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## Adherence to Published Antimicrobial Prophylaxis Guidelines for Wounded Service Members in the Ongoing Conflicts in Southwest Asia

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### Abstract

In 2008, a clinical practice guideline (CPG) was developed for the prevention of infections among military personnel with combat-related injuries. Our analysis expands on a prior 6-month evaluation and assesses CPG adherence with respect to antimicrobial prophylaxis for U.S. combat casualties medically evacuated to Landstuhl Regional Medical Center over a 1-year period (June 2009 through May 2010), with an eventual goal of continuously monitoring CPG adherence and measuring outcomes as a function of compliance. We classified adherence to the CPG as receipt of recommended antimicrobials within 48 hours of injury. A total of 1106 military personnel eligible for CPG assessment were identified and 74% received antimicrobial prophylaxis. Overall, CPG compliance within 48 hours of injury was 75%. Lack of antimicrobial prophylaxis contributed 2 to 22% to noncompliance varying by injury category, whereas receipt of antibiotics other than preferred was 11 to 30%. For extremity injuries, antimicrobial prophylaxis adherence was 60 to 83%, whereas it was 80% for closed injuries and 68% for penetrating abdominal

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injuries. Overall, the results of our analysis suggest an ongoing need to improve adherence, monitor CPG compliance, and assess effectiveness.

### Keywords

clinical practice guidelines; antimicrobial prophylaxis; guideline adherence; combat-related infections

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## BACKGROUND

Antimicrobial prophylaxis is critical for the prevention of infectious complications among patients who sustain traumatic injuries and is a principal component of consensus-driven clinical practice guidelines (CPG). Generally, antibiotic prophylaxis recommendations are related to specific injury patterns and surgical procedures that transpire in civilian life.<sup>1-7</sup> However, in response to the unique injury patterns and care situations associated with military deployment, along with a rise in the rate of infectious complications among wounded service members,<sup>8-13</sup> a CPG for combat-related infection management was published in 2008 by an expert consensus group convened by the Department of Defense (DoD) Joint Trauma System (JTS) and comprised of military and civilian authorities.<sup>14</sup>

The primary focus of the CPG was the immediate care and stabilization of wounded combatants with specific reference to treatment administered within hours of injury (combat zone) to the days following at Level IV facilities, such as Landstuhl Regional Medical Center (LRMC). Recommendations included injury-specific antimicrobial prophylaxis, in addition to wound irrigation, surgical debridement, delayed closure, bony stabilization, and basic infection control measures. The CPG advised that selection of therapeutic agent be based on the injury site requiring the broadest spectrum of antibacterial activity and advocated against the use of excessive broad spectrum antibiotics when it was not warranted.<sup>14</sup>

Previously, we evaluated antimicrobial prophylaxis compliance with the CPG over a 6-month period (June 1, 2009 through November 30, 2009) among injured U.S. military personnel medically evacuated to LRMC.<sup>15</sup> Antimicrobial prescribing adherence was 64 to 79% for extremity injuries, 73% for maxillofacial soft-tissue injuries and/or fractures, and 10% for penetrating abdominal injuries requiring antibiotic prophylaxis. Compliance for closed injuries (required no antibiotic prophylaxis) was 52%.

When antibiotic prophylaxis was warranted, CPG noncompliance usually resulted from administration of antimicrobials other than what was recommended. As possible explanations for noncompliance, it was noted that the CPG only became available 6 months before the analysis, other published recommendations conflicted with the CPG's guidance, and the study's methodology (i.e., use of International Classification of Disease 9<sup>th</sup> edition [ICD-9] injury code characterization) may not have been fully adequate to assess clinical decision making regarding antibiotic utilization.<sup>15,16</sup> We recommended further evaluation utilizing a larger sample size over a longer time period to improve precision.<sup>15</sup>

To support future revisions of the CPG and aid evaluations of process improvement initiatives and clinical outcomes, we investigated antimicrobial prophylaxis compliance with the published 2008 CPG<sup>14</sup> over a 1-year period (June 1, 2009 through May 31, 2010). Furthermore, we used a revised injury classification methodology utilizing Abbreviated Injury Scale (AIS) codes to better characterize combat-related injury patterns and antibiotic prophylaxis requirements.

