

Treatment of Suspected Invasive Fungal Infection in War Wounds

Original Release/Approval	26 Oct 2012	Note: This CPG requires an annual review.		
Reviewed:	Oct 2012	Approved:	1 Nov 2012	
Supersedes:	This is a new CPG and must be reviewed in its entirety.			
<input type="checkbox"/> Minor Changes (or)	<input type="checkbox"/> <i>Changes are substantial and require a thorough reading of this CPG (or)</i>			
<input type="checkbox"/> Significant Changes				

1. **Goal.** To provide guidance on the recognition and comprehensive management of invasive fungal infection (IFI) in war wounds.
2. **Background.**
 - a. Clinically significant infections, to include fungal wound infections, have occurred in our wounded warrior population since the beginning of the current conflicts. However, in the setting of increasing severe and frequent Improvised Explosive Device blast injuries, there has been a corresponding increase in the incidence of fungal wound infections. Of concern is an apparent recent increase in angioinvasive *Mucor* and *Aspergillus terreus* in this patient population. These are devastating infections once the fungi (which are typically opportunistic pathogens) gain a foothold. These fungal infections have led to increased mortality, morbidity, and in some cases prolonged hospitalization for survivors.
 - b. DoD review of IFI cases³ demonstrated that the most common clinical findings associated with IFI included dismounted blast injury, above knee traumatic amputations, and extensive perineal/pelvic injury, frequently requiring massive blood transfusion (often ≥ 25 units in the first 24 hours). The majority of these cases have occurred following injury in the Helmand or Kandahar provinces in southern Afghanistan.
 - c. Prevention strategies have not been clearly identified, but early and aggressive debridement of devitalized tissue and removal of debris are universally accepted as the most important factors. The role of topical antifungal therapy in the prevention of IFI is not clear.
 - d. The treatment of IFI is based on three main principles: debridement of infected tissue, minimization of immunosuppression (e.g. malnutrition, excessive blood transfusion), and utilization of systemic anti-mold medications.
 - e. The morbidity associated with IFI in the severe war wounds, which includes tissue loss, has led to a renewed interest in early treatment of patients identified as high risk. The outcome using this earlier treatment is being monitored closely.
3. **Evaluation and Treatment.**
 - a. **The most important aspect of evaluation and treatment of war wounds is early, aggressive, and frequent surgical debridement of all devitalized tissue and organic material.**
 - b. After initial debridement, risk factors for invasive fungal infection will be assessed. Identified risk factors include:

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- 1) Dismounted blast injury
 - 2) Above knee immediate traumatic amputation, or progressive transition from below knee to through knee to above knee amputation
 - 3) Extensive perineal, GU, and/or rectal injury
 - 4) Super massive transfusion > 25 units PRBC + Whole Blood
- c. **Initiate topical anti-fungal therapy on patients with at least three of the above risk factors.** Topical anti-fungal therapy should be initiated with 0.0025% Dakins solution (5 ml of 0.5% Dakins in 995 ml sterile water *or* 10 ml of 0.25% Dakins in 990 ml sterile water). Begin with Dakins irrigations in the OR after the first or second operative debridement—use in lieu of saline irrigations for patients meeting criteria. Dress with Dakins-soaked kerlix dressing. Alternatively, an instillation vacuum dressing may be created by placing one additional infusion catheter per suction port on the vacuum dressing sponge; hold suction for 5 min and instill 50 cc 0.0025% Dakins, then clamp catheters and restart vacuum; repeat every 1-2 hours.
- d. **A standardized op note for wound description** to be used throughout the continuum for patients with increased risk of IFI has been developed. This will greatly facilitate the early detection of progressive wound necrosis, the first sign of IFI. Document initial Bastion Class only. See [Appendix B](#) for op note.
- e. **For patients transferred to Bagram** (or any Level III/Role 3 strategic evacuation hub), risk factors for IFI will be assessed and ongoing resuscitation requirements will be addressed. The patient should undergo debridement and wound washout within 12 hours of arrival. Dakins wound irrigations and topical antifungal dressings as described above will be initiated/continued.
- f. Topical anti-fungal treatment using 0.0025% Dakins solution via instillation vacuum dressing will be continued throughout the **evacuation phase**. Flight teams will receive instruction on management of the instillation prior to leaving the MTF. In the event of malfunction during flight, the instillation may be held while vacuum dressing is continued. The trauma surgeon on call will be then be contacted to evaluate the dressing immediately on arrival to the next level of care.
- g. **On arrival to the Level IV MTF**, the patient will undergo debridement and wound washout within 18 hours. Histopathology and microbiology specimens will be obtained at Level IV on all patients with at least three risk factors for IFI. Continue topical anti-fungal therapy with 0.0025% Dakins solution using an instillation vacuum dressing or 0.0025% Dakins soaked kerlix if there is continued suspicion or three risk factors for invasive fungal infection.
- h. **On arrival to the Level V MTF**, the patient will undergo debridement and washout within 18 hours. Histopathology and microbiology specimens will be obtained at Level V on all patients with at least three risk factors for IFI who have poor wound appearance, tissue necrosis or compromise.

