JOINT TRAUMA SYSTEM CLINICAL PRACTICE GUIDELINE (JTS CPG)

Invasive Fungal Infection in War Wounds

Provide guidance on the recognition and comprehensive management of invasive fungal infection (IFI) in war wounds.

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SUMMARY OF CHANGES

1. Updates to IFI wound epidemiology to include surgical and wound healing outcomes
2. Addition of pan-fungal PCR as a potential rapid molecular diagnostic modality
3. Updates on the use of IV voriconazole in those with impaired renal function
4. Updates on posaconazole administration
5. Addition of isavuconazole as a mold active triazole
6. Addition of tissue sample handling considerations to increase culture yield of fungi (i.e. Mucor)
7. Updated Jul 2021 with the Dakin's half-strength solution

BACKGROUND

Clinically significant infections, including invasive fungal wound infections (IFIs), have occurred in the DoD's wounded warrior patient population since the beginning of the current conflicts in Iraq and Afghanistan. During 2009-2010, a substantial increase in the incidence of IFIs was observed among military personnel with wounds sustained in Afghanistan, corresponding to a greater frequency of improvised explosive device blast injuries sustained while on foot patrol in Helmand and Kandahar provinces.[1-3] Mold contamination of the wounds was associated with regions in southern Afghanistan characterized by lower elevation, warmer temperatures,[4] and followed waterways. Of particular clinical concern was an apparent association between patient outcome and the presence of angioinvasive filamentous fungi (e.g., order Mucorales, Aspergillus species, and Fusarium species) often called "molds."[5,6] In general, IFIs are devastating infections associated with increased mortality, morbidity, limb loss, and prolonged hospitalization for survivors.[2,7-10] In civilian literature, mortality rates have been reported as high as 38%.[5] Among the military population, the crude mortality rate was as high as 8% during the first two years of increased prevalence.[11] Dismounted blast injuries were highly contaminated with debris (e.g., soil, plant matter, and shrapnel) and coinfection with bacteria and other fungi was common.[12-14]

Following recognition of the high number of IFI cases, the Joint Trauma System, in collaboration with the Uniformed Services University of the Health Sciences Infectious Disease Clinical Research Program (IDCRP) Trauma Infectious Disease Outcomes Study (TIDOS), launched an outbreak investigation. Review of the findings demonstrated that the most common mechanistic and clinical factors associated with IFI included dismounted blast injury, above-knee traumatic amputations, extensive perineal/pelvic injury (observed trend, but not statistically significant), and massive packed red blood cell transfusion (≥20 units in the first 24 hours).[1,2] Importantly, all IFI patients had a suspicious wound (i.e. unhealthy appearance), defined as recurrent tissue necrosis following at least two surgical debridements. Additional work on IFI classification emphasizes the temporal relationship between surgical findings and laboratory evidence of IFI. (See Appendix A: Examples of Suspicious Wounds.)[15]

The morbidity associated with IFI in war wounds, which may include significant tissue loss, necessitates early surgical and antifungal treatment of patients identified as high risk. Early and aggressive debridement of devitalized tissue and removal of debris are universally accepted as the most important interventions. Patients frequently require surgical amputations and/or amputation revisions, which include extending to more proximal levels (e.g., transtibial to transfemoral or transfemoral to proximal transfemoral, hip disarticulation, or hemipelvectomy.[16] IFI wounds with order Mucorales and Gram-negative bacterial co-infections were observed to have longer time to wound closure, highlighting the need for antifungal and antibacterial therapy.[14]

Early and aggressive debridement of devitalized tissue and removal of debris are universally accepted as the most important interventions.

The 3 main principles of IFI treatment:

1. Surgical debridement of infected tissue;
2. Minimization of immunosuppression (e.g., avoidance of malnutrition or excessive blood product transfusion); and
3. Utilization of empiric dual antifungal medications (e.g., amphotericin B and a broad-spectrum triazole agent) when there is a strong suspicion of an IFI.[9]

Wounds with IFI require a significantly higher number of surgical (not bedside) debridement compared to other wound infections. There are also more changes in amputation level (e.g., revision of a transfemoral amputation to either a hemipelvectomy or hip disarticulation); longer duration following injury to wound closure; and an increased frequency of return to the operating room after wound closure due to infectious complications or drainage.[12] The role of topical antifungal therapy in the prevention of IFI is not clear, but topical therapies have not been demonstrated to have adverse local or systemic effects.

