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Clinical Relevance of Mold Culture Positivity With and Without Recurrent Wound Necrosis Following Combat-Related Injuries

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Abstract

Background—Invasive fungal wound infections (IFI) are a recognized threat for personnel who sustain combat-related blast trauma in Afghanistan. Blast trauma, particularly when dismounted, has wounds contaminated with organic debris and potential for mold infection. Trauma-associated IFI is characterized by recurrent wound necrosis on serial debridement with histologic evidence of invasive molds and/or fungal culture growth. Wounds with mold growth, but lacking corresponding recurrent necrosis present a clinical dilemma of whether to initiate antifungal treatment. Our objective was to assess the clinical significance of fungal culture growth without recurrent wound necrosis.

Methods—United States military personnel wounded during combat in Afghanistan (June 2009 - August 2011) were assessed for growth of mold from wound cultures and/or histopathological evidence of IFI. Identified patients were stratified based upon clinical wound appearance (with/without recurrent necrosis) and the resultant groups were compared for injury characteristics, clinical management, and outcomes.

Results—A total of 96 patients were identified: 77 with fungal elements on histopathology and/or fungal growth plus recurrent wound necrosis and 19 with fungal growth on culture but no wound necrosis after initial debridements. Injury patterns and severity were similar between the groups. Patients with recurrent necrosis had more frequent fevers and leukocytosis during the first two weeks post-injury, and the majority received antifungal therapy compared to only three (16%)

patients without recurrently necrotic wounds. Overall, patients without recurrent wound necrosis had significantly less operative procedures (p=0.02), shorter length of stay in the intensive care unit (p<0.01), and lower rates of high-level amputations (5% versus 20%) and deaths (none versus 8%) despite no or infrequent antifungal use.

Conclusions—The finding of molds on wound culture among patients with blast trauma in the absence of recurrently necrotic wounds on serial debridement does not require systemic antifungal chemotherapy.

Keywords

invasive fungal infections; invasive mold infections; combat-related infections; recurrent wound necrosis; fungal colonization

Introduction

While advances in body armor and combat casualty care have led to improved survival rates from complex injuries during recent military conflicts,[1-3] new complications during wound stabilization, treatment, and reconstruction are being observed. In particular, invasive fungal wound infections (IFI) have emerged in association with dismounted (foot patrol) blast injuries in southern Afghanistan.[2,4-6] This environment is thought to harbor molds capable of inoculating wounds following detonation of improvised explosive devices.[4,5] Wound contamination, a known factor related to IFI development among civilian trauma cases, allows for mold colonization or fungal invasion of viable tissue surrounding wound sites.[2,5,7,8]

Although not all wound contamination leads to IFI, the high mortality associated with the disease makes it a legitimate concern. A review of 929 cases of mucormycosis (primarily sinus, pulmonary, and cutaneous) reported a survival rate of 57% with surgery alone, 64% with only antifungal treatment, 70% when antifungal therapy was combined with surgery, and 3% when no treatment was initiated.[9] In addition, following the tornado disaster in Joplin, Missouri, 13 patients developed IFI, of which 5 (38%) died despite antifungal and surgical treatment.[8] Hence, once an IFI diagnosis is established, commencement of prompt treatment is critical. Given these high mortality rates, the risks of antifungal therapy (e.g., drug interactions, nephrotoxicity, and hepatotoxicity)[10] are justified. When the diagnosis is less clear, the hazards of antifungal use warrant further scrutiny. This is often the case when wound cultures yield fungi, but histopathological evidence of infection and/or recurrent wound necrosis consistent with IFI are lacking.

With the rising awareness that early recognition and treatment were critical to effectively manage IFI, our clinicians were faced with a dilemma when wounds grew mold, but lacked the IFI hallmark of recurrent necrosis despite serial debridement. Consequently, there was uncertainty about the utility of antifungal therapy in these scenarios. Therefore, we evaluated the clinical relevance of fungal growth in association with wound appearance with respect to outcome by comparing data from patients with and without recurrent wound necrosis in order to provide clinicians with information to aid decision-making regarding the initiation of antifungal therapy.

Methods

Study Population

Data were collected from U.S. military personnel who were injured in combat in Afghanistan (June 2009 through August 2011), medically evacuated to Landstuhl Regional Medical Center (LRMC) in Germany for initial care, and then admitted to a participating U.S. military treatment facility (MTF): Walter Reed Army Medical Center in Washington, DC, National Naval Medical Center in Bethesda, MD, and San Antonio Military Medical Center in San Antonio, TX. The overarching project for this analysis is the ongoing five-year observational cohort study of short- and long-term infectious complications following deployment-related traumatic injuries during recent military conflicts; the U.S. Department of Defense (DoD) – Department of Veterans Affairs, Trauma Infectious Disease Outcomes Study (TIDOS).[1]

As previously described,[4,11,12] a subset of the combat casualty population with suspected IFI was identified by reviewing the TIDOS database for wound cultures with fungal growth and/or fungal elements on histology (i.e., viable tissue invasion with/without fungal hyphae angioinvasion) in association with traumatic wounds. As part of the process to identify patients for inclusion, histopathology (reviewed by two surgical pathologists) and clinical mycology reports were evaluated. Moreover, records from the infectious disease and trauma surgery services were examined.