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- i. Topical Dakins dressings may be discontinued at any level of care when the treating surgeon observes healthy granulation, or when histology and cultures are negative for fungal infection or colonization.
- j. **If there is significant progressive tissue necrosis of wounds on two consecutive debridements, not including the first two debridements**, broad-spectrum antifungal and antibiotic medications should be started immediately and Infectious Disease consultation obtained. In addition to broad spectrum antibiotics, begin
 - 1) **Voriconazole**
 - 2) **Liposomal Amphotericin B**
- k. Particular attention should be given to aggressive debridement of non-viable tissue at each washout and documentation of the amount of necrosis and appearance of the wound prior to transfer to higher level of care. [Appendix B](#) contains **standardized op note for wound description** to be used for patients with increased risk of IFI.
- l. **Whenever a significant amount of necrotic tissue is debrided, then repeat debridement should be performed in 24 hours or less.**
- m. Topical antibacterial and antifungal beads may be considered in cases of proven or strongly suspected IFI, used in conjunction with a vacuum dressing. The beads should be made with L-Amphotericin B-500 mg, Voriconazole-200 mg, Tobramycin-1.2 gm, and Vancomycin-1 gm.
- n. **Tissue biopsy in OR.**
 - 1) Biopsy should be done at the time of wound exploration at LRMC and repeated on subsequent explorations if there are persistent fevers and/or wound necrosis raising suspicion for IFI.
 - a) Tissue samples will be taken from each lower extremity in patients with bilateral lower extremity amputations. Muscle and adipose tissue should be sampled.
 - b) Other sites sampled will be at the discretion of the operative surgeon.
 - c) At least one specimen should be taken of necrotic tissue and one from the junction of viable and necrotic tissue (the last piece of borderline-viable tissue removed).
 - d) **For each site sampled, two tissue samples will be collected fresh in two separate sterile specimen containers.**
 - i. One specimen (1 cm³) for histological examination.
 - ii. One specimen (1 cm³) for fungal and bacterial culture
 - 2) OR staff responsibilities
 - a) Order histopathology and cultures (aerobic, anaerobic, and fungal). Special studies are not routinely done, but may be requested (eg. mycobacterial).