EVALUATION AND TREATMENT

The most important aspect of evaluation and treatment of war wounds is a high index of suspicion for fungal infection, with the early recognition of unhealthy or suspicious wounds followed by early, aggressive, and repetitive surgical debridement of all devitalized tissue and organic material.

After initial debridement, risk factors for invasive fungal infection will be assessed. Identified risk factors include:

- Dismounted blast injury.
- Above-knee immediate traumatic amputation, or progressive transition from below-knee to through-knee to above-knee amputation.
- Extensive perineal, genitourinary, and/or rectal injury.
- Massive transfusion > 20 units packed red blood cells within 24 hours of injury.
- Extensive deep-partial-thickness or full-thickness burns (note: covered elsewhere).[17]

DIAGNOSIS CRITERIA

Diagnostic criteria for an IFI are:

1. Presence of a traumatic wound(s).
2. Recurrent necrosis following at least two consecutive surgical debridements.
3. Laboratory evidence of fungal infection following at least two surgical debridements (i.e. mold culture positivity and/or histopathology indicating tissue invasion).[9,15] This is usually not available at deployed Role 2 or Role 3 Military Treatment Facilities (MTFs), so clinical suspicion is key to early intervention.
4. Fungal wound infection is often manifested by 'tinctorial' or color changes in a wound; early detection of such changes requires repeated inspection by an experienced clinician.[18]
5. IFIs are often diagnosed through routine histopathological examination of tissue specimens. The evaluation of the performance of periodic acid-Schiff (PAS) and Gomori methenamine silver (GMS) in combat trauma-associated IFI demonstrated that the two stains were 84% concordant with false negative rates of 44% for PAS and 15% for GMS; however, neither stain was significantly superior at identifying fungal elements. Overall, there is no added benefit for increasing diagnostic yield with use of both stains.[19]
6. Where available, pan-fungal PCR, for identification of filamentous fungi evaluation offers promise for rapid identification of IFI which can lead to a more timely and accurate diagnosis.

Compared to histopathology, panfungal PCR was specific (99%), but not as sensitive (63%); however, sensitivity improved to 83% in specimens from sites with angioinvasion.[19]

TOPICAL TREATMENT

Initiate topical antifungal therapy on patients with at least three of the above risk factors above in Evaluation and Treatment.[20,22] There is no clear evidence that any topical treatment improves outcomes; however, Dakin's Solution is commonly used. Dakin's used an irrigation solution, which is how it was originally described for use, is likely beneficial for severe infections, including fungal infections. Use Dakin's solution in lieu of saline irrigations for patients meeting criteria.[23,24]

In terms of wound dressings in patients with concern for IFI, nothing has been definitively proven to improve outcomes, but using a topical antifungal is still conditionally recommended. Options include Dakin's-soaked Kerlix dressings, Silver Nitrate Solution, or honey[20,22-28] VAC (negative pressure wound dressings) are not recommended early in the treatment of IFI, or suspected IFI, because daily trips to the operating room are needed for debridement/washout, diagnostics, and source control.

Use of Dakin's solution in the prevention or treatment of IFI, though widespread and probably superior to saline or dry gauze, is unproven. At the US Army Burn Center, a 0.5% aqueous solution of silver nitrate, rather than Dakin's solution, is the preferred treatment for open wounds at risk of IFI. Established IFIs may be treated with topical Nystatin powder. Topical Silver Nitrate is not always available in the deployed environment.[29]

A standardized operative note for wound description is available and should be used throughout the continuum of care for patients at increased risk for IFI. Utilization of this operative note may facilitate the early detection of sequential wound necrosis , which is the crucial first sign of IFI – Appendix B. Description of Bastion Classification of lower limb injuries is presented in Appendix C. Document on the first page of the Operative Note.

