wound contamination in the combat zone (Table 4). In the previous guidelines, we recommended the use of the first-generation cephalosporin cefazolin because of its antibacterial coverage of likely infection pathogens and its use as the standard of care in the United States for extremity trauma.[16] This has remained the therapy of choice, without enhanced anaerobic or aerobic gram-negative bacterial coverage. In addition, dose modification and methods of delivery are outlined more specifically in this updated guideline.

Antimicrobials initially provided by the surgeon are selected to eradicate virulent bacteria likely inoculated into the wounds at the time of injury to prevent local and systemic infection. Yet, multiple studies reveal that the bacteria contaminating open fractures at the time of injury are not the same bacteria cultured from infected open fractures after debridement.[42–46] Instead, these infections are thought to be caused by hospital-acquired bacteria.[22,42,47] Nosocomial infections with late onset wound infections were well described during World War II.[48–50] In the Korean War, pathogens infecting wounds within 8 hours of injury included *Clostridium* species along with gram-positive and gram-negative pathogens.[51] In addition, wounds appeared to have varying types of bacteria isolated from them over the course of a serviceman's hospitalization, but infections only occurred when wounds had necrotic tissue remaining.[52] During the Vietnam War, there was a transition over 5 days from an even mix of gram-negative and gram-positive bacteria within wounds at the time of injury to primarily gram-negative pathogens, notably *P. aeruginosa*, despite (or because of) broad spectrum antimicrobial therapy (typically penicillin and streptomycin) active against the bacteria initially found in the wound.[53] Notably, wound cultures did not always correlate with matching blood cultures, and infections primarily occurred in wounds with necrotic tissue remaining. Bacteria recovered in Japan, ~7 days after injury, had a predominance of *P. aeruginosa* and *S. aureus* followed by *Enterobacter* spp. In addition, when comparing the susceptibility patters of these organisms over time, it appeared that antimicrobial resistance increased over the course of their hospitalization.[54] The presence of these pathogens remained in wounds upon arrival in the United States.[55] During the wars in Iraq and Afghanistan, one study found that cultures from wounds at the time of injury reveal a predominance of gram-positive bacteria without MDR gram-negative rods.[56] Overall, numerous wounds appear to be colonized and possibly infected upon reaching care within the United States or England with the burden of MDR pathogens increasing over time, as appears to have occurred in previous wars.[10,19–21,57,58]

The International Committee of the Red Cross (ICRC) recommends intravenous penicillin for compound fractures, amputations, and major soft tissue wounds.[59] The British military has traditionally provided penicillin-based regimens at the initial time of surgery, including intravenous amoxicillin/clavulanate for abdominal injuries; however, there is debate as to the ideal agent.[21,60] The Israelis' management of injuries (predominantly from blasts) has included a combination of cephalexin and metronidazole intravenously followed by ortal therapy.[61]

Among civilian trauma care, a Cochrane review indicated that antimicrobials were protective against early infection compared with no antimicrobials (relative risk 0.41, 95% confidence interval 0.27–0.63; absolute risk reduction of 0.08, 95% confidence interval 0.04–0.12; and number needed to treat of 13).[62] This effect was attributed to the activity of β-lactams antimicrobials against streptococci and staphylococci. The Eastern Association for the Surgery of Trauma guideline committee concluded that antimicrobials were useful, but further work was needed, especially regard-

TABLE 4. Randomized or Prospective Studies of Antimicrobial Prophylaxis in Open Fracture

Reference	Year	No. of Patients	Fracture Type	Grade	Wound Management	Antimicrobial Strategy	Duration of Antimicrobial	Outcomes	Comments
Patzakis et al.[31]	1974	310	Long bones	No	Primary suture	Cefazolin vs. penicillin plus aminoglycoside vs. placebo	10–14 d	Cefazolin (2%) < penicillin plus aminoglycoside (10%) < placebo (14%)	
Bergman[280]	1982	180	Mostly long bones	Yes	Primary suture	Dicloxacillin vs. penicillin vs. placebo	2 d	2 deep infections in placebo group only	12 Type II and III treated with dicloxacillin, 10 with benzyl penicillin, and 13 with saline
Benson et al.[259]	1983	82	Long bones	No	Variable	Clindamycin vs. cefazolin	5 d	Clindamycin = cefazolin (~3%)	
Sloan et al.[91]	1987	85	Distal phalanx	No	N/A	Cephradine	1 d vs. 5 d	5 d = 1 d	
Braun et al.[281]	1987	100	Long bones	No	Not reported	Dicloxacillin vs. placebo	10 d	Dicloxacillin (2%) < placebo (12%)	
Johnson et al.[282]	1988	86	Tibia	Yes	Delayed closure	Cefazolin vs. cefotaxime	Variable	Cefazolin (24%) = cefotaxime (19%)	Some more gram-negative failures in cefazolin and gram-positive in cefotaxime
Dellinger et al.[34]	1988	248	Long bones	Yes	Delayed closure	Cefonicid 1 d vs. 5d vs. cefamandole 5d	1 d vs. 5 d	Cefonicid 1 d = 5 d—cefamandole 5 d (12–13%)	
Peacock et al.[283]	1988	87	Hand	No	N/A	Cefamandole intravenous then oral cephalexin vs. placebo	4 d	Antimicrobials (0%) = placebo (2.1%)	
Dickey et al.[284]	1989	67	All injuries	No	Closed	24-h cefazolin vs. no therapy	1 d	1 infection each arm	Low-velocity gun shots, 29 lost to follow-up
Swiontkowski[285]	1989	60	Lower extremity	Yes	Prospectively varied	All received cephalosporin plus aminoglycoside	Variable	None	
Robinson et al.[164]	1989	89	Lower extremity	Yes	Delayed closure	All received cefoxitin plus aminoglycoside for Type III	Variable	None	
Suprock et al.[286]	1990	91	Finger	No	N/A	3 d gram-positive coverage vs. placebo	3 d	Antimicrobials (9%) = placebo (9%)	
Hansraj et al.[287]	1995	100	All injuries (gunshot wounds)	No	N/A	Ceftriaxone vs. cefazolin	2 d	Ceftriaxone = cefazolin (0%)	30% lost to follow-up
Knapp et al.[288]	1996	186	Mostly long bones	No	Delayed closure	Intravenous cephapirin plus gentamicin vs. ciprofloxacin	3 d	2 infections in each arm	Low-velocity gunshot wound
Vasenius et al.[70]	1998	227	Mostly long bones	Yes	Delayed closure	Clindamycin vs. cloxacillin	3 d or until closed	Clindamycin (9%) < cloxacillin (20%)	Most infections were in Type I fractures

