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Antimicrobial Prophylaxis in Patients with Major Trauma

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Abstract

Purpose of Review Prophylactic antibiotics are used to reduce infection after major trauma, but their use remains controversial. The purpose of this review is to revisit evidence-based practical guidelines in the use of prophylactic antibiotics in major trauma.

Recent Findings For head trauma, prophylactic antibiotics can reduce ventilator-associated pneumonia and are indicated for penetrating injury. For thoracic trauma, antibiotic use can reduce empyema after chest tube insertion in penetrating chest trauma but not indicated for blunt chest trauma. In abdominal trauma, prophylactic antibiotics are suggested for 24 h after laparotomy if hollow viscus injured. Regarding to open fracture, an antibiotic to cover gram-positive organisms should be administrated as soon as possible after injury and gram-negative coverage is added for type III fractures.

Summary The use of prophylactic antibiotics in major trauma should take local factors and guideline suggestions together into consideration. Liberal use is not recommended and individualized consideration is crucial.

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Introduction

Trauma and accident injuries remain one of the leading causes of mortality worldwide. The trimodal pattern of mortality has been conventionally used for describing trauma deaths. In the pattern, the first phase is death on the scene; improving the survival rates in this phase necessitates management such as injury prevention, prehospital triage, and appropriate judgment of patient disposition. The second phase, death during acute care, entails management in emergency departments and intensive care units (ICUs), and a complete and precise primary survey, resuscitation, a secondary survey, and definite care are crucial for decreasing trauma death rates in the second phase. The third phase is typically a late stage during ICU admission or further treatment in wards, wherein infections complicated by single or multiple organ failure are frequent major concerns.

Patients with trauma are considered to have a high risk of infections due to several factors. First, trauma event occurrence is usually unpredictable, and trauma events mostly occur in outdoor fields or on roads, which are places with a high load of infectious pathogens. Second, the mechanical energy impacting the human body during trauma events can result in severe destruction of the skin surface and soft tissues, which are a natural barrier to infections. Third, shock and resuscitation can render patients more susceptible to an exacerbated immune response to subsequent inflammatory infections [1]. Therefore, prophylactic antibiotic treatment for patients with trauma was proposed in and has been administered since 1982 [2]; however, the results have been controversial. The efficacy of prophylactic antibiotics in trauma treatment depend on

trauma mechanisms (penetrating or blunt trauma), injury sites (head, torso, and limb trauma), and the degree of wound contamination. Moreover, patient comorbidities, the severity of the injury, the collateral damage of adjacent organs, and locoregional microbiological epidemiology are factors strongly affecting the efficacy of antibiotic use.

The present literature review revisits the current strategies and recommendations of evidence-based practical guidelines on prophylactic antibiotic use for major trauma. This review is divided into four sections on the basis of the anatomical locations of trauma as (1) head trauma, (2) thoracic trauma, (3) abdominal trauma, and (4) open fractures, including long-bone and pelvic fractures.

Head Trauma

Head trauma or traumatic brain injury (TBI) significantly increases patient susceptibility to infections through various mechanisms. Approximately 4% of all head injuries include skull base fractures, and 90% of these fractures are secondary to closed head trauma. Patients with skull base fractures are at a high risk of meningitis because of the potential bacterial contact between the paranasal sinuses, nasopharynx, or middle ear with the central nervous system. The risk of contracting meningitis is higher in the presence of cerebrospinal fluid (CSF) leakage. Although prophylactic antibiotic use is frequently adopted, this practice has been questioned. In 2015, the Cochrane Database of Systematic Reviews reported a study on the use of antibiotic prophylaxis for preventing meningitis in patients with basilar skull fractures. The author concluded that the currently available evidence did not support prophylactic antibiotic use in patients with skull base fractures, regardless of CSF leakage [3•]. In 2016, Yellinek et al. reported that the rate of meningitis in patients with skull base fractures was low and that prophylactic antibiotic use was not required [4].

Ventilator-associated pneumonia (VAP) is another cause of infections in patients with TBI. Because of compromised airway protection capability after TBI and the requirement of robust tissue oxygenation, mechanical ventilation is frequently recommended in patients with TBI, and therefore VAP is often encountered after TBI. Sirvent et al. conducted a randomized controlled trial involving 86 patients with severe TBI by evenly dividing these patients into treatment (administration of cefuroxime [1.5 g] for two doses within 6 h after intubation) and control (without antibiotic administration after intubation) groups and revealed that the incidence of pneumonia significantly decreased in the treatment group but without differences in mortality [5]. In 2017, Esnault et al. reported that antibiotic prophylaxis exerts protective effects against early-onset VAP (odds ratio [OR] 0.3, 95% confidence interval [CI] 0.1–0.8) [6••].