DEBRIDEMENT AND ANTIFUNGAL THERAPY

1. For patients transferred to any Role 3 strategic evacuation hub, risk factors for IFI should be assessed and ongoing resuscitation requirements should be addressed as needed. The patient should undergo surgical examination, wound washout, and debridement (if indicated) within 6-12 hours of arrival. Dakin's wound irrigations and topical antifungal treatments as described above should be initiated/continued.
2. Evacuation should be deferred in patients who are clinically unstable and require debridement / wound care every 6-12 hours. Reassess patient to meet evacuation criteria every 24 hours. The surgeon on call should be contacted to evaluate the patient and their wounds immediately on arrival to the next level of care.
3. Upon arrival to the Role 4 MTF (i.e. regional treatment facility outside of the combat zone, but prior to arrival in the United States), the patient should undergo operative exploration, wound washout, and debridement (as indicated) within 6-12 hours. Obtain histopathology and microbiology specimens on all patients with at least three risk factors for IFI and any with clinical suspicion. Topical antifungal therapy should be continued.
4. Upon arrival to an MTF in the United States, the patient should undergo surgical exploration, wound washout, and debridement within 6-12 hours. Obtain histopathology and microbiology

specimens on all patients with at least three risk factors for IFI and/or who have an unhealthy wound appearance (e.g., tissue necrosis). Topical antifungal dressings may be discontinued at any level of care when the treating surgeon observes healthy granulation, or when histopathology and cultures are negative for fungal infection or colonization.

5. Following the first two debridements in theater, if tissue necrosis is observed in wounds after two consecutive debridements, start broad-spectrum antifungal and antibiotic medications immediately and obtain infectious disease consultation. Liposomal amphotericin B is the primary choice due to its effectiveness against mucormycosis, and its reduced potential to induce nephrotoxicity compared to the non-liposomal formulation.[30] Although voriconazole is ineffective against mucormycosis, it has shown to be an active agent against molds that are resistant to amphotericin B (e.g., *Aspergillus terreus* and *Scedosporium prolificans*).[31]
6. In general, patients with IFI are severely injured, and intravenous formulations of antifungal agents are prescribed due to concern for inadequate gastrointestinal antifungal absorption in the septic patient. As soon as feasible, parameters for monitoring antifungal drug toxicities should be implemented (EKG, renal function and LFTs).
7. When voriconazole is administered intravenously, it requires a solubilizing excipient (i.e. sulfobutyl ether β-cyclodextrin), which may accumulate in patients with impaired renal function. A black box warning has been issued due to adverse effects of the accumulating solute in an animal model. Nevertheless, the effects of elevated sulfobutyl ether β-cyclodextrin are unknown in humans.[32] An IV route of administration of voriconazole did not predict worsening renal dysfunction in a small retrospective study with the caveat that only a few patients received voriconazole for ≥ 7 days.[33] Clinical experience to date has not shown permanent renal impairment with this off-label use of voriconazole in the wounded military population.[34]
8. Posaconazole is another triazole agent that has been found to have a 60-70% response rate as a salvage regimen against mucormycosis when prescribed orally.[35-37] Posaconazole tablets are preferred over oral suspension as there is less variability in absorption. Therapeutic drug monitoring should be used if available to achieve trough concentrations > 1.0 µg/mL.[38] Recently, an intravenous formulation was approved and has shown to be useful.[39]

> The recommended dose of posaconazole (tablet formulation) is 300mg by mouth every 12 hours for 2 doses, then 300mg once daily. A posaconazole trough should be obtained on day 7 of therapy. Note that if other formulations of posaconazole are used, the dosing will be different.
>
> The typical starting dose of voriconazole is 6 mg / kg IV every 12 hours for 2 doses, followed by 4 mg/ kg (the patient's actual body weight should be used for dosing). A voriconazole trough should be obtained on day 4 of therapy. Goal trough is 1 - 1.5 mcg / mL.

9. Dual administration of liposomal amphotericin B and a broad-spectrum triazole is recommended as the first-line antifungal agents. Among triazoles, clinical experience has been primarily with voriconazole. Many of the wounds incurred by combat casualties grow more than one mold.[32] Furthermore, prescribe broad-spectrum antibiotics covering both gram-positive and gram-negative organisms (e.g., vancomycin and meropenem)are prescribed as fungal-infected wounds frequently also have bacterial growth

   Initial studies have shown that combat IFI wound cultures growing order Mucorales will have a second non-Mucorales fungus present 30% of the time. Aspergillus species is more difficult to

grow than order Mucorales but should be suspected and empirically treated initially as it has been shown to be virulent in this patient population.[40] Therefore, dual use of a broad-spectrum triazole 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 should be targeted based on culture results.