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- b) Clearly label specimens as “blast biopsy protocol”. Labels should also contain the following information:
 - i. Site (e.g., left lower extremity)
 - ii. Patient’s name, DOB, and hospital identification number
 - c) Directly contact the histology lab during working hours and the on-call pathologist after hours and on weekends.
 - 3) The histopathology specimen must leave the OR as a fresh specimen.
 - 4) Call the Pathology Lab to let them know they will receive a histopathology specimen shortly and deliver the histopathology specimen to the Pathology Lab as soon as possible.
 - 5) Pathology staff will coordinate processing as rapidly as possible (≤ 48 hours)
 - a) Histological specimen will be stained with H&E and GMS stains, and evaluated for fungal organisms.
 - b) Microbiological specimen will be cultured for aerobes, anaerobes, and fungi.
 - c) Mycobacterial cultures will not be done routinely under this protocol, but may be done with special request.
 - o. **If angioinvasive fungal elements or fungal elements among necrotic debris** are reported on histopathology, or if cultures are positive in the setting of recurring necrosis, begin treatment with systemic antifungal medications. Treatment will require close consultation with Infectious Disease; however, as a general guideline, stop systemic antifungal medications after 2 weeks if the patient remains clinically stable and the wounds remain clean/viable. If the patient has fungal infection in more than one body region—e.g., extremity/pelvis and abdomen, chest, etc., long term treatment may be indicated.
- NOTE:**
- 1) Fungal cultures can take up to 6 weeks to grow. It is therefore recommended that the cultures be checked frequently for 2 weeks; then once a week for 4 more weeks before they are considered final.
 - 2) Initial studies have shown that combat IFI wound cultures growing *Mucor* will have a second non-*Mucor* fungus present 30% of the time. *Aspergillus Terreus* is more difficult to grow than *mucor*. Therefore, dual use of Voriconazole and Liposomal Amphotericin B is suggested for wounds infected with either or both of these fungi. If long term treatment is required, the antifungal medications may be focused based on culture results.
- p. **Aggressive surgical debridement** of all necrotic and infected tissue remains the mainstay of treatment for invasive fungal infection. Debridements should continue at least every 24 hours until further debridement is not required. Wound coverage and closure should not occur until after the wound is clean, contracting, and granulating.

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4. Performance Improvement (PI) Monitoring.

Correct identification and documentation by the trauma team of patients at increased risk for IFI (≥ 3 risk factors).

Debridement within 18 hours of arrival at each facility for patients at increased risk for IFI (≥ 3 risk factors).

Appropriate biopsy including site & specimen selection, specimen handling, and notification of the pathology department.

Topical Dakins dressing initiated in theater in patients at increased risk for IFI (≥ 3 risk factors).

Appropriate documentation of wound appearance at each level of care using standardized op note for patients at increase risk for IFI (≥ 3 risk factors).

Antifungal medications started when there is significant progressive tissue necrosis on two consecutive debridements, not including the first two debridements.

Systemic and topical antifungal treatments stopped when no evidence of IFI on histology or culture.

a. Intent (Expected Outcomes).

- 1) Casualties at risk for invasive fungal infections will be identified early along continuum of care.
- 2) Documentation with specific attention to risk factors for invasive fungal infection will be performed at each level of care.

b. Performance/Adherence Measures.

- 1) Casualties with three or greater of invasive fungal risk factors are taken to OR within 12 hours upon arrival at Level III or Level IV MTFs.
- 2) Casualties with three or greater of invasive fungal risk factors have Dakin's solution applied to wounds.
- 3) Standardized op note will be used at Level III facilities in theater and Level IV facilities for casualties with two or greater risk factors for invasive fungal infection.

c. Data Source.

- 1) Patient Record
- 2) Joint Theater Trauma Registry (JTTR)

d. System Reporting & Frequency.

The above constitutes the minimum criteria for PI monitoring of this CPG. System reporting will be performed annually; additional PI monitoring and system reporting may be performed as needed.

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The system review and data analysis will be performed by the Joint Theater Trauma System (JTTS) Director, JTTS Program Manager, and the Joint Trauma System (JTS) Performance Improvement Branch.

5. References.

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Approved by CENTCOM JTTS Director,
JTS Director and CENTCOM SG

Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the Services or DoD.
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APPENDIX A

BASTION CLASSIFICATION OF LOWER LIMB INJURY

Bastion classification of lower limb injury caused by IED. The most proximal extent.	
Class of limb injury	Description
1	Injury confined to foot
2	Injury involving lower leg permitting effective below-knee tourniquet application
3	Injury involving proximal lower leg or thigh, permitting effective above-knee tourniquet application
4	Proximal thigh injury, preventing effective tourniquet application
5	Any injury with buttock involvement

References.