## METHODS

### Study Population and Data Collection

Trauma patients were included in the analysis if they were active-duty personnel or DoD beneficiaries, at least 18 years of age, and injured during combat requiring medical evacuation through LRMC (Germany). In addition, we restricted the study population to patients with injury documentation associated with the recent military conflicts in Iraq or Afghanistan, Operations Iraqi or Enduring Freedom (OIF/OEF). These data were collected as part of an ongoing 5-year observational cohort study of short- and long-term infectious complications following deployment-related traumatic injuries: the U.S. DoD – Department of Veterans Affairs Trauma Infectious Disease Outcomes Study (TIDOS).<sup>11</sup> The DoD Trauma Registry (DoDTR, formerly the Joint Theater Trauma Registry),<sup>17</sup> supplemented by the TIDOS infectious disease module,<sup>15</sup> was used to capture data on the study population. This study was approved by the Infectious Disease Institutional Review Board of the Uniformed Services University of the Health Sciences.

### Injury Characterization and Classification

Injuries were characterized using AIS-defined codes obtained from the DoDTR. The AIS is a consensus-derived anatomically-based injury severity scoring system with a coding schema specific to body regions, which allows for the categorization of distinct injury types (e.g., blunt force and penetrating trauma). Specifically, we used the sixth iteration of AIS, which was intended for use in coding combat-related injuries (AIS 2005-Military),<sup>18</sup> to classify injuries in our analysis.

Patients were classified into one of five injury categories based on their injury pattern.<sup>15</sup> In brief, categorization was based on requirement for antibiotic prophylaxis starting with injuries requiring coverage for penetrating abdomen (highest antibiotic requirement) followed by maxillofacial, open fracture, and open soft tissue (lowest antibiotic requirement). Patients were placed in the “closed” category if they did not meet criteria for the other categories and, thus, did not require antibiotic prophylaxis. Individuals with a penetrating central nervous system injury category were excluded from the analysis.

### Antimicrobial Coding/Classification

Antibiotic use was determined via prospective chart review in the TIDOS study and antimicrobial regimen classes were assigned as previously described.<sup>15</sup> In brief, the antibiotic classes were: Gram-positive (GP) only (e.g., cefazolin), GP plus Gram-negative (GPGN), GP and anaerobic coverage with limited GN coverage (e.g., amoxicillin-clavulanate or ampicillinsulbactam), and GPGN plus anaerobic (GPGNA) coverage (e.g.,

piperacillin-tazobactam). Because amoxicillin-clavulanate use is common at non-U.S. coalition medical treatment facilities (MTFs) within the combat zone, patients who were started on this medication and transitioned to a different antibiotic regimen were classified based on what antibiotic they were transitioned to when/if they reached a U.S. MTF. Regimens that did not meet one of these classes were assigned to an “other” category. Unlike the previously used regimen coding methodology,<sup>15</sup> regimens were categorized as GPGNA even if another broad-spectrum antibiotic was also given to provide additional GN and/or GP coverage (e.g., vancomycin or levofloxacin).

### **Antimicrobial Prophylaxis Compliance**

In accordance with 2008 CPG recommendations,<sup>14</sup> we classified adherence as receipt of acceptable therapeutic agents (Table I) and it was assessed in the immediate period following injury for up to 48 hours post-injury to account for the potential of documentation omissions and multiple transitions of care associated with combat trauma care/medical evacuation. This methodology was also used because both time of injury and antibiotic administration are recorded by day (not hours) in the TIDOS database.

Although the 2008 CPG did not recommend GN coverage for open fractures or maxillofacial injuries, a JTS CPG published in March 2010 (which is no longer publically available because of subsequent publication of a new guideline)<sup>19</sup> provided the option of extending coverage to include GN organisms in certain open fractures and maxillofacial injuries (e.g., sinus fractures). Therefore, we assessed compliance with and without GN coverage in these injury categories. In addition, our analysis examined duration of antimicrobial use specific to injury patterns.

### **Statistical Analysis**

Categorical variables were assessed using Fisher’s exact and Chi-square tests. Nonparametric tests were used to compare overall continuous variable distributions. We performed our statistical analysis using SAS version 9.3 (SAS, Cary, NC) and R version 2.13.2 (R Project for Statistical Computing, Vienna, Austria). Significance was defined as  $p < 0.05$ .

## **RESULTS**

### **Patient Demographics and Characteristics**

A total of 1106 military personnel whose injuries allowed for CPG assessment were identified for the study period of June 1, 2009 through May 31, 2010. As shown in Table II, patients were predominantly young men, and most were serving in OEF (76%) at the time of injury. Mechanism of injury varied, but blast was the most common.

At admission to LRMC, the median injury severity score was 9, indicating moderately severe injuries. In addition, 33% of patients were admitted to the intensive care unit and 20% required mechanical ventilation. Of the LRMC admissions, 632 (57%) transferred to a participating U.S. MTF.