Patients with TBI who undergo intracranial pressure monitoring or external ventricular drainage (EVD) may have increased infection rates as high as 27% [7]. Regarding the use of EVD, whether intravenous (IV) prophylactic antibiotic administration reduces infections or increases the risk of drug-resistant organisms remains unclear. In a moderate-quality systematic review that compared the incidence of CSF infections between patients with antimicrobial-impregnated catheters (AICs) and those with standard catheters, AICs had significantly lower rates of CSF infections, 20-day infection, and catheter bacterial colonization [8].

Infections are common after penetrating brain injury (PBI) because of the presence of contaminated foreign objects in the brain tissue along the projectile track and are associated with high morbidity and mortality rates. Infectious complications are more frequent after PBI in the presence of CSF leakage, air sinus wounds, transventricular injuries, or midline-crossed grafts [9]. *Staphylococcus aureus* is the most frequent infection-causing organism; however, other gram-negative bacteria also cause intracranial infections after PBI. The infectious complications in PBI were approximately 58.8% in the preantibiotic era; however, it has now been estimated to be 1–5% with the use of broad-spectrum antibiotics [10]. Broad-spectrum antibiotics (e.g., IV co-amoxiclav [1.2 g q 8 h] or IV cefuroxime [1.5 g followed by 750 mg q 8 h] with IV metronidazole [500 mg q 8 h]) should be prescribed to all patients with PBI as soon as possible and continued for at least 7–14 days [11].

Chest Trauma

Chest trauma is common in patients sustaining either blunt or penetrating trauma. Thoracic wounds account for 20–25% of all trauma deaths, and nearly 10% require thoracotomy, whereas the remaining 85% can be managed through closed-tube thoracostomy. Empyema is a major morbidity associated with tube thoracostomy. Posttraumatic empyema is a major concern in blunt and penetrating chest injuries. Potential etiologies include (1) iatrogenic infections during chest tube placement, (2) direct contamination resulting from penetrating injuries, (3) secondary infections of the pleural cavity caused by associated intra-abdominal organ injuries with diaphragmatic disruption, (4) secondary infections of an undrained or inadequately drained hemothorax, (5) hematogenous or lymphatic spreading of subdiaphragm infections to the pleural space, and (6) parapneumonic empyema complicated from posttraumatic pneumonia or pulmonary contusion. Causative organisms of chest infections vary with the mechanism and degree of contamination. In infections related to chest tube insertion, empyema typically involves gram-positive *S. aureus* or streptococcus cultures.

In secondary contamination from pneumonic processes or other routes of spreading, gram-negative or mixed bacterial pathogens are involved.

The role of prophylactic antibiotics in the reduction of infectious complications remains controversial in the literature on trauma (Table 1). A study revealed that patients who receive prophylactic antibiotic treatment have significantly decreased incidence of infectious complications and suggested that patients with chest trauma who undergo tube thoracostomy can benefit from this treatment [12]. A meta-analysis demonstrated that prophylactic antibiotic use reduced the incidence of posttraumatic empyema and pneumonia in patients with chest trauma [13].

Although several studies have showed favorable effects, some reports did not report any benefits of antibiotic use [14, 15]. Many factors contribute to the development of posttraumatic empyema, including tube insertion mechanism (emergent or urgent), trauma mechanism, retained hemothorax drainage, and ventilator use. Therefore, considering the emergence of antibiotic-resistant strains and associated costs and benefits of the treatment, prophylactic antibiotics should be administered conservatively. *The Eastern Association for the Surgery of Trauma Practice Management Guidelines* published in 1998 have sufficient class I and II data to recommend prophylactic antibiotic use in patients receiving tube

thoracostomy after chest trauma but not in those with empyema. The data suggested that the incidence of pneumonia rather than empyema decreased on prophylactic antibiotic treatment after tube thoracostomy, and the administration of first-generation cephalosporin for not more than 24 h was the preferred treatment choice [16].