10. Isavuconazole is a triazole agent available in IV and oral formulations with mold activity including against mucormycosis. Isavuconazole has not been studied in randomized controlled trials but in one multicenter open-label single-arm study, isavuconazole demonstrated similar efficacy to amphotericin B formulations in an external matched control group.[40]
11. Particular attention should be given to aggressive debridement of non-viable tissue at each debridement procedure. The extent of necrosis and appearance of the wound before and after completion of the operation should be documented in the operative note. Appendix B shows a standardized operative note for wound description to be used for patients at increased risk for IFI. Whenever a significant amount of necrotic tissue is debrided, repeat debridement should be performed in 24 hours or less.

    As aggressive surgical debridement of all necrotic and infected tissue remains the mainstay of treatment for IFI, surgical exploration and debridement should continue at least every 24 hours until cessation of necrosis occurs. Wound coverage and closure should not occur until after the wound is clean, contracting, and granulating.
12. If angioinvasive fungal elements or fungal elements among tissue are reported on histopathology, or if cultures are positive in the setting of recurrent necrosis, initiate (or continue) treatment with systemic antifungal medications. Treatment will require close consultation with infectious disease; however, as a general guideline, stop systemic antifungal medications if the wound remains clean/viable for two weeks and if the patient remains clinically stable. If the patient has a fungal infection in more than one body region (e.g., extremity/pelvis, abdomen, and chest), long-term treatment may be indicated.

BIOPSY AND TISSUE CULTURE IN OR

Biopsy should be done at the time of wound exploration (after initial surgical debridement) once the casualty has been evacuated from the theater of conflict (in theater if patient evacuation is delayed) and repeated on subsequent explorations if there are persistent findings (e.g., sepsis physiology, wound necrosis) raising suspicion for IFI.

1. Tissue samples should be obtained from each lower extremity in patients with bilateral lower extremity amputations. Sample all suspected areas.
2. Other sites sampled should be at the discretion of the operative surgeon.
3. At least one specimen should be taken from the junction of viable and necrotic tissue (the last piece of borderline-viable tissue removed).
4. For each site sampled, two tissue samples will be collected fresh in two separate sterile specimen containers.
    - One specimen (1 cm3) for “rush” histopathological examination
    - One specimen (1 cm3) for fungal and bacterial culture

OR STAFF RESPONSIBILITIES

The histopathology specimen is placed in formalin. It is not necessary to send fresh samples.

Order histopathology and cultures (aerobic, anaerobic, and fungal). Special studies are not routinely done, but may be requested (e.g., mycobacterial and viral).

1. Clearly label specimens. Labels contain the following information:
   - Site (e.g., left lower extremity)
   - Patient's name, date of birth, and hospital identification number
   - Date and time obtained
   - "Rush" sticker if available
   - Initials of the person labelling the container
2. Directly contact the on-call pathologist to let them know they will receive a "rush" histopathology specimen for IFI shortly. Deliver the histopathology specimen to the pathology lab immediately.

PATHOLOGY STAFF RESPONSIBILITIES

Pathology staff will coordinate processing as rapidly as possible (≤ 24 hours).

1. Histopathological specimen will be stained with hematoxylin and eosin (H&E) and GMS/PAS stains and evaluated for (1) presence of fungal elements; (2) presence of fungal elements in viable or non-viable tissue; (3) presence of angioinvasion.
2. Microbiological specimen will be cultured for aerobes, anaerobes, and fungi.
3. Mycobacterial and/or viral cultures will not be done routinely under this protocol but may be done with special request.

NOTE:
Fungus can take up to six weeks to grow in culture medium. Therefore, it is recommended that the cultures be checked frequently for two weeks; then once a week for four additional weeks before they are considered final. In addition, wounds without recurrent tissue necrosis may have mold colonization and not a true infection.[41]
Tissue preparation for culturing typically destroys the ribbon-like hyphal elements of fungi belonging to the order Mucorales, reducing growth. The microbiology laboratory should be notified that an IFI is suspected so samples are handled appropriately to maximize culture yield.

PERFORMANCE IMPROVEMENT (PI) MONITORING

POPULATION OF INTEREST

- Identify patients with IFI
- Patients with 3 or more risk factors for invasive fungal infection (dismounted blast, above knee amputation, perineal genitourinary or rectal injury, MT> 20 units RBC + WB within 24h of injury.)