## Injury Patterns

Among the 1106 subjects, a total of 10,680 distinct injuries were documented. Extremity injuries were predominant, accounting for 65% of injuries. On a per patient basis, 35% were categorized as open fractures, followed by open soft-tissue injuries (24%), and closed injuries (22%). The injury patterns that required prophylaxis for maxillofacial and penetrating abdomen injuries each accounted for 10% of injuries.

## Antimicrobial Use Patterns

In the study population, 74% received antimicrobial prophylaxis within the first 48 hours following injury. Cefazolin was the most common antimicrobial prescribed (72%), followed by levofloxacin (34%), and amoxicillin/clavulanate (11%).

## Adherence to Antimicrobial Prophylaxis Recommendations

Antimicrobial prophylaxis adherence for the predefined injury classifications is shown in Table III. Open soft-tissue injuries resulted in the lowest compliance rate (60%). This was due to lack of antimicrobial administration (22%) and administration of antibiotic regimen other than a preferred/acceptable alternative (18%). The injury pattern of open fracture(s) had the highest adherence (83%), but this included use of the acceptable alternative of GN coverage as recommended in the 2010 JTS CPG (no longer publically available), which accounted for 48% of the overall “adherent” practice. Adherence in patients with maxillofacial injuries was 74%, although 28% of adherent practice included GN coverage. There was no statistical difference in adherence rates between the first and second 6 months in the study period (75% versus 72%;  $p = 0.27$ ).

Closed injuries, which are not recommended to receive antibiotic prophylaxis, had the second highest compliance (80%; Table III). When antibiotic prophylaxis was administered to these patients, it was usually a GP regimen (73%) and for a duration less than 72 hours (80%). Compliance with the CPG for duration of antimicrobial prophylaxis in patients recommended to receive antibiotic prophylaxis ranged from 42 to 69% (Table IV), suggesting prolonged duration of antibiotic use in a large number of patients.

## DISCUSSION

Our analysis evaluates the 2008 combat-related CPG<sup>14</sup> with respect to antimicrobial prophylaxis prescribed to injured U.S. service members medically evacuated to LRMC during a 1-year period. This analysis represents the second evaluation of adherence to antimicrobial prophylaxis recommendations among combat casualties using a revised methodology and a longer evaluation period (1 year versus 6 months). Compliance for the various injury patterns in the current analysis was assessed to be 60 to 83% versus 10 to 79% in the prior 6-month analysis.<sup>15</sup> Specifically, adherence for open soft tissue injuries, open fractures, and maxillofacial injuries was similar to the values reported previously. However, adherence improved in the current analysis for penetrating abdominal (68% versus 10%) and closed injuries (80% versus 52%).

To investigate the possibility that increased adherence from December 2009 to May 2010 resulted in the overall observed improvement in compliance, we analyzed adherence data from the first 6 months (i.e., the same study period used in our first publication on this topic)<sup>14</sup> relative to the second 6 months, and found no statistical difference. Therefore, we feel that the observed improvement in CPG adherence is attributable to enhanced injury categorization methodologies, and not improved adherence during the last 6 months of the study period. In fact, our own post-hoc review of penetrating abdominal and closed injuries from the 6-month evaluation showed that by using AIS 2005-Military to categorize penetrating abdominal injuries, assessment of compliance improved by 24% and closed injury compliance improved by 5%.<sup>16</sup> This is not surprising as other authors have also commented on the inadequacy of relying on ICD-9 codes for severe trauma.<sup>20</sup> Specifically, ICD-9 has only a limited number of codes for multiple injuries,<sup>21</sup> whereas AIS 2005-Military accounts for multiple wounds, including those resulting from explosive devices,<sup>18</sup> through the use of a dictionary organized by anatomical regions and incorporation of the degree of injury severity.<sup>18,22</sup>

The updated antibiotic regimen categorization methodology also contributed to the improvements in compliance, particularly with penetrating abdominal injuries. For example, in the 6-month analysis, if a patient received a dose of clindamycin, cefazolin, or vancomycin along with meropenem, then the regimen was counted as noncompliant because of the use of the GP agent. However, in the present analysis, we counted regimens as GPGNA if they received an additional narrower spectrum antibiotic along with a GPGNA agent. Although some may argue for stricter interpretation of the guidelines (as used in our first analysis), we feel the methodology used herein better accounts for real-life scenarios, such as the administration of cefazolin in the trauma bay on presentation followed by the administration of a broader spectrum antibiotic when injuries requiring such coverage are discovered. In addition, we plan further analysis evaluating infectious outcomes relative to adherence. Thus, we felt it was more appropriate to categorize a patient who received both a GP and a GPGNA agent as compliant with the guideline, considering the coverage was equal even though more antibiotics were used.