In 2004, Maxwell et al. conducted a prospective, randomized, double-blind trial to compare the outcomes of cefazolin use for the duration of tube placement (group A) vs 24 h (group B) vs placebo (group C) [17]. In total, 224 patients with 229 tube thoracostomies were enrolled. Logistic regression analysis revealed that the duration of tube placement and thoracic acute injury scores were predictive factors of empyema ($p < 0.05$). Empyema occurred more frequently in patients with penetrating injuries, and pneumonia occurred more frequently in patients with blunt injuries than in patients with penetrating injuries. However, presumptive antibiotic use did not significantly affect the incidence of empyema or pneumonia. Therefore, they concluded that the incidence of empyema was low, and presumptive antibiotic use did not reduce the risk of empyema or pneumonia.

Two review articles published in 2012 addressed the concerns regarding prophylactic antibiotic use. Bosman et al. conducted a systematic review and meta-analysis on antibiotic prophylaxis to prevent infections from chest

Table 1 Studies regarding prophylactic antibiotic use in chest trauma

Author	Year	Antibiotics	Antibiotic group (*n*)/infection (*n*)	Control group (*n*)/infection (*n*)	Conclusion
Gonzalez RP.[a]	1998	Cefazolin	71/0	68/4	Reduced incidence of infection with antibiotics
Villegas-Carlos et al.[b]	2009	Cefalotin	63/3	63/5	Antibiotics was not beneficial in the prevention of pleural infections
Maxwell RA.[c]	2004	Cefazolin	157/0	72/4	Antibiotics did not reduce the risk of empyema or pneumonia
DuBose J.[d]	2012	11 different types	126/32	202/81	Antibiotics not significant for post chest trauma empyema
Grigorescu D.[e]	2012	Various	86/2	853/52	Antibiotic prophylaxis was justified by severity and risk factors and was effective and cost-efficient
Heydari MB et al.[f]	2014	Cefazolin	54/2	50/5	Antibiotic did not reduce the incidence of empyema or pneumonia

[a] Am Surg 1998;64:617–20

[b] Cir Cir. 2009 Jan–Feb;77(1):29–32

[c] J Trauma 2004;57:742–8

[d] J Trauma Acute Care Surg. 2012 Sep;73(3):752–7

[e] Rev Med Chir Soc Med Nat Iasi. 2012 Oct–Dec;116(4):1157–61

[f] J Inj Violence Res 2014;6:91–2

drains in blunt and penetrating thoracic injuries and concluded that antibiotic prophylaxis reduces the risk of infection after tube thoracostomy (OR 0.28, CI 0.14–0.57) in patients with penetrating thoracic injuries, whereas it had no effects on patients with blunt thoracic injuries [18]. The Practice Management Guidelines Committee of the Eastern Association for the Surgery of Trauma updated the 1998 guidelines in 2012 regarding the use of antibiotics in injured patients requiring tube thoracostomy to reduce the incidence of empyema and pneumonia. Of the 98 articles identified, seven articles that satisfied the criteria were selected for review. Two questions related to presumptive antibiotic use after tube thoracostomy for traumatic hemopneumothorax were addressed: (1) Do presumptive antibiotics reduce the incidence of empyema or pneumonia? and (2) what is the optimal duration of antibiotic prophylaxis? They concluded that routine presumptive antibiotic use for reducing the incidence of empyema and pneumonia after tube thoracostomy for traumatic hemopneumothorax is controversial and that evidence either for or against this practice is insufficient [19].