Clinical Definitions and Data Collection

Based upon histopathological and/or culture evidence of mold, patients were identified for inclusion in the study population and then stratified by clinical wound appearance after two initial debridements (with/without recurrent necrosis). The DoD Trauma Registry[3] was utilized to obtain trauma and inpatient data for the subjects included in the subset. Mycological data were collected using the supplemental TIDOS infectious disease module. Operative notes from the U.S. MTFs were retrospectively reviewed for evidence of recurrent necrosis on successive debridements. The study was approved by the Infectious Diseases Institutional Review Board of the Uniformed Services University of the Health Sciences (Bethesda, MD).

Statistical Analysis

A prior analysis compared patients with histopathological evidence of mold to those with culture evidence of mold (all with recurrent wound necrosis) and did not find many significant differences in clinical characteristics or outcomes; therefore, these two groups were combined for the current analysis and were compared to patients with culture evidence of mold without recurrent wound necrosis.[13] Categorical variables were compared using Chi-square or Fisher's exact testing. When appropriate, exact nonparametric testing (t-test or Wilcoxon Rank Sum test) for continuous variables was conducted. Statistical analysis was performed using SAS® version 9.3 (SAS, Cary, NC) and R® version 2.13.2 (R Project for Statistical Computing, Vienna, Austria) and significance was defined as $p<0.05$.

Results

Patient Demographics and Injury Patterns

An examination of data from 1133 combat casualties identified 96 patients with fungal growth from wounds and/or fungal elements on histopathology, of which there were 77 (6.8% of 1133) patients with recurrent wound necrosis following at least two successive surgical debridements. The remaining 19 patients had fungal culture growth without associated fungal elements on histopathology and did not have recurrent wound necrosis, representing a convenience sample for comparison based upon available data. All subjects were male with a median age of 23 and were predominantly Marines. There was no significant difference ($p=1.00$) regarding mechanism of injury between the groups with approximately 95% of injuries resulting from blasts and over 89% occurring while dismounted. Injury pattern was also comparable with 38% and 53% of patients with and without recurrent wound necrosis, respectively, involving traumatic above the knee amputations ($p=0.30$).

Clinical Characteristics

An examination of shock indices and clinical characteristics (Table 1) assessed at combat support hospitals, LRMC, and the U.S. MTFs largely reported similar results between the groups. One difference was that upon presentation to combat support hospitals, patients with wounds that were eventually complicated by recurrent necrosis were significantly more hypotensive (median systolic blood pressure: 99 versus 130; $p=0.02$) and acidotic (median pH: 7.2 versus 7.3; $p=0.03$) compared to patients without recurrent necrosis. Due to severe hemorrhage at the time of injury, large-volume blood product transfusions were required during the initial 24 hours of care with no statistical difference between the patient groups. On admission to LRMC, both groups had a median injury severity score of 21; however, the overall median sequential organ failure assessment score was higher, although not statistically significant, for the patients who developed recurrently necrotic wounds (Table 1). Indicators of an infection (elevated white blood cell count and temperatures) were comparable between the groups at LRMC (approximately two days of hospitalization), but were statistically increased among patients with recurrent necrosis following transition to the U.S. MTFs during the first two weeks of hospitalization ($p<0.05$).

Wound Mycology

By definition, all of the patients in the group without recurrent necrosis had fungal growth, whereas only 78% of patients with recurrent wound necrosis grew mold (remainder had fungal elements seen on histopathology). The proportion of *Mucorales* growth was comparable between the groups; however, patients without recurrent necrosis had significantly more growth of *Aspergillus* at LRMC ($p=0.03$; Table 2).

Invasive Fungal Infection Management

Only 16% of subjects without recurrent necrosis were prescribed antifungal therapy compared to 84% of patients with recurrently necrotic wounds ($p<0.01$; Table 3). Patients without recurrent necrosis who were prescribed amphotericin B (liposomal) also received it

for a significantly shorter duration compared to subjects with recurrent wound necrosis (p=0.01). In addition, the number of operating room visits for surgical debridements was increased (p=0.02) among patients with recurrently necrotic wounds.