TABLE 4. Randomized or Prospective Studies of Antimicrobial Prophylaxis in Open Fracture (continued)

Reference	Year	No. of Patients	Fracture Type	Grade	Wound Management	Antimicrobial Strategy	Duration of Antimicrobial	Outcomes	Comments
Carsenti-Etesse et al.[42]	1999	616	Leg Type I-II	Yes	Delayed closure	Pefloxacin vs. cefazolin plus oxacillin	1 d vs. 5 d	Pefloxacin (7%) = cefazolin plus oxacillin (8%)	More gram-negative infections in cefazolin group but more *S. aureus* in pefloxacin group
Sorger et al.[76]	1999	71	Mostly long bone	Yes	Delayed closure	Cefazolin plus gentamicin 5 mg/kg q 12 h vs. 6 mg/kg q24 h	48 h after each operation until wound closed	q 12 h gentamicin (13.6%) = q 24 h (5.4%)	
Moehring et al.[130]	2000	67	Leg Type II-IIIb	Yes	Delayed closure	"Conventional antimicrobials" vs. same plus tobramycin beads	Until closed	"Conventional antimicrobials" (5%) = same plus tobramycin beads (8%)	Conventional antimicrobials not controlled, 20% randomization error
Patzakis et al.[65]	2000	171	Mostly long bones	Yes	Delayed closure	Ciprofloxacin (intravenous or oral) vs. cefamandole plus gentamicin	3–8 d	Ciprofloxacin- cefamandole plus gentamicin	>12 h to antimicrobials, >24 h to operating room. High infection rates in Type III fractures
Stevenson et al.[289]	2003	193	Phalynx	N/A	N/A	Flucloxacillin vs. placebo	N/A	3% vs. 4% infection	

N/A, not available.

ing Type IIIb fractures. They recommend systemic antimicrobials directed at gram-positive organisms with additional gram-negative coverage for Type III fractures. They indicated that fluoroquinolones offer no advantage over cephalosporin plus aminoglycosides with the possibly association of excess harm.[30,63] The Surgical Infection Society concluded that current studies for determining antimicrobial recommendation suffer from methodological and statistical flaws, older publications and studies not adequately reflecting the bacterial resistance, or the available antimicrobial agents used today.[64] These guidelines do not support the addition of enhanced gram-negative coverage with an aminoglycosides for Type III fractures.

Enhanced Gram-Negative Coverage

A major area of controversy in the selection of postinjury antimicrobials involves the role of additional gram-negative coverage for Type III fractures. Prospective studies with ciprofloxacin have shown no improved outcomes and actually worse outcomes for Type III fractures in comparison with cefamandole and gentamicin.[65] There is also in vitro and animal data which has associated fluoroquinolone use with impaired fracture healing.[66,67] The role of additional aminoglycoside coverage was only assessed prospectively in one study evaluating no antimicrobials, penicillin plus streptomycin, and cephalothin for 10 days.[31] That study did not describe the types of fractures. There was a 13.9% infection rate in the placebo group (11 of 79 wounds), 9.7% in the penicillin plus streptomycin group (9 of 92 wounds), and 2.3% in the cephalothin group (2 of 84 wounds) (no significant difference between placebo or penicillin plus streptomycin group [$p = 0.45$] but significant difference between cephalothin and placebo and penicillin plus streptomycin groups [$p < 0.05$]). Cultures were wound swabs but were not obtained for clinical evidence of infection. The bacteria in the penicillin plus streptomycin had the highest rate of recovered resistant pathogens after therapy. Interestingly, the cultures from the placebo group for pathogenic bacteria remained stable around 40% before antimicrobials until wound closure, whereas for the penicillin plus streptomycin group, pathogenic bacteria increased from 32% before surgery to 83% at wound closure. For the cephalothin group, bacteria recovery was 33% before antimicrobials and negative at the final wound closure culture. Although this study by Patzakis et al. has been referred to as prospective research supporting the use of enhanced gram-negative coverage, the reported results do not appear to support this recommendation. The data supporting the recommendations for aminoglycosides are typically cumulative studies that includes this prospective study just mentioned in combination with a retrospective study in which a combination of cefamandole plus tobramycin in 109 wounds had five infections (4.5%).[32,68,69] An additional argument that has been made is based upon a prospective study comparing clindamycin versus dicloxacillin with high rates of failure with Type III fractures.[70] The authors propose that success rates could be improved by the addition of gram-negative coverage. Notably, an evaluation of possible infecting pathogens (removing likely skin pathogens such as diphteroid,

micrococcus, *Bacillus* species, and *Streptococcus viridians*) recovered from initial wound swabs were 35% gram-negative and 65% gram-positive. Clinical failure included pathogens that should have been adequately covered with initial regimens. Overall, these studies support adequate irrigation and debridement as primary therapy, with antimicrobials as adjuvants relegating later infections to primarily nosocomial transmission with antimicrobial potentially selecting pathogens.

Given the MDR nature of the gram-negative bacteria found to be subsequently infecting combat casualties' injuries after the current antimicrobial regimens were used in the combat zone (e.g., cefazolin and levofloxacin or aminoglycoside), it is currently not clear whether the use of fluoroquinolones with enhanced gram-negative activity or aminoglycosides is resulting in the selection of these resistant pathogens, as shown in the civilian literature. Although not rigorously evaluated, data derived from the Yom Kippur War indicated that overly broad spectrum antimicrobial agents led to the development of infections with resistant bacteria.[71] Those authors proposed that the severity of combat trauma wounds and contamination "leads toward the temptations to 'sterilize' the wound with massive doses of antimicrobials and favors a false security with less reliance on good surgical technique."