In conclusion, prophylactic antibiotic treatment using first-generation cephalosporin for not more than 24 h is reasonably indicated in patients with penetrating chest trauma having chest tube insertions because some evidence has supported that this practice reduces the incidence of empyema. However, prophylactic antibiotic use is not indicated in patients with blunt chest trauma.
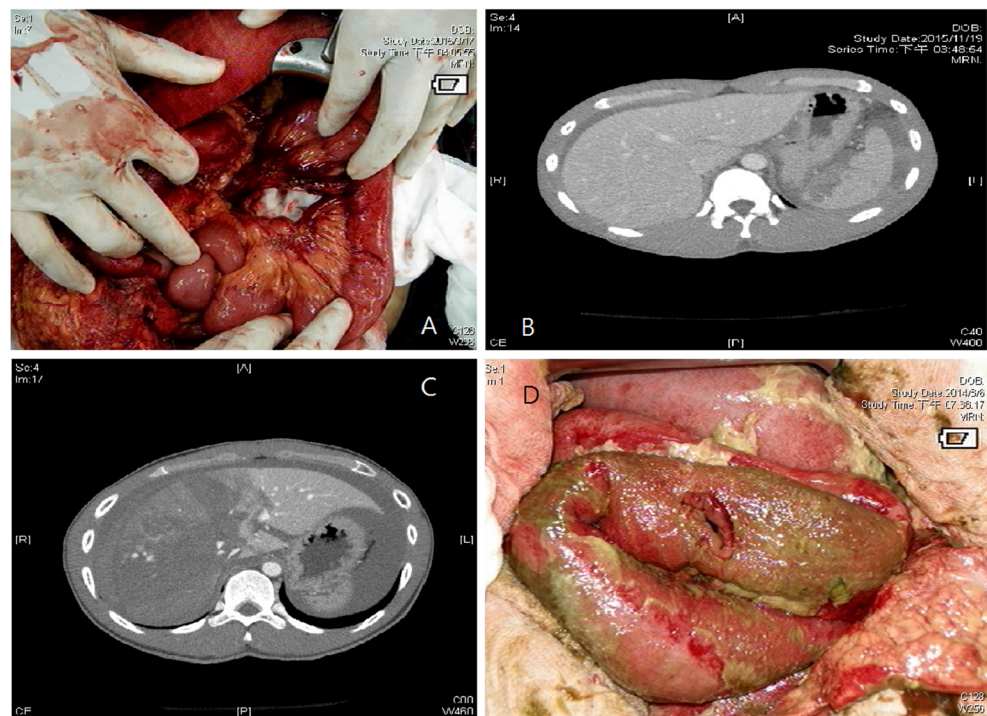
Abdominal Trauma

Abdominal trauma is typically very complicated because it involves blunt or penetrating injuries as well as solid or hollow organ injuries (Fig. 1). Prophylactic antibiotic use for abdominal trauma treatment has many considerations, including the choice of antibiotics, the timing of administration, and the duration of usage. Other crucial factors include patient age, injury site, the involvement of hollow organs, and treatment choice (nonoperative or operative).

Prophylactic antibiotic use is not required in patients with blunt abdominal trauma without hollow organ injury and no other indication for laparotomy. Moreover, patients with blunt abdominal trauma who undergo damage-control laparotomy only require preoperative antibiotic administration. The abdomen is often left open for some duration after a damage-control laparotomy, particularly in patients with coagulopathy or acidosis or those at a risk of abdominal compartment syndrome.

According to a study conducted at Virginia Commonwealth University in Richmond, a level 1 trauma center, on patients with trauma who underwent damage-control laparotomy, preoperative antibiotic administration protected against intra-abdominal infections (OR 0.20; 95% CI 0.05–0.91; $p = 0.037$); however, postoperative antibiotic administration substantially increased the risk of infections (OR 6.7; 95% CI 1.33–33.8; $p = 0.044$). After satisfactory hemostasis and the successful reconstruction of gastrointestinal tract continuity, postoperative antibiotic use was not required.

Fig. 1 Various types of injuries in abdominal trauma. **a** Mesentery injury. **b** Spleen injury. **c** Liver injury. **d** Bowel perforation

Penetrating abdominal trauma occurs with peritoneal cavity violation and has a high risk of abdominal organ injury. Routine laparotomy for penetrating abdominal injuries was first performed in the 1800s, and antibiotics were first used in World War II for septic complications associated with such injuries. The Eastern Association for the Surgery of Trauma first published its guidelines on prophylactic antibiotic use for penetrating abdominal trauma in 1998 [20]. Although class I studies providing a definitive standard of care (level I recommendation) are lacking, the results of this literature review support the preoperative administration of a single dose of prophylactic antibiotics with broad-spectrum aerobic and anaerobic coverage and its postoperative use for 24 h if patients with trauma sustained penetrating abdominal wounds with an intestinal injury. Furthermore, the review revealed that additional doses of antibiotics are not required in the absence of a hollow viscus injury. However, whether prophylactic antibiotics are required to prevent infectious complications after penetrating abdominal trauma remains controversial.

