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Contribution of bacterial and viral infections to attributable mortality in patients with severe burns: An autopsy series☆

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ABSTRACT

Bacterial infections are a common cause of mortality in burn patients and viral infections, notably herpes simplex virus (HSV) and cytomegalovirus (CMV) have also been associated with mortality. This study is a retrospective review of all autopsy reports from patients with severe thermal burns treated at the US Army Institute of Research (USAISR) burn unit over 12 years. The review focused on those patients with death attributed to a bacterial or viral cause by autopsy report. Of 3751 admissions, 228 patients died with 97 undergoing autopsy. Death was attributed to bacteria for 27 patients and to virus for 5 patients. Bacterial pathogens associated with mortality included *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae* and *Staphylococcus aureus*. This association with mortality was independent of % total body surface area burn, % full thickness burn, inhalation injury, and day of death post burn. Bloodstream infection was the most common cause of bacteria related death (50%), followed by pneumonia (44%) and wound infection (6%). Time to death following burn was ≤7 days in 30%, ≤14 days in 59% and ≤21 days in 67%. All of the viral infections associated with mortality involved the lower respiratory tract, HSV for 4 and CMV for 1. Four of these 5 patients had evidence of inhalation injury by bronchoscopy, all had facial and neck burns, and 2 had concomitant *Staphylococcus* pneumonia. Time to death following burn ranged from 14 to 42 days for the 5 patients. Despite advances in care, gram negative bacterial infections and infection with *S. aureus* remain the most common cause of bacteria related mortality early in the hospital course. Viral infections are also associated with mortality and numbers have remained stable when compared to data from prior years.

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1. Introduction

According to the American Burn Association (ABA), roughly 500,000 patients with burn injuries seek medical attention in the US each year. Approximately 40,000 of those who seek medical care require hospitalization and over 60% of those hospitalized require intensive care in a specialized burn center [1]. Once hospitalized, multiple organ system failure as a result of burn related shock is the most frequent cause of death in the first 24 48 h [2]. Following adequate burn shock resuscitation, infection emerges as the leading cause of death in these patients. Six of the top ten complications in a 10 year (1998 2007) rolling review by the ABA of persons suffering fire/flame injury injuries (13,666 complications) were infectious: 4.6% of patients having pneumonia, 2.7% septicemia, 2.6% cellulitis/traumatic injury, 2.5% respiratory failure, 2.2% wound infection, 2.0% other infection, 1.5% renal failure, 1.4% line infection, 1.2% acute respiratory distress syndrome and 1.0% arrhythmia (www.ameriburn.org/2007NBRAnnualReport.pdf, accessed 25 May 2008).

Historically, bacterial pathogens have been the most common cause of infections in burn patients and wound infections a common clinical manifestation. However, the widespread use of topical anti microbials has resulted in the decline, though not the elimination, of bacterial wound infections [3]. In addition to wound infection, bacterial pneumonia and bloodstream infection are often cited as leading causes of mortality in burn patients, though specific data are limited [3]. It is also recognized that fungal infections are associated with poor outcome and a recent review at this institution over a 12 year period revealed that 14 of 97 patients undergoing autopsy had fungus identified as an attributable cause of death [4]. In addition to infections caused by bacteria and fungi, there are data implicating viral infections as a cause of death among severely burned patients. An autopsy study from this institution in 1970 documented 14 burn patients with herpes simplex virus (HSV) infection; a 10% rate. Disseminated herpes likely contributed to mortality in only 2 of these patients [5]. A recent evaluation of cytomegalovirus (CMV) reactivation in critically ill patients, of which 20 were burn patients, revealed serum CMV viral loads were greater than 10,000 copies/ml in 4 of the 20 burn patients; however, the presence of CMV associated disease was not reported and the contribution of this virus to mortality in burn patients remains unknown [6]. This current study is a retrospective review of an autopsy series designed to describe and evaluate the mortality attributable to bacterial and viral infections in patients with severe burns admitted to the US Army Institute of Surgical Research (USAISR) over a 12 year period.

2. Methods

This is a retrospective medical records review of all autopsy reports from patients with severe burns treated at the USAISR burn unit from February 1991 November 2003. The USAISR burn center is a 40 bed intensive care unit (ICU) dedicated to the care of burn patients within the Department of Defense and local civilian population. In 1996 Brooke Army Medical Center (BAMC) and the USAISR Burn Unit relocated to a new facility with modern infection control measures such as dedicated anterooms. During the entire study period burn patient care consisted of resuscitation and stabilization upon arrival with early wound excision and skin grafting. There was a gradual shift toward earlier and more complete burn wound excision throughout the period studied. Topical antibiotic creams, specifically mafenide acetate and silver sulfadiazine, were routinely utilized. Aggressive infection control practices included contact isolation and strictly enforced hand hygiene practices. In addition, a protocol was in place to ensure that central lines were changed to a new site every 3 days and arterial lines were changed to a new site every 7 days during the period studied.