If an aminoglycoside is to be used to "enhance gram-negative coverage," it will be a challenge to determine which agent to use based upon the varying resistance profiles of the gram-negative rods being recovered from combat-related extremity injury infections.[72–75] For *P. aeruginosa* and *E. coli* isolates from patients managed on the US Comfort, 94% were amikacin susceptible, and only 40% were susceptible to gentamicin or tobramycin.[74] For *Enterobacter* species, 78% were gentamicin susceptible, whereas 40% were amikacin or tobramycin susceptible. If aminoglycosides use is implemented, daily dosing appears adequate, at least for gentamicin; however, higher doses might be required in a severe trauma patient, especially with these MDR bacteria.[76]

Addition of Penicillin for Dirty Wounds

Justification for penicillin therapy has traditionally focused on gas gangrene infections or *Streptococcus pyogenes* (Group A streptococci). During World War I, there was a 5% incidence of gas gangrene, with 28% mortality; during World War II, the incidence ranged between 0.3% and 1.5%, depending upon the combat zone, with 15% mortality.[77–80] During the Korean War, there were no reported cases of mortality as a result of this complication.[81] This decrease was largely attributable to decreasing the time from injury to definitive care and adequate surgical debridement, not specific antimicrobial therapy. In the current era, there is some controversy about the use of penicillin after trauma. The Eastern Association for the Surgery of Trauma practice management guidelines for civilian injuries recommends high-dose penicillin when there is concern for fecal/clostridial contamination such as in farm-related injuries.[30,63] However, penicillin therapy is discouraged by the Surgical Infection Society regardless of the mechanism of injury.[64] The primary reason for not providing penicillin is the rarity of gas gan-

grene seen among wounds, especially combat-related extremity injuries in wartime as a result of aggressive surgical management and delayed primary closure. To date, no cases have been described in Iraq or Afghanistan. Of increasing concern is the increase in in vitro resistance to penicillin in *Clostridium* species and limited animal data that reveal no improved outcomes with antimicrobial therapy for gas gangrene in comparison with untreated controls.[21,56,77,82,83] Finally, other antimicrobials, typically provided during extremity wound care by physicians, have adequate Group A streptococci coverage limiting the utility of additional penicillin coverage.

Point-of-Injury Tactical Combat Casualty

A panel of military trauma experts published a list of antimicrobials that were recommended as part of TCCC or care provided at the point-of-injury. These include oral moxifloxacin and intravenous/intramuscular ertepenem or cefoxitin.[24,25,84] Although the ICRC, the British military, and the Israeli military recommend various antimicrobials for combat-related injuries, these are not designed to be given at point-of-injury by the patient or the medic but upon evaluation by definitive medical personnel often times during the medical evacuation flight.[21,59–61]

The core issues surrounding the determination of the ideal point-of-injury field antimicrobial is multifactorial. As addressed in articles assessing point-of-injury antimicrobial agent, the goal is to include agents that are active against the likely infecting pathogen for the body part injured along with agents that are stable and able to be delivered in a reasonable manner on the battlefield without possible adverse events to the patient.[24,25,60,84] A recent study evaluating point-of-injury antimicrobials by Army Rangers did not appear to show a clear infection prevention benefit, although the numbers were small. Of note, no increase in colonization or infection with MDR bacteria was noted nor were there medication toxicities reported.[27] There are clear arguments for choosing an agent with focused antibacterial spectrum of activity; however, it appears the antimicrobials recommended by the TCCC Committee are not causing harm and might be beneficial.

Dosing of Antimicrobials

To better optimize antimicrobial pharmacodynamics and pharmacokinetics, higher doses of antimicrobials are being recommended for perioperative antimicrobials to prevent surgical site infection.[85,86] Most recommendations for perioperative antimicrobials are for a cefazolin dose of 2 g with some recommendations being weight-based: 1 g for those ≤80 kg (176 lbs), 2 g for those 81–160 kg (177–352 lbs), and 3 g for those >160 kg (>352 lbs).[87,88] The package insert for cefazolin does recommend higher dosing (1–1.5 g every 6 hours) for severe, life-threatening infections with dosing up to 12 g per day being given.[89] Given the volume of distribution in a trauma patients and the size of the typical US servicemember, a 2 g dose of cefazolin is recommended and appears to be safe.

Duration of Antimicrobials

The ICRC recommends a total of 5 days of antimicrobial therapy after injury, which is similar to the Israeli recommendation of 5 days after missile injury.[59,61] Per the ICRC, if redebridement is performed instead of delayed primary closure, antimicrobials should be stopped if there are no signs of infection or local inflammation. If patients present after 72 hours or are injured as a result of antipersonnel landmines, then the addition of metronidazole in an intravenous form for 48 hours followed by oral therapy until delayed primary closure is suggested. Most authors and guidelines focusing on civilian injuries recommend 24 hours to 72 hours of postinjury antimicrobial therapy depending upon severity of injury, with shorter durations for Type I fractures and longer durations for Type III fractures.[30,63,64,90] Prospective and some retrospective studies have revealed therapy as short as 1 day may be as effective as the traditionally recommended 3 days to 5 days of therapy and 3 days better than 5 or more days.[32,34,43,91] There also are data suggesting that prolonged courses of antimicrobials are associated with systemic infections with MDR bacteria.[92,93] In addition, 72 hours is typically the time in which wounds are surgically reevaluated in a combat setting, allowing antimicrobials to be discontinued if there is no evidence of ongoing infection.

Redosing of Antimicrobials

In addition to higher dosing, repeat dosing before the 2-hour to 4-hour interval, typically recommended for surgical site infection prevention, should occur if blood loss exceeds 1,500 mL to 2,000 mL.[86,94–96] Although the literature does not necessarily apply to the very large volumes of blood loss and potential whole blood requirements among casualties of war, it is reasonable to redose cefazolin when there is large volume blood loss and possible large volume fluid resuscitation.[97–101]

Alternate Routes of Systemic Antimicrobial Delivery

Methods to deliver antimicrobials is challenging during combat operations due to logistical constraints associated with supplying medications, storage of medications, and obtaining and maintaining adequate venous access. The use of intraosseous (IO) delivery of fluids or analgesia has been recommended as part of TCCC; however, in the TCCC guidelines for point-of-injury antimicrobials for those unable to take oral agents (shock, unconscious, or penetrating torso injures), the recommendation is for delivery by intravenous (IV) or intramuscular (IM) route.[24,25,102] IO antimicrobial delivery has not been systematically studied in military populations or trauma patients.[103,104] In animal studies, those antimicrobials that are highly protein bound have been associated with lower serum concentrations with IO delivery than IV delivery.[105] Both cefazolin and ertapenem are highly protein bound antimicrobials.[106,107] IM delivery has also not been studied in military or trauma patient populations but has been used and FDA approved for cefazolin and ertapenem.[107–109] An animal study assessing a first-generation cephalosporin revealed that highest peak levels were achieved by IV push; however, IM route was associated with sustained serum levels of drug.[110] As bone to serum penetration ratio for ertapenem is ~0.15 and for cefazolin it is 0.25, this low concentration of antimiocrobial would limit IO or IM delivery, especially with severely ill patients and resistant bacteria.[111–114]