The Eastern Association for the Surgery of Trauma revised its practice guidelines in 2012 and recommended that prophylactic antibiotics should only be administered for 24 h if a hollow viscus injury is present. However, evidence supporting the continuous use of prophylactic antibiotics for more than 24 h after damage-control laparotomy is lacking [21]. In a Cochrane Database review published in 2013, the authors concluded that randomized controlled trial data did not support or refute antibiotic use in patients with penetrating abdominal trauma [22]. Recently, plasma mitochondrial DNA was reported to be associated with sepsis, multiple organ dysfunction syndrome, and mortality in patients with intra-abdominal infections caused by severe abdominal trauma, and the role of prophylactic antibiotics was emphasized [23•]. A study on bacteriology and antimicrobial susceptibility in patients with abdominal trauma complicated with intra-abdominal infections reported that *Escherichia coli* (29.1%) was the most common pathogen, followed by *Klebsiella pneumoniae* (22.5%). The production rate of extended-spectrum beta-lactamases among *E. coli*, *K. pneumoniae*, and *K. oxytoca* were 69.6, 45.1, and 25.0%, respectively. All pathogens had high resistance rates against the studied antibiotics, and imipenem (88.7%) and ertapenem (90.7%) remained the only practical treatment options [24].

In conclusion, a single dose of prophylactic antibiotics with broad-spectrum aerobic and anaerobic coverage should be administered preoperatively to all patients who sustain penetrating abdominal injuries. Prophylactic antibiotics should not be administered for more than 24 h if a hollow viscus injury is present after either blunt or penetrating abdominal trauma. Moreover, hollow viscus injury does not require postoperative antibiotic administration after achieving successful hemostasis and reconstruction of the gastrointestinal tract. If infections or peritonitis are observed during operation (obvious hollow organ perforation with extensive peritoneal soiling, massive tissue necrosis and destruction, and sepsis with septic shock), therapeutic antibiotics rather than prophylactic antibiotics should be administered for complicated intra-abdominal infections.

Open Fractures

Open fractures are a major cause of morbidity and mortality in adult trauma, and wound infections are one among the severe complications associated with open fractures. High-grade open fractures in the lower extremities after high-energy injury considerably increase the risk of infections than do those in the upper extremities. The tibia shaft is the most common site of open long-bone fractures and is also prone to infections because of limited soft-tissue coverage and poor blood supply. Antibiotic use is an important adjunctive treatment. Antibiotics have been a part of the standard management protocol, including wound washing (irrigation), wound and fracture cleaning (surgical debridement), and fracture stabilization. However, the effects of antibiotics remain uncertain (Table 2).

The risks of infections vary with the types of open fractures. By using Gustilo typing, the most commonly used method for classifying open fractures, a study reported the following infection rates—type I 0–2%, type II 2–7%, type IIIA 7%, type IIIB 10–50%, and type IIIC 25–50% [25]. Gustilo type III open fractures involve extensive soft-tissue damage; therefore, therapeutic antibiotics rather than prophylactic antibiotics are used. Moreover, only few controlled studies on patients with open fractures have been reported [26, 27], and pre-emptive antibiotics with a duration of approximately 10 days rather than prophylactic antibiotics were used in these studies.

In 1974, Patzakis et al. reported that the infection rate in open fractures was 14% in the control arm but was significantly reduced (2%) in the cephalothin arm ($p < 0.03$) [28]. The significant reduction in the infection rate in these studies indicates that a pre-emptive therapy of first- or second-generation cephalosporin for 5–10 days is suitable for open fractures with internal fixation operation. However, appropriate prophylactic antibiotic regimen and the duration and timing of antibiotic treatment for infection prevention in open fractures remained controversial. In 2004, a Cochrane Database review including 1106 participants from eight trials reported that antibiotics effectively reduced the incidence of wound infections compared with no antibiotics or placebos [29].

In 2011, the Eastern Association for the Surgery of Trauma published a practice guideline on prophylactic antibiotic use in

Table 2 Studies regarding prophylactic antibiotic use in open fracture

Author	Year	Study type	No. of patients	Regimen	Conclusion
Whittaker et al.[a]	2005	placebo controlled RCT	170	IV flucloxacillin at induction + 5-day oral flucloxacillin	No significant difference in wound infection rates (15 vs 13 vs 4%, $p > 0.05$)
Altergott et al.[b]	2008	RCT	135	7-day course of cefalexin	No significant difference in wound infection rates (1.45 vs 1.52%, $p > 1$)
Gerhardt et al.[c]	2009	Retrospective cohort study	53	IV 3rd generation cephalosporin	increased wound infection in those not using prophylactic antibiotics (7 vs 40% $p < 0.05$)
Saveli et al.[d]	2013	Prospective randomized trial	130	cefazolin vs vancomycin + cefazolin	No significant difference in SSI rates
Dunkel et al.[e]	2013	Retrospective case-control	1492	1 day of antibiotics vs 2–3 days	No difference in infection risk

[a] J Hand Surg Br. 2005 May;30(2):162–7

[b] Pediatr Emerg Care. 2008 Mar;24(3):148–52

[c] Prehosp Emerg Care. 2009 Oct–Dec;13(4):500–4

[d] J Orthop Trauma 2013;27:552–557

[e] Bone Joint J 2013;95-B:831–7

open fractures [30] and provided several level I and level II recommendations.