Only patients with thermal burns who underwent autopsy were included in the analysis. Autopsy was routinely performed for all active duty military personnel. Non military patients underwent autopsy at the discretion of their family. Death was attributed to bacterial or viral infection if the infection was determined to be the primary cause of death rather than simply an association. All autopsies and cause of death determinations were performed by a single experienced burn pathologist (SHK). For death attributed to a bacterial bloodstream infection, the pathologist required the presence of a positive pre mortem blood culture in conjunction with a clinical course consistent with sepsis. Death was attributed to pneumonia if patient had a clinical course consistent with pneumonia and had organisms cultured from bronchioalveolar lavage or respiratory specimens obtained at autopsy. There were no changes in the protocol with regard to performance of bronchoscopy and/or bronchioalveolar lavage during the period studied. Wound infection was defined by the pathologist according to histopathologic criteria that differentiates wound colonization from wound infection based upon the location of the microorganism within the wound (Table 1). The pathologist defined wound infection as histopathologic classification Stage II, Grades A C. In the case of death attributed to a viral etiology, Hematoxylin and Eosin (H&E) staining was primarily used, looking for typical histologic changes. Immunohistochemical staining supported the diagnosis in some cases. Data obtained included age, gender, inhalation injury, % total body surface area (TBSA) burn, % full thickness burn (FTB), days to death after burn, autopsy culture results, and cause of death as determined by autopsy.

Non parametric values were analyzed using the Wilcoxon test and parametric values were analyzed using the Student's

Table 1 – Classification of burn wound colonization and infection.

Stage	Grade
I.	A. Microbes present on eschar surface B. Microbes present throughout eschar C. Microbes multiplying beneath eschar
II.	A. Foci of microbes in viable tissue immediately beneath eschar B. Multifocal or diffuse penetration of microbes into viable tissue C. Microbes present in unburned blood vessels and lymphatics

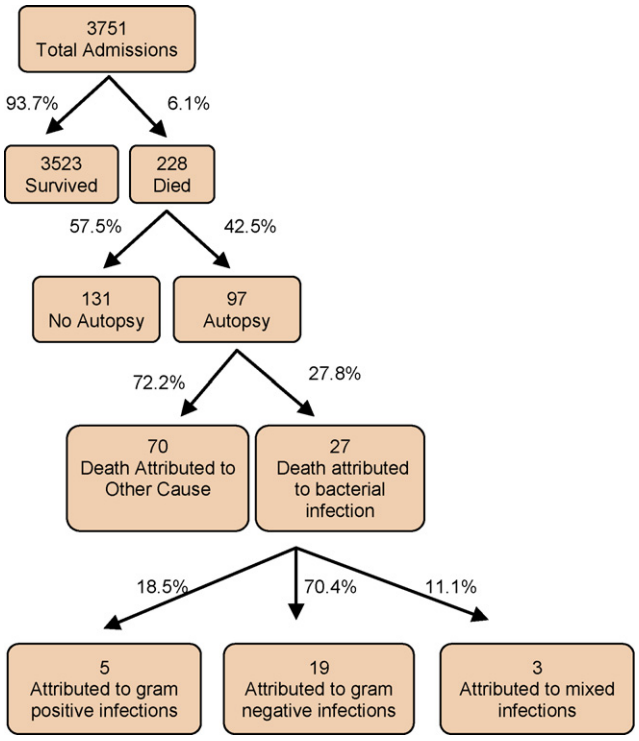

Fig. 1 – Mortality attributed to bacterial infection in autopsied patients over a 12-year period (February 1991–November 2003).

T test. Analysis included comparing before and after the 1996 move, but these two periods were not associated with any significant findings. This study was approved by the Institu tional Review Board of BAMC and the USAISR.

3. Results

3.1. *Bacteria related mortality*

There were 3751 patients admitted to the burn unit during the study period, of whom 228 (6.1%) died, with autopsies performed on 97 (42.5%) (Fig. 1). Death was attributed to a bacterial cause in 27 (27.8%) (Table 2). There was no statistically significant difference with regard to age, % TBSA, % FTB, presence of inhalation injury, and day of death after burn between patients with death attributed to a non bacterial cause and those with death due to a bacterial cause (Table 3). In those patients with death attributed to a bacterial cause, several organisms were found to have an association with mortality (Table 4). The gram negative organisms with attributable mortality were *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Escherichia coli*. Infection with *Acinetobacter baumannii* was not associated with mortality although there was only 1 case in this series. *Staphylococcus aureus* was the only gram positive organism statistically associated with mortality. Although wound infections continued to occur, bloodstream infection was the most common cause of death followed by pneumonia (Table 5). The majority of bloodstream infections were due to gram negative organisms (78.9%). Of those gram negative organisms responsible for bacteremia, *P. aeruginosa* was the most common etiology (50%). The majority of the gram positive bloodstream infections were due to *S. aureus*. The origin of the bacteremia is difficult to ascertain. Three of the sixteen bacteremic patients had concurrent pneumonia and one had a concurrent wound infection with the same organism. The source of bacteremia for the remaining 13 patients remains unknown. Central venous catheters (CVC) are a potential, though unlikely, source given the unit policy of changing central lines every 3 days. Pneumonia is also a consideration but would have been detected on autopsy. Undetected wound infection is a more likely explanation given the strict definition for wound infection utilized during the study. In addition, open wounds likely serve as a portal of entry for organisms even in the absence of overt clinical or histopathological wound infection.