Local Antimicrobial Delivery

Local delivery of antimicrobials as a powder or solution was discouraged by Alexander Fleming in 1919 while he served in the British Army.[115] During World War II, antimicrobials were shown to be more effective if given systemically than through local delivery.[116–118] During the Vietnam War, topical therapy was not broadly implemented, although it appeared to be associated with lower rates of bacteria in wounds in some animal studies.[119–124]

During the current wars in Iraq and Afghanistan, there have been a number of reports of the utilization of local delivery of antimicrobials through beads or bead pouches, but limited comparative trials and no prospective trials are available to support this use.[125] One retrospective study comparing antimicrobial bead pouch to negative pressure wound therapy (NPWT) revealed fewer infections with the antimicrobial bead pouch.[126]

There is extensive use of local delivery of antimicrobials through beads, which might benefit in clearing infections due to high local drug concentrations, especially those associated with biofilms or bacteria resistant to standard levels of antimicrobials.[127,128] Traditionally, vancomycin and tobramycin have been the agents of choice, but other agents such as colistin have been pursued because of the MDR nature of infecting pathogens.[129] A randomized, prospective study of civilian open fractures with 67 patients and 75 open fractures revealed 2 of 24 (8.3%) with antimicrobial beads alone developed an infection in contrast to 2 of 38 (5.3%) of those treated with conventional systemic antimicrobial therapy.[130] A large retrospective study of open extremity fractures revealed statistically significant reduction in infections in those patients receiving local delivery of antimicrobials (tobramycin) versus those receiving only systemic therapy (12% vs. 3.7% [$p < 0.01$]).[131] In that study, the patients with impregnated beads had their wounds closed earlier, introducing a potential bias into the study conclusions. The use of antimicrobial bead pouches has also been retrospectively assessed in combination with intramedullary nails for Type II, IIIa, and IIIb tibia fractures.[132] Of 50 patients who received the antimicrobial bead pouches, only 2 developed an infection, in contrast to four infections in the 25 patients who did not receive the pouches.

In animal models, local delivery of antimicrobials appears promising.[133] However, there is possible toxicity to osteoblasts associated with local delivery of some antimicrobial agents.[67] Of note, antimicrobials used in combination with NPWT appears effective; however, NPWT also pulls antimicrobials out of the wound and reduces their effectiveness when compared with standard bead pouch (see NPWT section below).[134] The practical use of bead pouches during aeromedical transport and frequent serial debridements remains a difficult technical challenge. It also appears that earlier delivery of local antimicrobials with earlier surgery

might improve outcomes.[135] Moreover, the appearance of wounds might differ with local delivery of agents, especially silver, potentially impeding clinical diagnosis of wound infection.

DEBRIDEMENT AND IRRIGATION

The gross contamination of wounds at the time of injury necessitates adequate irrigation and debridement to prevent ongoing bacterial replication. In addition, the presence of devitalized tissue is an ideal culture media, which must be adequately controlled to prevent subsequent infections.

Irrigation Fluid Additives

No combat-related extremity injury studies have evaluated the role of additives to irrigation fluid for wound management, although one study assessing NPWT in a combat support hospital did describe the role of irrigation in wound management.[136] In addition, another study assessing minor wounds that did not require evacuation for surgical care revealed the primary importance of wound irrigation over antimicrobials.[137]

A large, multicenter collaborative project assessing various irrigation pressures and irrigation solutions of open fractures is under way and should provide insight into the ideal irrigation strategies.[138] This group performed a thorough review of the current irrigation literature. Preliminary data have revealed that low volume with castile soap might be beneficial.[139] The only prospective, randomized clinical trial was limited to a single institution with relatively small numbers of enrolled participants.[140] Patients were randomized to irrigation with a bacitracin solution or a nonsterile castile soap solution with overall findings indicating that bacitracin was no better than nonsterile castile soap but was associated with a possible increased risk of wound-healing problems. Another study limited to lacerations revealed no difference between normal saline and sterile water.[141] Reviews and surveys of provider practice patterns indicate no clear support for additives into irrigation fluids, supporting the role of normal saline or sterile water and even potable water if the other fluids are not available.[90,142–144] Animal studies have also supported this conclusion.[145,146]

Volume of Irrigation Fluid

Although not the primary focus of a study evaluating the use of NPWT performed on casualties in Iraq, the use of pulsatile jet irrigation with at least 3 L of saline was shown to be very successful overall management strategy that decreased combat-related injury infection rates.[136] No clear studies have proven the efficacy of the commonly used volumes for various Type of fractures (3 L for Type I fractures, 6 L for grade II fractures, and 9 L or more for grade III fractures), but this appears to be standard of care throughout the world.[144] In animal models, it has been shown that greater volumes removes more bacteria and that greater volumes are likely needed in removing debris when low-pressure irrigation is used.[147]

Pressure Employed to Deliver Irrigation Fluids

Irrigation fluid pressure includes gravity flow (1–2 psi [pounds per square inch] typically obtained by hanging the irrigation fluid bag 6 feet to 8 feet above the ground), low-pressure irrigation (5–10 psi), or high-pressure irrigation (>20 psi), although these definitions are not standardized. Overall, the reasoning behind which pressure provides the best patient outcomes was well outlined in a recent review of the subject. It showed that higher pressure initially cleans the wounds very well, but tissue and bone damage along with rebound bacterial colonization noted 24 hours after initial irrigation limits its overall positive impact.[90,138] It is anticipated that the Fluid Lavage and Open Fracture Wounds multicenter, randomized trial will provide adequate data to answer this clinical delima.[138] Pilot data from the Fluid Lavage and Open Fracture Wounds study does demonstrate a trend toward more wound complications with high-pressure devices.[139]

Timing of Irrigation

Currently, there are limited data available regarding the timing of irrigation fluid delivery, as it is often lumped with routine surgical care. It is vital to have this information to show whether delivery of earlier field irrigation with point-of-injury field antimicrobials might improve infectious complications in a combat setting when evacuation is not possible.[137] Animal studies have shown that earlier irrigation improves bacterial clearance as irrigation within 3 hours decreased bacteria counts by 70% in contrast to 52% if irrigation was delayed to 6 hours or 37% if delayed to 12 hours.[148]