Duration of antibiotic use was also assessed, and our results indicate that prophylaxis durations often exceed CPG recommendations. Potential reasons for prolonged duration of antibiotic use are antibiotic indication change (e.g., from prophylaxis to a regimen targeting an infectious syndrome) or frequent perioperative prophylaxis. Future analysis is needed to investigate antibiotic prescribing practice relative to changing clinical circumstances.

Because of the release of the updated JTS combat-related CPG in August 2011,<sup>19</sup> we plan to re-assess compliance with the revised recommendations during the corresponding period. A 4-year evaluation of CPG compliance would allow for comparisons of adherence to the respective 2008 and 2011 CPGs. It would also allow for a robust multivariate evaluation of factors affecting adherence and an assessment of outcomes based on differing prophylaxis strategies since there are significant differences between the 2008 and 2011 guidelines.

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Table 1

## 2008 Clinical Practice Guideline Antimicrobial Prophylaxis Recommendations

Injury	Microbial Contamination Coverage	Preferred Regimen	Duration
Soft-Tissue/Bone injuries			
Closed Fractures	GP Coverage (Nonanaerobes)	Cefazolin (Clindamycin or Vancomycin as Alternatives) Monotherapy	72 hours
Open Fractures <sup>a</sup>	GP Coverage (Nonanaerobes) +/- Expanded GN Coverage (GPGN)	GP Monotherapy +/- Expanded GN Agent (e.g., Fluoroquinolone, Ceftriaxone, and Aminoglycoside)	72 hours
Penetrating Abdominal Injury	GP (coverage) + GN + Anaerobic Coverage (GPGNA)	Carbapenem, Moxifloxacin, Cefoxitin, Piperacillin/Tazobactam, or Fluoroquinolone Plus Metronidazole	24 Hours After Definitive Cleaning
Maxillofacial Injury <sup>a</sup>	GP +/- Expanded GN Coverage	GP Monotherapy +/- GN Agent (e.g., Fluoroquinolone, Ceftriaxone, and Aminoglycoside)	24 Hours

Table based on Hospenthal et al.14

<sup>a</sup>Enhanced GN coverage was not recommended for type III fractures or for maxillofacial injuries (e.g., sinus fractures) by Hospenthal et al.14, but was considered to be acceptable in other guidance documents (2010 JTS CPG; no longer publically available)

**Table II**

Demographic and Clinical Characteristics for Wounded Military Personnel ( $N = 1106$ ) Admitted to LTRMC Following Traumatic Injury (June 2009-May 2010)

Characteristic	Total (%)
Combat Operation	
OIF	266 (24)
OEF	840 (76)
Time Period	
June – November 2009	576 (52)
December 2009 – May 2010	530 (48)
Gender	
Male	1082 (98)
Female	24 (2)
Injury Mechanism	
Gunshot Wound	186 (17)
Motor Vehicle Crash	77 (7)
Blast	608 (55)
Other	252 (23)

**Table III**  
Antimicrobial Prophylaxis in Combat-Related Trauma: Adherence to Published CPG

Injury pattern	Antimicrobial prophylaxis						
	None (%)	Enhanced GN coverage (%)	Consistent with CPG <sup>a</sup> (%)	CPG Consistency 95% Confidence Limit	Consistent with CPG <sup>b</sup> (%)	Other antibiotics (%)	Total
Closed	192 (80)	/	192 (80)	74.6-84.7	/	49 (20)	241
Open Soft tissue	60 (22)	/	159 (60)	53.9-65.7	/	47 (18)	266
Open Fractures	20 (6)	191 (48)	329 (83)	79.8-87.2	138 (35)	45 (11)	394
Penetrating Abdomen	1 (2)	/	29 (68)	53.4-81.4	/	13 (30)	43
Maxillofacial	13 (12)	30 (27)	81 (74)	65.4-81.9	51 (46)	16 (14)	110

Based upon 2008 CPG14

<sup>a</sup> Consistency includes expanded GN coverage.

<sup>b</sup> Consistency does not include expanded GN coverage

**Table IV**

Antimicrobial Therapy Duration for Selected Injury Patterns by Antibiotic Agent Adherence to Published Guidance

Injury Pattern	Total Number of Compliant Patients	Percent of Patients Receiving Antimicrobial Therapy			Duration of 72 Hours
		1 Day	2-3 Days		
Antibiotic Selection Consistent with CPG					
Abdomen	22	14	36	50	
Open Fractures	143	19	24	43	
Maxillofacial	38	8	34	42	
Open Soft Tissue	118	32	37	69	

CPG – Clinical Practice Guideline

In accordance with 2008 CPG14