- ^{1.} Jacobs N, et al. Lower limb injuries caused by improvised explosive devices: Proposed 'Bastion classification' and prospective validation. *Injury*. 2012;Epub 18 Aug 12.

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APPENDIX B

MD TRAUMA WOUND DEBRIDEMENT OP NOTE

Date of Operation:	
Pre-Operative Diagnosis:	
Post-Operative Diagnosis:	
Initial Bastion Amputation Class:	1 (foot) 2 (below knee) 3 (above knee) 4 (proximal thigh) 5 (involves buttock/perineum)
Surgeon(s):	
Anesthesia:	
EBL:	
Fluids/Blood Products Administered:	
OPERATIVE SITE #1: (specify)	
Procedure <input type="checkbox"/> Initial amputation (level) _____ <input type="checkbox"/> Revision amputation (level) _____ <input type="checkbox"/> Debridement/Washout Number _____ <input type="checkbox"/> DPC <input type="checkbox"/> Exam/Dressing change under Anesthesia <input type="checkbox"/> Ex-Fix (initial) <input type="checkbox"/> Ex-Fix (revision) <input type="checkbox"/> ORIF <input type="checkbox"/> Orthopedic hardware removal <input type="checkbox"/> Other _____	Wound Description Total size of wound: _____ cm ² <input type="checkbox"/> Clean <input type="checkbox"/> Approx 25% necrotic <input type="checkbox"/> Approx 50% necrotic <input type="checkbox"/> Approx 75% necrotic <input type="checkbox"/> Completely necrotic <input type="checkbox"/> Grossly purulent <input type="checkbox"/> Gross mold
Samples Sent <input type="checkbox"/> None <input type="checkbox"/> Aerobic culture <input type="checkbox"/> Anaerobic culture <input type="checkbox"/> Fungal culture <input type="checkbox"/> Histopathology <input type="checkbox"/> Other _____	Adjunctive Therapy <input type="checkbox"/> Antimicrobial beads (type) _____ <input type="checkbox"/> Dakins soaked dressings <input type="checkbox"/> Dakins Instill Device (started) <input type="checkbox"/> Dakins Instill Device (Renewed) <input type="checkbox"/> Negative pressure therapy <input type="checkbox"/> Other _____
Comments:	

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MD TRAUMA WOUND DEBRIDEMENT OP NOTE