Pre- and/or Postdebridement Bacterial Wound Cultures

A study in Vietnam pertaining to cultures of wounds collected ~7 days from injury revealed that an initial negative culture was associated with 32% of patients developing a subsequent infection and a positive culture was associated with 50% of patients becoming infected.[149] Other military studies from the Korean War, the Vietnam War, and other conflicts have described similar bacterial patterns recovered from wounds and nosocomial infections.[51,52,54,55,71,150,151]

There are limited reports of wound cultures from casualties at the time of injury in Iraq or Afghanistan. A single study in Iraq describing 15 of 24 extremity injuries in US Servicemen found a predominance of gram-positive bacteria including occasional MRSA but recovered no MDR gram-negative bacteria at the time of injury.[56] A limitation of this study is that patients were not followed for subsequent infections. A number of studies have assessed the role of MRSA soft tissue infections in the combat zone, including extremity injuries, but the wounding pattern and long-term complications have not been characterized.[152–155] After leaving the combat zone, patients are presenting to US military hospitals with a much higher rate of MDR gram-negative bacteria colonizing and infecting wounds.[10,19–21] It is remarkable that gram-positive pathogens are often found later in a patient's hospital course and typically after eradicating patient's initial colonization or infection with gram-negative

pathogens. It is not clear whether these gram-positive bacteria were the same pathogens initially seen at the time of injury or reflective of nosocomial transmission.[10] A recent study using tissue biopsy culture characterization of wounds reports that 69% of 242 wound biopsies from 34 patients had no growth at the time of presentation to a US military treatment facility.[58] The most commonly recovered pathogen in this study was *A. baumannii*, and of note, the incident colonization of wounds increased when examined serially over the course of 3 weeks. This study did not provide details concerning quantity of bacteria in 1 cm^3 of tissue biopsied or infections associated with the wounds that underwent biopsy. Another study of British soldiers with mangled extremities revealed that bacteria initially recovered from injuries that were not the same as those later infecting wounds, but the presence of bacteria in general was possibly predictive of future infections.[21] In addition, ~25% of war wounded patients admitted to Walter Reed Army Medical Center developed new colonization with MDR gram-negative bacteria during their hospitalization, although this study did not evaluate the infection rates.[75]

The Surgical Infection Society guideline for prophylactic antimicrobial use provides a summary of the limited role of cultures associated with open fractures.[64] Available civilian data support similar findings to the military, with gram-positive bacteria predominating at the time of injury and a transition to gram-negative bacteria causing ultimate infection. In addition, empiric therapy can modify the bacteria recovered.[32,42,44] Pre- or postdebridement cultures do not appear to be consistently predictive of infection or infecting bacteria, and initial choice of early antimicrobial agents can result in bacteria that escape the initial spectrum of activity.[32,42,44–46,156–163] Although postdebridement cultures have been reported to be more predictive of infection in some studies, they are not always reflective of the infecting bacteria.[43,44] Some studies have supported cultures obtained 1 day after debridement that reveal the same pathogen as previously recovered are reflective of failure of debridement and subsequently high risk of infection.[164] Additional studies have also looked at correlation with bacterial counts, notably >10^5 bacteria per gram of tissue, but these studies did not appear to substantially correlate with infections.[43,165–168] In addition, some studies have supported a standardized approach to culture to predict closure success.[169] At this time, we are unable to predict which patients will go on to develop infection based upon wound cultures alone. Therefore, novel diagnostic platforms are required to describe the bioburden in the wound.[170]

Removal of Retained Metal Fragments

Many of the weaponry systems used in combat can result in numerous fragments lodged into the body with associated tissue damage.[171–176] The fragments can be associated with the deposition material that impact infectious complications.[177–179] Two strategies, one in Gaza City and the other along the Afghan border, have been employed for nonoperative management of retained metal fragments in the following list of injuries: soft tissue injuries (no fractures, no major vascular involvement, and no break of pleura or peri-

toneum), small wound entry or exit maximum dimensions, wounds not frankly infected, and wounds not caused by mines.[61,171] Management in both cases included cleaning and dressing the wounds and administration of antitetanus immunoglobulin and toxoid, penicillin IM/IV for 1 day and then orally for the next 4 days, or cephalexin and metronidazole for 2 days intravenously and then orally for 3 days. Minimal complications occurred with these management strategies.

Management of victims of suicide bombers has included small fragments remaining in patients, but no clear management strategy for fragment removal or management strategies to prevent infections has been described. Hepatitis B virus prophylaxis, due to reports in Israel of hepatitis B virus recovered from bomber's bone fragment, has been recommended for those not previously vaccinated, due to theoretical risk of transmission.[180–182] The decision not to remove small fragments has been questioned based upon a pediatric study associated with a suicide bomber in which the retained fragments became symptomatic.[183] However, the application of this patient population and injury pattern might not equate to the military. Studies of minor gunshot wounds with fragments remaining have also shown small infection rates when managed using similar criteria to the above.[184]

SURGICAL WOUND MANAGEMENT

Timing of Surgical Management

Historically, evacuation times have continued to decrease from 11 hours during World War II to 4 hours during the Korean War, to 3 hours during the Vietnam War, and to 1 hour to 3 hours in Iraq and Afghanistan.[81,185,186] Traditionally, it has been recommended that open fractures undergo operative procedures within 6 hours of injury to mitigate infectious complications. Data assessing outcomes based on time to procedures are limited for combat casualties (Table 5). Among those with extremity soft tissue injuries during the Falkland Campaign, there were 2 septic patients among 20 who underwent surgery within 6 hours in contrast to 7 of the 29 patients treated after 6 hours. Nine of those 29 went to surgery after 15 hours, 3 of whom became septic.[28] The US military experience in Somalia revealed 14 of the 16 casualties that developed infection were treated either outside of Somalia and/or after 6 hours, but long-term infectious outcomes were not described.[187] During the war in Afghanistan, an evaluation of British military personnel with mangled extremities revealed that time to surgery had no impact on infectious complications, but this group of wounded were all evacuated rapidly to surgical care.[21] There is military experience with delayed surgical interventions during humanitarian missions, with good outcomes being reported in host nation patients.[188]