INTENT (EXPECTED OUTCOMES)

- Patients with ≥3 IFI risk factors undergo surgical debridement undergo surgical debridement in the OR within 6-12 hours of arrival at Role 3 or 4 MTFs.
- Patients with ≥3 IFI risk factors and wounds concerning for IFI are:
  - taken to the OR at least every 24 hours
  - are started on IV or PO antifungals.
- An operative note for wound debridement includes the extent of necrosis quantified as a percentage of each wound.

PERFORMANCE/ADHERENCE METRICS

- Number and percentage of patients in the population of interest who undergo surgical debridement in the OR within 6-12 hours of arrival at Role 3 or 4 MTFs.
- Number and percentage of patients in the population of interest who have an operative note that quantifies the extent of wound necrosis as a percentage of each wound.

DATA SOURCES

- Patient Record
- Department of Defense Trauma Registry (DoDTR)

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.

The system review and data analysis will be performed by the JTS Chief and the JTS PI Branch.

RESPONSIBILITIES

It is the trauma team leader's responsibility to ensure familiarity, appropriate compliance, and PI monitoring at the local level with this CPG.

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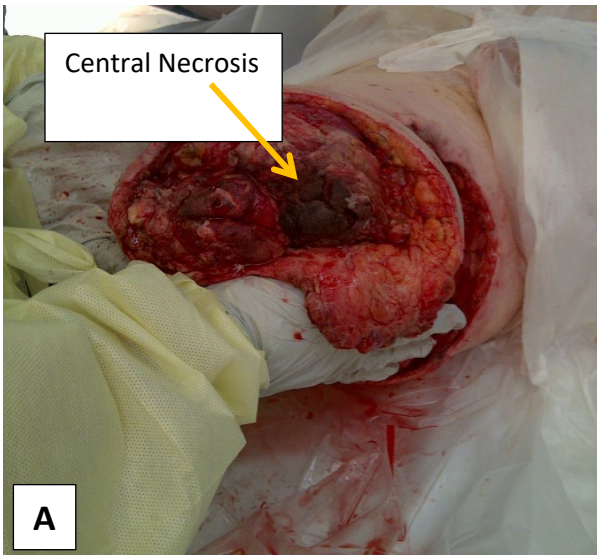
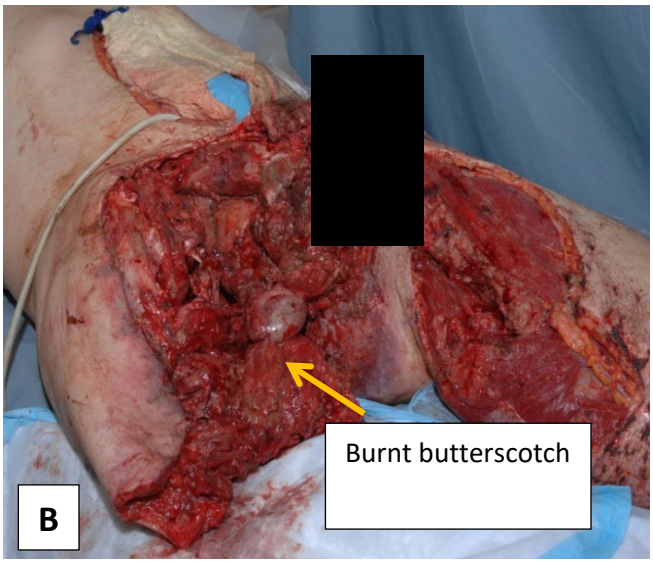
APPENDIX A: EXAMPLES OF SUSPICIOUS WOUNDS

All photos are from different patients.

(A) Patient is 8 days out from injury. His wound is showing central necrosis. Debridement day prior revealed healthy appearing, bleeding tissue.