Clinical Outcomes

Patients with recurrent wound necrosis had a significant increase in the total time spent in the intensive care unit (ICU; p<0.01; Table 3). Moreover, there were a greater number of patients who sustained high-level amputations (i.e., total hip disarticulation or hemipelvectomy) within the group with recurrently necrotic wounds, but the increase was not statistically significant. Although there were no deaths within the group without recurrent wound necrosis and six (7.8%) among the patients with recurrently necrotic wounds, the overall difference in crude mortality between the groups was not statistically significant.

Discussion

Although not as common as bacterial infections, IFI have significant impact on the morbidity and mortality of wounded military personnel.[4,11-14] Due to the progressive and serious nature of trauma-related IFI, there is general agreement that early diagnosis, aggressive serial debridement, minimization of immunosuppression, and treatment with systemic antifungal therapy comprise the soundest strategy for management of this disease.[4,7,8,14-16] The clinical significance of cultures growing mold without the clinical stigmata of IFI presents challenges in determining the appropriate management. While we recognize the critical need for early empiric antifungal therapy to properly manage IFI, treatment should be based upon clinical indicators of the disease in order to avoid the unnecessary use of intravenous antifungals as they may result in nephrotoxicity and hepatotoxicity. Consequently, the aim of this study was to compare injury patterns, baseline clinical characteristics, clinical mycology, treatment modalities, and outcomes among patients with confirmed IFI[4,11,12] to those with wound cultures growing mold without associated recurrent tissue necrosis.

The groups were not significantly different regarding mechanisms and patterns of injury, along with most clinical characteristics. Therefore, it was reasonable to assume that the patients in both groups were at risk for developing IFI, particularly since dismounted blast injuries and above the knee amputations are recognized risk factors for the disease.[12] Although the clinical relevance is not definitively known, patients who developed recurrent wound necrosis were statistically more hypotensive and acidotic upon initial presentation suggesting wounds complicated by more severe exsanguinating hemorrhage. Once the patients were admitted to U.S. MTFs following their short hospitalization at LRMC, clinical courses diverged as patients with recurrently necrotic wounds presented with indicators consistent with an infection (i.e., more febrile and leukocytosis).

In general, patients with recurrent wound necrosis did have significantly longer lengths of stay in the ICU and a greater number of operating room visitations. While no deaths were reported in the group without recurrent necrosis, there were six among the cases with recurrently necrotic wounds. This may be in part due to the limitation of having a relatively

small retrospective comparison group (19 patients without recurrent wound necrosis), which was a convenience sample.

The predominant fungal isolates identified among both groups were *Mucorales* and *Aspergillus*. While *Aspergillus* is known to be associated with contamination,[14,17] *Mucorales* is not.[18] Of the group without recurrent wound necrosis, 11% grew *Mucorales* and all were treated with antifungal medications; however, the medications were stopped typically by five days. Use of antifungal agents (notably liposomal amphotericin B) in this situation may reflect the practice of many clinicians placing a higher relevance on a wound culture yielding *Mucorales*. In our opinion, this practice is justified based on the known potential of this pathogen to cause locally invasive IFI with high morbidity and mortality. While not statistically significant, patients with *Mucorales* growth from a wound culture in our analysis were much more likely to have recurrent wound necrosis.

Overall, our analysis indicates that clinicians from LRMC and the participating U.S. MTFs demonstrated antimicrobial stewardship based upon the fact that very few subjects (three patients, 16%) without recurrent wound necrosis received antifungal therapy and, if they did, it was discontinued after short durations. This group of patients was not negatively impacted because of the lack of antimicrobial therapy, as evidenced by reduced length of ICU stay, fewer high-level amputations, and zero mortality, suggesting the patients did not have an IFI.

In summary, our data corroborate the supposition that the presence of fungal growth without recurrent necrosis does not support an IFI diagnosis, nor does it constitute a need for antifungal therapy. In order to optimize the care of trauma patients, a clinician must consider the whole clinical picture (e.g., injury mechanism/pattern that are recognized risk factors,[12] recurrent wound necrosis, extent of leukocytosis, and temperature elevation) supplemented by tissue histopathology in order to conclude that fungal growth in wound tissue is the result of colonization rather than IFI.

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Table 1

Median (IQR) Clinical Characteristics among U.S. Military Personnel Injured in Combat (2009-2011) with Wound Cultures Showing Fungal Growth