Wound debridement and irrigation removes foreign material, blood clots, bone fragments, and marginally vascularized tissues, which are penetrated poorly by antimicrobials and provide a good medium for bacterial proliferation.[64] Civilian guidelines recommend that rapid surgical debridement is the primary treatment, and antimicrobials only adjuvant therapy, in the prevention of infection in open fracture management.[30,90,189] A study by Friedrich[190] has historically

TABLE 5. Relationship Between the Time to Debridement and Subsequent Infection Rates

Author	Year	Study Type	Fractures (n)	Time to Debridement	Infection Rates of Early vs. Late Debridement	Significant Difference
Jackson[28]	1984	Military, retrospective, soft tissue extremity injuries	49	0–3, 4–6, 7–9, 10–11, and >13 h	9% (1 of 11) vs. 11%(1 of 9) vs. 25% (2 of 8) vs. 10% (1 of 10) vs. 31% (4 of 1)	No <3 h or <6 h total data
Patzakis and Wilkins[32]	1989	Civilian, retrospective	1,104	12 h	6.8% vs. 7.1%	No?
Bednar and Parikh[290]	1993	Civilian, retrospective	82	6 h	9% vs. 3.4%	No
Kreder and Armstrong[194]	1995	Civilian, retrospective	56	6 h	12% vs. 25%	Yes
Kindsfater and Jonassen[163]	1995	Civilian, retrospective	47	5 h	7% vs. 38%	Yes
Skaggs et al.[291]	2000	Civilian, retrospective	118	6 h	2.5% vs. 6%	No
Harley et al.[195]	2002	Civilian, retrospective	215	13 h	8% vs. 7%	No
Rohmiller et al.[292]	2002	Civilian, retrospective	390	8 h (average)	N/A	No
Taitsman et al.[293]	2002	Civilian, retrospective	334	<8, 8–18, >8 h	N/A	No
Khatod et al.[294]	2003	Civilian, retrospective	106	6 h	16% vs. 20%	No
Ashford et al.[295]	2004	Civilian, retrospective	48	6 h	17% vs. 11%	No
Spencer et al.[296]	2004	Civilian, retrospective	115	6 h	10.1% vs. 10.8%	No
Noumi et al.[220]	2005	Civilian, retrospective	89	6 h	5.3% vs. 2.9%	No
Skaggs et al.[297]	2005	Civilian, retrospective	554	6 h	3% vs. 2%	No
Charalambous et al.[298]	2005	Civilian, retrospective	383	6 h	53% vs. 51% (overall infection) 8% vs. 8% osteomyelitis	No
Mathes and Brasher[299]	2006	Civilian, retrospective	891	6, 8, 12, 16, and 24 h	N/A	No
Naique et al.[300]	2006	Civilian, retrospective	73	6 h	7.1% vs. 16%	No
Al-Arabi et al.[33]	2007	Civilian, prospective	248	6 h	7.8% vs. 9.6%	No
Tripuraneni et al.[301]	2008	Civilian, retrospective	215	6, 6–12, 12–24, >24 h	10.8% vs. 9.5% vs. 5.6% vs. 0%	No
Pollak et al.[35]	2010	Civilian, retrospective	215	<5, 5–10, >10 h	28.0% vs. 29.1% vs. 25.8%	No
Brown et al.[21]	2010	Military, retrospective	74	<3, <6, <12 h	50% vs. 75% vs. 94%	Yes

N/A, not available.

been cited as the source for the "6-hour rule" for time to debridement of open fractures. An additional study evaluated 46 patients with Type II and III open fractures and found that 1 of 15 (7%) who underwent debridement in <5 hours from the injury became infected, whereas 12 in 32 (38%) became infected when debridement occur >5 hours after the initial injury.[163] Notably, Type III fractures comprised 33% of the <5-hour group and 53% of the >5-hour group. Multiple studies by Gustilo et al., as well as Patzakis et al., have shown that there is an increased risk of infection associated with an more severe Gustilo Type of open fractures and with delayed surgery.[32,191–193] Thus, the disproportionate number of severe fractures in the delayed debridement group could have skewed their results to favor early debridement. In addition, a small study of 56 open fractures in children showed increased infections when debridement was delayed more than 6 hours.[194] A more recent study looked at 248 open fractures and found infection rates of 7.8% and 9.6% when debridement occurred within 6 hours or >6 hours after injury, respectively ($p = 0.6$).[33] These data are in accordance with a larger study which showed that whether debridement occurred <12 hours or >12 hours after injury, the infection rate was not significantly different; 7.1% versus 6.8%.[32] Another study showed that the risk of an adverse outcome, deep infection or nonunion, was not increased by debridement or definitive treatment >13 hours from the time of injury.[195] A

recent study of 315 severe high-energy extremity injuries revealed that time to debridement was not associated with infection rate (<5 hours, 28% infection rate [93 patients]; 5–10 hours, 29.1% infection rate [86 patients]; and >10 hours, 25.8% infection rate [128 patients]).[35] Interestingly, this study indicated that time to arrival at a definitive care trauma center was the most important factor associated with decreased infection rate.

Timing of Wound Closure

It is currently recommended that closure of wounds in combat environments be delayed, based upon lessons learned during prior wars and supported by recent conflicts and civilian literature.[59,136,196–198] However, wounds are still recommended to be closed at ~5 days if there is no evidence of infection, if it is technically possible. For vascular injuries, covering the artery with healthy tissue, to include flaps, is recommended.[12,13,199] If there is a need to reconstruct an artery within a large zone of injury, tunneling the bypass or repair through clean tissue planes has been recommended. The use of autogenous tissue is also better than prosthetic, but prosthetic may need to be used in patients who do not have appropriate veins to harvest.

There have been an increased number of civilian trauma centers evaluating early closure of wounds due to the findings that nosocomial bacteria are typically causing infec-

tious complications.[90,200–204] Two retrospective studies have reported immediate wound debridement and closure in open fractures.[200,201] A retrospective comparative review of early versus delayed closure in open fractures showed no difference in infectious complications with primary (2%) versus delayed (4%) closure.[202] A review in 2007 recommended primary closure if certain criteria are met: (a) debridement performed within 12 hours, (b) no skin loss primarily or secondarily during debridement, (c) skin approximation possible without tension, (d) no farmyard or gutter contamination, (e) debridement performed to the satisfaction of the surgeon, and (f) no vascular insufficiency.[205] Unfortunately, most military injuries are not compatible with this injury pattern and criteria.