OPERATIVE SITE #2: (specify)	
Procedure <input type="checkbox"/> Initial amputation (level) _____ <input type="checkbox"/> Revision amputation (level) _____ <input type="checkbox"/> Debridement/Washout Number _____ <input type="checkbox"/> DPC <input type="checkbox"/> Exam/Dressing change under Anesthesia <input type="checkbox"/> Ex-Fix (initial) <input type="checkbox"/> Ex-Fix (revision) <input type="checkbox"/> ORIF <input type="checkbox"/> Orthopedic hardware removal <input type="checkbox"/> Other _____	Wound Description Total size of wound: _____ cm ² <input type="checkbox"/> Clean <input type="checkbox"/> Approx 25% necrotic <input type="checkbox"/> Approx 50% necrotic <input type="checkbox"/> Approx 75% necrotic <input type="checkbox"/> Completely necrotic <input type="checkbox"/> Grossly purulent <input type="checkbox"/> Gross mold
Samples Sent <input type="checkbox"/> None <input type="checkbox"/> Aerobic culture <input type="checkbox"/> Anaerobic culture <input type="checkbox"/> Fungal culture <input type="checkbox"/> Histopathology <input type="checkbox"/> Other _____	Adjunctive Therapy <input type="checkbox"/> Antimicrobial beads (type) _____ <input type="checkbox"/> Dakins soaked dressings <input type="checkbox"/> Dakins Instill Device (started) <input type="checkbox"/> Dakins Instill Device (Renewed) <input type="checkbox"/> Negative pressure therapy <input type="checkbox"/> Other _____
Comments:	
OPERATIVE SITE #3: (specify)	
Procedure <input type="checkbox"/> Initial amputation (level) _____ <input type="checkbox"/> Revision amputation (level) _____ <input type="checkbox"/> Debridement/Washout Number _____ <input type="checkbox"/> DPC <input type="checkbox"/> Exam/Dressing change under Anesthesia <input type="checkbox"/> Ex-Fix (initial) <input type="checkbox"/> Ex-Fix (revision) <input type="checkbox"/> ORIF <input type="checkbox"/> Orthopedic hardware removal <input type="checkbox"/> Other _____	Wound Description Total size of wound: _____ cm ² <input type="checkbox"/> Clean <input type="checkbox"/> Approx 25% necrotic <input type="checkbox"/> Approx 50% necrotic <input type="checkbox"/> Approx 75% necrotic <input type="checkbox"/> Completely necrotic <input type="checkbox"/> Grossly purulent <input type="checkbox"/> Gross mold
Samples Sent <input type="checkbox"/> None <input type="checkbox"/> Aerobic culture <input type="checkbox"/> Anaerobic culture <input type="checkbox"/> Fungal culture <input type="checkbox"/> Histopathology <input type="checkbox"/> Other _____	Adjunctive Therapy <input type="checkbox"/> Antimicrobial beads (type) _____ <input type="checkbox"/> Dakins soaked dressings <input type="checkbox"/> Dakins Instill Device (started) <input type="checkbox"/> Dakins Instill Device (Renewed) <input type="checkbox"/> Negative pressure therapy <input type="checkbox"/> Other _____
Comments:	

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APPENDIX C

ADDITIONAL INFORMATION REGARDING OFF-LABEL USES IN CPGs

1. **Purpose.** The purpose of this Appendix is to ensure an understanding of DoD policy and practice regarding inclusion in CPGs of “off-label” uses of U.S. Food and Drug Administration (FDA)–approved products. This applies to off-label uses with patients who are armed forces members.
2. **Background.** Unapproved (i.e., “off-label”) uses of FDA-approved products are extremely common in American medicine and are usually not subject to any special regulations. However, under Federal law, in some circumstances, unapproved uses of approved drugs are subject to FDA regulations governing “investigational new drugs.” These circumstances include such uses as part of clinical trials, and in the military context, command required, unapproved uses. Some command requested unapproved uses may also be subject to special regulations.
3. **Additional Information Regarding Off-Label Uses in CPGs.** The inclusion in CPGs of off-label uses is not a clinical trial, nor is it a command request or requirement. Further, it does not imply that the Military Health System requires that use by DoD health care practitioners or considers it to be the “standard of care.” Rather, the inclusion in CPGs of off-label uses is to inform the clinical judgment of the responsible health care practitioner by providing information regarding potential risks and benefits of treatment alternatives. The decision is for the clinical judgment of the responsible health care practitioner within the practitioner-patient relationship.
4. **Additional Procedures.**
 - a. **Balanced Discussion.** Consistent with this purpose, CPG discussions of off-label uses specifically state that they are uses not approved by the FDA. Further, such discussions are balanced in the presentation of appropriate clinical study data, including any such data that suggest caution in the use of the product and specifically including any FDA-issued warnings.
 - b. **Quality Assurance Monitoring.** With respect to such off-label uses, DoD procedure is to maintain a regular system of quality assurance monitoring of outcomes and known potential adverse events. For this reason, the importance of accurate clinical records is underscored.
 - c. **Information to Patients.** Good clinical practice includes the provision of appropriate information to patients. Each CPG discussing an unusual off-label use will address the issue of information to patients. When practicable, consideration will be given to including in an appendix an appropriate information sheet for distribution to patients, whether before or after use of the product. Information to patients should address in plain language: a) that the use is not approved by the FDA; b) the reasons why a DoD health care practitioner would decide to use the product for this purpose; and c) the potential risks associated with such use.