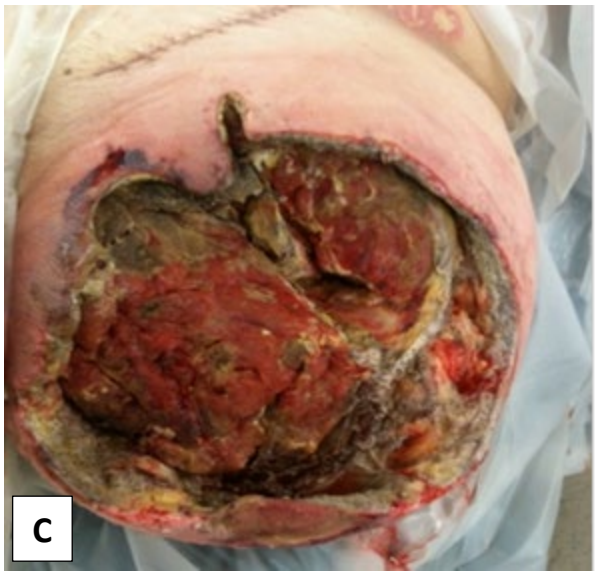
(B) Patient is also 8 days out from injury. Patchy necrosis is seen throughout his right-sided hemipelvectomy. Upon closer inspection, one notices a 'burnt butterscotch' appearance overlying tissue. Anecdotally, this is an additional IFI clinical indicator.

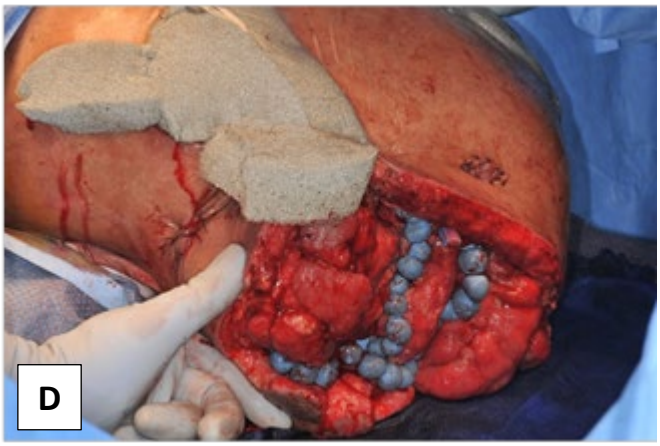




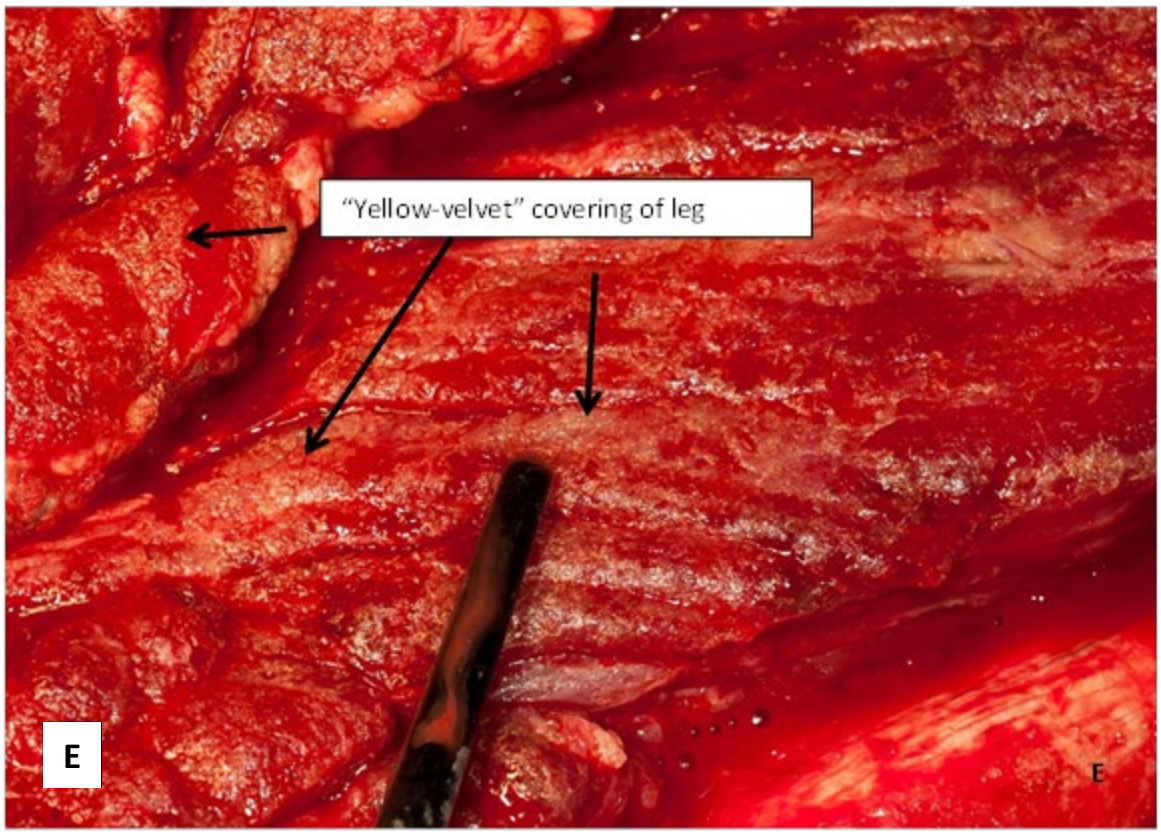
(C) Provides example of tissue necrosis in a previously healthy-appearing wound bed.