Fracture Fixation Strategies

Staged fixation in combat injuries has emerged as the strategy of choice in the current conflicts.[16] Temporary external fixation has been commonly used as a bridge to definitive fixation with few significant complications.[206] Although a few selected cases of low-energy injuries have been safely internally fixed in the combat zone, it is still considered "ill-advised" in combat-related injuries.[207,208] The use of plaster and earlier internal fixation might be possible as evident by the British military experience.[21,188,209] In addition, there can be delays associated with femoral neck fractures >48 hours and talar neck fractures, which are consistent with civilian data.[210–214]

Because little data on combat-related femur fractures have been published in the past 4 years, the recommendation for intramedullary nailing is supported by civilian data.[215,216] Reamed intramedullary nailing of open femur fractures has been associated with infection rates of 1.8% to 5%.[217–219] Most infections in open femur fractures occur in Type III open injuries.[217,220] Based upon available literature on femur fractures, temporary spanning external fixation could be placed at Role 2b-3 with skeletal traction and Thomas's splint as alternatives. Conversion to definitive fixation at Role 4 remains controversial. Delayed conversion of external fixation to a reamed, locked intramedullary nail can be performed at Role 5 facilities after appropriate wound management.

Open tibia fractures typically have higher infection rates than open femur fractures when converted to internal fixation.[221,222] Despite these moderate infection rates, the intramedullary nailing of open tibia fractures after external fixation demonstrated significantly faster union and greater range of motion with less malunion and shortening compared with casting in a randomized trial.[223] Because of the higher prevalence of Type III open injuries of the tibia with a large proportion of blast injuries seen in military conflicts, circular external fixation has been used in several small previous series with favorable results.[224–228] A recent series of 38 patients with combat-related Type III open tibia fractures were treated with a standardized protocol including circular (Ilizarov/Taylor Spatial Frame) external fixation. Although the overall deep infection rate was 8%, exclusion of the two infections in the four patients with IIIc injuries would lower this deep infection rate to 3%.[229] In contrast, a review of tibia fractures from Operation Iraqi Freedom treated at a single

institution with intramedullary nailing demonstrated an overall infection rate of 14.3%.[230]

The available literature on fixation of combat-related tibia fractures is the source of greatest debate in this review. External fixation is supported by literature at Role 2b to 3. Conversion to definitive fixation at Role 4 remains controversial. At Role 5, reamed, intramedullary nailing can be performed safely in selected patients with a lesser soft tissue injury. For Type III open injuries, circular external fixation has been shown to have lower deep infection rates.

Open fractures of the upper extremity seem to be best managed ultimately with plate fixation.[231–233] Some high-energy open fractures may benefit from a staged protocol with initial temporary external fixation.[234,235] One series of soldiers with high-energy gunshot fractures to the humerus showed a very low infection rate when managed with definitive external fixation.[236] Although functional bracing, even with war-related humerus fractures, may be favored over external fixation,[237] the current literature supports the use of temporary spanning external fixation or splint immobilization placed at Role 1–3 and transition to open plate and screw osteosynthesis for some open humerus and forearm fractures after soft tissue stabilization and closure.

Negative Pressure Wound Therapy

Wound coverage with NPWT (e.g., the Vacuum-assisted Closure (VAC) [KCL, San Antonio, TX]) has become standard of care in most military and civilian medical facilities. A review of the use of NPWT in the military was performed revealing overall success with the implementation of the device.[238] The use of NPWT in the combat zone appears effective, but the studies are limited by a lack of adequate control arms for comparison.[1,136] Studies have shown the device is feasible for intercontinental aeromedical evacuation without excess wound complications.[239,240] A retrospective study of combat-related injuries that assessed the role of NPWT in comparison with antimicrobial bead pouch therapy revealed that those with NPWT had more late MRSA infections, more unanticipated returns to the operating room, and overall more surgeries until closure.[126] The higher rate of *S. aureus* recovery has been previously shown in animal and human studies.[241,242] This finding of better clearance of *P. aeruginosa* in a wound versus *S. aurues* might be due to virulence of the pathogen or host factors.[242]

A randomized prospective study showed that of 58 patients with 62 open fractures those receiving NPWT had fewer infections (5.4%) compared with those not receiving NPWT (28%) ($p = 0.024$).[243] Another civilian prospective randomized study evaluating the use of NPWT in 20 calcaneous fractures, 4 pilon fractures, and 20 tibial plateau fractures found no infectious differences between NPWT and standard wound care.[244] Of note, the use of NPWT should not be employed as a substitute, or delaying method, for wound flaps, as higher rates of infections occur with delaying use of wound flaps.[245]

In an animal model, it appears that silver-impregnated gauze with the NPWT system was associated with greater reduction in bacterial load for *P. aeruginosa*, and to a greater degree, *S. aureus* than standard gauze.[246] However, wound tissue did not appear normal with this combination, raising

concern that use of this product might result in surgeons suspecting infection even when there is no infection present. Antimicrobial beads have been assessed with and without NPWT in an animal model of *S. aureus* infection.[134] Although the NPWT and antimicrobial beads were associated with substantially more bacterial growth than antimicrobial beads alone, there was still activity in the wounds indicating that in certain situations, such as with possible issues with power loss to the suction apparatus, antimicrobial beads, and NPWT might be used effectively in combination (Joseph C. Wenke, personal communication). This study indicated that antimicrobial beads with NPWT were better than NPWT alone. It appeared that instillation of an antiseptic in a NPWT system was more effective than NPWT alone or with saline solution alone; however, there was decreased tissue viability with the antiseptic (Joseph C. Wenke, personal communication). Instillation of saline in conjunction of NPWT did not demonstrate a benefit over NPWT alone in a complex orthopedic injury goat model using *P. aureuginosa*. Instillation of an antiseptic, hypochlorous acid solution, did reduce the bacteria within the wound in comparison with NPWT alone, NPWT with saline instillation, or NPWT with polyhexanide and surfactant. Clinical impression of the wounds treated with instillation of the antiseptic solutions was that they had a less healthy appearance in terms of color and consistency and the subjective impression that a greater amount of nonviable tissue was debrided from these wounds at each interval. Overall, antispectic has not been widely assessed clinically, and data discouraged hypochlorous acid (Dakin's) solution use during World War I.[247] The use of NPWT with Dakin's solution instillation (i.e., Dakin's 0.025% with the NPWT set at 125 mm Hg with instillation every 2 hours for 30 seconds with dwell time of 5 minutes) has been recently implemented for injuries that primarily occur in the lush vegetative areas of Afghanistan in patients with high bilateral lower extremity injuries, often with perineal involvement that are noted to have higher rates of invasive fungal wound infections. These severely injured patients typically require massive blood volume support and are associated with injury patterns that are not amenable to very aggressive debridement during initial or follow-up surgical management. This strategy appears to be effective but needs to be systematically analyzed to determine the unique patient populations this strategy might best be applied.