Clinical Parameters	Wounds with Recurrent Necrosis[a] (N = 77)	Wounds without Recurrent Necrosis (N = 19)	p-value
In Theater Shock Indices (combat support hospital)			
Heart Rate	125 (103, 140)	135 (110, 153)	0.22
Systolic blood pressure	99 (80.0, 123)	130 (103, 147)	0.02
Blood gas – base deficit	9 (13, 4)	5 (7, 3)	0.07
Blood gas – pH	7.2 (7.1, 7.3)	7.3 (7.3, 7.3)	0.03
Blood Product Requirements in Theater (1st 24 hours)			
Packed red blood cells + whole blood	30 (17, 42)	25 (14, 33)	0.16
Fresh frozen plasma + whole blood	29 (18, 40)	27 (12, 31)	0.07
LRMC			
Maximal WBC count (10^9 cells/L)	11 (7, 14)	11 (7, 12)	0.88
Maximal temperature (°C)	39 (39, 40)	39 (39, 39)	0.47
ISS	21 (17, 26)	21 (14, 21)	0.22
SOFA score	7 (4, 10)	5 (4, 7)	0.05
U.S. MTF			
Maximal WBC count - 1st week (10^9 cells/L)	22 (15, 31)	15 (13, 20)	0.01
Maximal temperature - 1st week (°C)	39 (39, 40)	39 (39, 39)	0.02
Maximal WBC count - 2nd week (10^9 cells/L)	27 (19, 34)	15 (11, 24)	<0.01
Maximal temperature - 2nd week (°C)	39 (39, 39)	38 (38, 39)	0.01
SOFA score	5 (1, 8)	3 (2, 4)	0.28

IQR - Interquartile Range; ISS - Injury Severity Score; LRMC - Landstuhl Regional Medical Center; MTF - Military Treatment Facility; SOFA - Sequential Organ Failure Assessment; WBC - White Blood Cell

[a] Patients met the invasive fungal wound infection case definition[4]

Table 2

Mycology Culture Results by Clinical Wound Appearance, No. (%), Following Combat-Related Injuries, 2009-2011

	Wounds with Recurrent Necrosis[a] (N=77)	Wounds without Recurrent Necrosis (N=19)	p-value
Patients with wound cultures at LRMC	44 (57.1)	15 (78.9)	0.11
Patients with wound cultures positive for mold[b,c]	28 (63.6)	14 (93.3)	0.05
Mucorales	4 (9.1)	0	0.56
Aspergillus	11 (25.0)	9 (60.0)	0.03
Other non-*Mucorales* organisms[d]	13 (29.6)	5 (33.3)	0.76
Mucorales and non-*Mucorales* organisms	2 (4.5)	0	1.00
No fungal organisms	16 (36.4)	1 (6.7)	0.05
Patients with wound cultures at U.S. MTFs	72 (93.5)	14 (73.7)	0.02
Patients with wound cultures positive for mold[b,c]	45 (62.5)	5 (35.7)	0.72
Mucorales	23 (31.9)	2 (14.3)	0.33
Aspergillus	16 (22.2)	2 (14.3)	0.51
Other non-*Mucorales* organisms[d]	11 (15.3)	1 (7.1)	0.68
Mucorales and non-*Mucorales* organisms	14 (19.4)	0	0.11
No fungal organisms	27 (37.5)	9 (64.3)	0.08

LRMC – Landstuhl Regional Medical Center; MTFs – military treatment facilities

[a] Patients met the invasive fungal wound infection case definition[4]

[b] Percentages are based upon the number of patients who had a wound culture

[c] Wound cultures commonly grew more than one fungal organism; therefore, the column data total more than the number of cases with positive wound cultures

[d] Growth of non-*Mucorales* organisms other than *Aspergillus*

Table 3

Management and Clinical Outcomes among U.S. Military Personnel Injured in Combat (2009-2011) with Wound Cultures with Fungal Growth

	Wounds with Recurrent Necrosis[a] (N = 77)	Wounds without Recurrent Necrosis (N = 19)	p-value
Surgical Debridements, median (IQR)			
Overall OR visits	15 (9, 18)	8 (7, 12)	0.02
IFI Antifungal Treatment Regimen, No. (%)			
Received treatment	65 (84.4)	3 (15.8)	<0.01
Systemic Antifungal Agents, No. (%)			<0.01
Amphotericin B (liposomal) alone	5 (6.5)	1 (5.3)	
Voriconazole alone	4 (5.2)	0	
Amphotericin B plus Voriconazole	55 (71.4)	2 (10.5)	
Antifungal Duration, median days (IQR)			
Amphotericin B (liposomal)	21 (12, 30)	4 (2, 6)	0.01
Voriconazole	17 (9, 26)	15 (11, 18)	0.78
Total antifungal treatment	18 (7, 29)	4 (3, 14)	0.18
Hospitalization, median (IQR)[b]			
Total duration in ICU (days)	11 (6, 20)	4 (3, 6)	<0.01
High-level amputations[c], No. (%)	15 (19.5)	1 (5.3)	0.18
Deaths, No. (%)	6 (7.8)	0	0.60

ICU - Intensive Care Unit; IFI – invasive fungal wound infections; IQR - Interquartile Range; OR - Operating Room

[a] Patients met IFI case definition[4]

[b] Data are from both Landstuhl Regional Medical Center (Germany) and U.S. military treatment facilities

[c] High-level amputations are defined as total hip disarticulation or hemipelvectomy