(D) Patient is recovering well, but still being treated with anti-microbial beads





(E) Looking closely at the wound, one can see a 'yellow-velvet' covering to the wound. This is indicative of an Aspergillus infection.



APPENDIX B: MD TRAUMA WOUND DEBRIDEMENT OP NOTE

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 Initial amputation (level) _____ Revision amputation (level) _____ Debridement/Washout Number_____ DPC Exam/Dressing change under Anesthesia Ex-Fix (initial) Ex-Fix (revision) ORIF Orthopedic hardware removal Other_____	**Wound Description** Total size of wound:_____cm^2 Clean Approx 25% necrotic Approx 50% necrotic Approx 75% necrotic Completely necrotic Grossly purulent Gross mold
Samples Sent None Aerobic culture Anaerobic culture Fungal culture Histopathology Other_____	**Adjunctive Therapy** Antimicrobial beads (type) _____ Dakin's-soaked dressings Dakin's Instill Device (started) Dakin's Instill Device (Renewed) Negative pressure therapy Other_____
Comments:	

MD Trauma Wound Debridement Op Note

OPERATIVE SITE #2: (specify)

Procedure	**Wound Description**
Initial amputation (level) _____	
Revision amputation (level) _____	Total size of wound:_____cm^2
Debridement/Washout Number_____	Clean
DPC	Approx 25% necrotic
Exam/Dressing change under Anesthesia	Approx 50% necrotic
Ex-Fix (initial)	Approx 75% necrotic
Ex-Fix (revision)	Completely necrotic
ORIF	Grossly purulent
Orthopedic hardware removal	Gross mold
Other_____	
Samples Sent	**Adjunctive Therapy**
None	Antimicrobial beads (type) _____
Aerobic culture	Dakin's-soaked dressings
Anaerobic culture	Dakin's Instill Device (started)
Fungal culture	Dakin's Instill Device (Renewed)
Histopathology	Negative pressure therapy
Other_____	Other_____
Comments:	

OPERATIVE SITE #3: (specify)

Procedure	**Wound Description**
Initial amputation (level) _____	
Revision amputation (level) _____	Total size of wound:_____cm^2
Debridement/Washout Number_____	Clean
DPC	Approx 25% necrotic
Exam/Dressing change under Anesthesia	Approx 50% necrotic
Ex-Fix (initial)	Approx 75% necrotic
Ex-Fix (revision)	Completely necrotic
ORIF	Grossly purulent
Orthopedic hardware removal	Gross mold
Other_____	
Samples Sent	**Adjunctive Therapy**
None	Antimicrobial beads (type) _____
Aerobic culture	Dakin's-soaked dressings
Anaerobic culture	Dakin's Instill Device (started)
Fungal culture	Dakin's Instill Device (Renewed)
Histopathology	Negative pressure therapy
Other_____	Other_____
Comments:	

APPENDIX C: 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

Reference: Jacobs N, Rourke K, Rutherford J, et al. Lower limb injuries caused by improvised explosive devices: proposed 'Bastion classification' and prospective validation. Injury 2014; 45(9): 1422-28.

APPENDIX D: INFORMATION REGARDING OFF-LABEL USES IN CPGS

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.

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.

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.

ADDITIONAL PROCEDURES

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.

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.

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.