Level I:

1. Systemic antibiotic coverage directed at gram-positive organisms should be initiated as soon as possible after injury.
2. Additional gram-negative coverage should be provided for type III fractures.
3. High-dose penicillin therapy should be provided for fecal or potential clostridial contamination (e.g., farm-related injuries).
4. Compared with cephalosporins and aminoglycosides, fluoroquinolones are not advantageous, may have a detrimental effect on fracture healing, and result in higher infection rates in type III open fractures.

Level II:

1. In type III fractures, antibiotics should be continued for 72 h after injury or not more than 24 h after soft-tissue coverage has been achieved.
2. Once-daily aminoglycoside dosing is safe and effective for type II and III fractures.

Although narrow-spectrum antimicrobial prophylaxis is recommended by evidence-based guidelines, many trauma centers prefer broad-spectrum antibiotics.

A narrow spectrum of activity and short duration of antimicrobial agent use could result in higher rates of skin and soft-tissue infections after open fractures. However, some complications are associated with the use of broad-spectrum antibiotics, including potential kidney function impairment by aminoglycosides, the development of antimicrobial resistance after prolonged antibiotic use, and superinfections due to multidrug-resistant organisms.

In 2014, a study published by the University of Michigan group regarding the implementation of an evidence-based narrow-spectrum antimicrobial prophylaxis protocol for open fractures revealed that a significant decline in aminoglycoside and glycopeptide antibiotic use did not result in an increase in skin and soft-tissue infection rates [31•]. Their suggested regimen was as follows: IV cefazolin (1–2 g followed by 1 g q 8 h for 48 h) or IV clindamycin (900 mg q 8 h for 48 h) in the presence of penicillin allergy for type I or II open fractures and IV ceftriaxone (1 g q 24 h for 48 h) or IV clindamycin (900 mg q 8 h) with IV aztreonam (1 g q 8 h for 48 h) in the presence of penicillin allergy for type III open fractures.

Pelvic fractures are high-energy injuries with high morbidity and mortality rates. Antibiotic use in pelvic fractures is dependent on two parameters: (1) Is it an open fracture? and (2) does it have associated adjacent soft-tissue damage? In critically injured patients with multiple injuries and unstable pelvic fractures, peripelvic soft-tissue infections occasionally cause sepsis. Peripelvic infections are often accompanied by necrotic changes and easily develop into severe sepsis or result in multiple organ failure. The identification of high-risk patients and early diagnosis with prompt surgical treatment are indispensable for patient survival [32]. However, concerns regarding antibiotic use remain the same in patients with pelvic fractures as well as those with open fractures.

Conclusion

The present review discusses the current recommendations for prophylactic antibiotic use in various trauma settings. Because of the diversity in trauma settings, antibiotic use should be implemented by considering local factors as well as guideline suggestions. Because of the emerging threat of antibiotic-resistant bacterial strains and concerns regarding the alternation of the gut microbiota, the use of prophylactic antibiotics in major trauma has attracted substantial attention and is supported by increasing evidence. Liberal prophylactic antibiotic use is not recommended, and individualized consideration is crucial. Prophylactic or therapeutic antibiotic treatment in patients with major trauma is implemented to reduce the local bacterial contamination and improve the host's defense capacity. Therefore, antibiotic regimen should be modified for individual cases depending on local bacterial colonization and its potential pathogenic influence on infection development. Moreover, when local host damage is the predominant factor for the development or persistence of infections, antibiotic-mediated or other pharmacological agent-mediated reduction of bacterial colonization is secondary. Adequate debridement and effective source control is the first major step for infection treatment in patients with major trauma.

Compliance with Ethical Standards

Conflict of Interest   The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent   This article does not contain any studies with human or animal subjects performed by any of the authors.

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