Role of Oxygen Therapy

The role of hyperbaric oxygen (HBO) has been evaluated and pursued in previous wars, especially as a potential therapy for gas gangrene.[248–250] A war extremity injury review, from 1991 to 1995, which included 388 combat-related Type III fractures, described the impact of HBO (99 provided HBO and 289 without HBO) on wound healing and infectious complications.[251] Overall, the infectious complications were less when patient management included HBO. However, this effect was substantially more common among those not receiving standard wound management and antimicrobials recommended by North Atlantic Treaty Organization (NATO), and there were increased cases of osteomyelitis in the HBO-treated group. Systematic reviews of HBO therapy for acute

surgical and traumatic wounds revealed a lack of high-quality, valid research.[252,253]

In addition to the role that hyperbaric oxygen therapy may or may not have on wound infection and/or prevention, there is ongoing concern regarding what effect low oxygenation might have on wounds during aeromedical evacuation of injured personnel from the combat zone to Germany and from Germany to the United States. A complex soft tissue injury in a goat model using *P. aeruginosa* contamination revealed that animals taken to pressures equivalent to an elevation of 8,800 feet for 7 hours became mildly hypoxic (O_2 saturation of 88–92%) and their wounds had more bacterial growth than controls at ground level (Warren Dorlac, personal communication). Animals provided supplemental oxygen (to increase their oxygenation saturation to >94%) were found to have with no difference in bacterial growth compared with controls at ground level. There are prospective studies that have shown mixed efficacy in preventing infectious complications with the use of higher concentrations of oxygen concentration delivery for abdominal and pelvic surgeries, although these were not associated with elevation-induced hypoxia.[254–256] Studies of the efficacy of higher oxygen concentration delivery in orthopedic trauma injuries have not been performed.

UNRESOLVED ISSUES/POTENTIAL FUTURE RESEARCH TOPICS

Role of Fungal Infections

There have been reports from the British military that casualties in the lush vegetative area of Helmand Province in Afghanistan on dismounted patrols with severe bilateral high lower extremity injuries, typically due to blast injuries and necessitating the use of tourniquets and large blood volume resuscitation, have a higher rate of invasive fungal wound infections, chiefly due to fungi belonging to the order Mucorales.[257] In civilian trauma, a study of severe extremities injuries on farms also revealed a high rate of fungi recovered from wounds; however, the nature of the injuries described in this patient population varies from the typical blast injury seen in Afghanistan.[258] Another study comparing timing of wound closure and antimicrobials performed quantitative cultures that revealed the presence of *Aspergillus* spp., *Mucor* spp., and other fungus at the time of initial wound management; although no subsequent infections secondary to these pathogens occurred.[259,260] The role of early wound evaluation with fungal cultures, fluorescent (Calcofluor) staining, and fresh frozen and traditional histopathology looking for invasive fungal infections has not been determined. In addition, the role of early empiric antifungal therapy is not known at this time for trauma-associated wound colonization with fungi.[261] There are data indicating that activity of local antifungal delivery with amphotericin B loaded beads is adequate for fungal treatment.[262] Dakin's solution (sodium hypochlorite) appears to have some activity against *Aspergillus*, but no studies assessing its activity against the Mucorales have been reported.[263] In addition, soft-tissue toxicity associated with this agent has been described.[264,265] Case series and case-control studies are underway to better characterize

these infections and to better define risk factors, diagnostic strategies, and therapies.

The Role of Inflammatory Markers to Predict Infection

During the Vietnam War, there were preliminary data indicating that elevation of creatinine phosphokinase (CK), in contrast to lactic dehydrogenase (LDH) and serum glutamic oxaloacetic transaminase (SGOT), was associated with wound infections.[266] An evaluation of cytokines potentially associated with sepsis (from Belgrade, Serbia and Montenegro during 1999) revealed that IL-8, TNF-a, and IL-10 most specifically correlated with the diagnosis of combined trauma and sepsis.[267] During the current wars in Iraq and Afghanistan, a number of studies have been undertaken to evaluate various wound markers and their role with wound healing and infections. Markers that have shown an association with wound dehiscence include procalcitonin in the serum, along with increased procalcitonin, decreased RANTES protein, and decreased IL-13 concentrations in wound effluent.[268,269] Elevated metalloproteinase (MMP)-2 and MMP-7 serum levels and reduced levels of effluent MMP-3 were seen in wounds with impaired healing.[270] In addition, there has been the recovery of multipotent progenitor cells from war wound muscle tissue that might have a role in tissue engineering, and other markers of inflammation have been assessed.[271,272] Continued work needs to be undertaken in this area.

Role of Biofilms in Combat-Related Extremity Injuries

Although the role of biofilms in chronic infections is becoming more accepted, there are no data to date as to the role of biofilms in combat-related extremity injuries.[273] Although numerous investigators are assessing the ability of bacteria infecting combat-related extremity injury wounds to form biofilms in vitro, and evaluating potential therapies to prevent or disrupt these, clinical studies of the impact of biofilms are still needed.

Novel Antimicrobials and Pathogen Identification

At this time, there are inadequate antimicrobials active against MDR gram-negative pathogens in the pharmaceutical pipeline, necessitating renewed emphasis in this area. The current pathogen and antimicrobial resistant diagnostic platforms rely on old technology that typically provides a relevant clinical answer for management decision in 48 hours to 72 hours. This relegates most therapy to empiricism possibly resulting in excess antimicrobial resistance. Improvements in pathogen detection and resistance determination are necessary at this time.

CONCLUSION

Extremities are the most common injury pattern during the wars in Iraq and Afghanistan with an overall high infection rate. Continued improvement in wound care is necessary to mitigate any excess short- and long-term complications. Focus on antimicrobials, wound debridement and irrigation, and surgical interventions using the current evidence-based medicine recommendations should attempt to improve outcomes, but ongoing surveillance is necessary. In addition, continued focus on unresolved issues and future areas of research are needed to improve combat casualty care.

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