Gram negative organisms also led the way as the etiologic agents for pneumonia (62.5%) whereas *S. aureus* accounted for the remainder (37.5%). Of those gram negative organisms responsible for pneumonia, *P. aeruginosa* was the most common (40.0%). Only two wound infections were diagnosed on autopsy and both were attributed to *P. aeruginosa*. Time to death following burn was $\leq$7days in 30%, $\leq$14 days in 59% and $\leq$21 days in 67% of patients with a bacterial cause of death.

3.2. *Virus related mortality*

Of the 97 autopsies performed, death was attributed to a viral cause in 5 (5.2%). Four (4.1%) patients had HSV involvement of the lower respiratory tract, while 1 (1.0%) patient was diagnosed as having CMV pneumonia (Table 6). Four of the five patients had evidence of inhalation injury and acute respiratory distress syndrome (ARDS) and all patients had burns of the face or neck and all were intubated. Survival after burn ranged from 14 to 42 days. In all cases, the diagnosis of viral infection was not made until autopsy. Skin lesions suggestive of infection were not documented pre mortem for any of the patients.

3.3. *Pre-relocation and post-relocation analysis*

As previously noted, the burn unit relocated to a new facility with a modern infection control infrastructure in 1996. Of the 97 autopsies performed, 32 (32.9%) were for patients who received care prior to the 1996 relocation. Of the 27 patients with death due to a bacterial cause, only 6 (22.2%) were treated prior to the 1996 relocation. There was no statistically relevant difference in death due to a bacterial cause detected between the pre and post relocation data. However, the small number of autopsied patients who received care in the older facility is a significant limitation in the accurate analysis of the data. The analysis was not performed for the 5 patients with death due to a viral cause as HSV and CMV are not classically acquired through nosocomial transmission.

4. Discussion

Advances in burn shock resuscitation, ventilatory strategies, nutritional support, infection control practices and the use of

Table 2 – Characteristics of the 27 patients with bacteria noted as an attributable cause of death.

Age	Gender	% TBSA	% FTB	Inhalation injury	Time from burn to death (days)	Bacteria	Site of involvement
60	F	29.5	0	No	7	*P. aeruginsosa*	BSI
23	M	14	0	Yes	10	*S. aureus*	BSI, PNA
47	M	10	0	No	10	*P. aeruginsosa*	BSI
45	M	23	0	No	5	*S. aureus*	PNA
29	F	41	8	No	9	*E. coli*	BSI, PNA
22	M	36	5.5	No	35	*S. marcescens*	PNA
61	M	31.3	3	No	26	*Enterococcus sp.*	BSI
						A. baumannni	BSI
95	F	16.5	0	No	10	*P. aeruginsosa*	BSI
29	M	65.5	65.5	Yes	69	*P. aeruginsosa*	BSI, PNA
46	M	80.5	69.5	No	18	*P. aeruginsosa*	BSI
46	M	71	10	No	52	*P. aeruginsosa*	PNA
38	M	86	83.8	No	42	*P. aeruginsosa*	BSI
43	M	53.5	25.5	Yes	7	*K. pneumonia*	PNA
65	M	62.5	62	No	66	*P. aeruginsosa*	BSI, WI
50	M	53	47	Yes	14	*S. aureus*	PNA, BSI
						S.marcescens	PNA
21	M	71.5	68.5	Yes	4	*P. aeruginsosa*	BSI
18	M	75.3	74.5	No	19	*E. coli*	BSI
65	M	28.8	21.5	No	25	*P. aeruginsosa*	PNA
						S. aureus	BSI, PNA
24	M	70.5	57	No	11	*E. aerogenes*	BSI
38	M	97	85	No	89	*S. aureus*	BSI
55	F	8	0	No	47	*E. coli*	BSI
53	F	34	31.5	No	13	*S. aureus*	PNA
43	M	41.3	39.5	Yes	5	*E. coli*	PNA
75	M	2	0	Yes	5	*K. pneumoniae*	PNA
57	M	81	72	Yes	4	*S. aureus*	PNA
2	F	81	74	No	14	*P. aeruginosa*	PNA, WI
11	F	43	33	Yes	5	*K. pneumonia*	BSI

BSI: bloodstream infection; PNA: pneumonia; WI: wound infection.

prompt burn wound excision have led to improved morbidity and mortality in patients who suffer severe burns [7 12]. Infections are a leading cause of mortality (up to 75% of cases) if patients survive the initial burn and resuscitative period [9,13 17]. Infection precedes multiple organ dysfunction by a median of 4 days, with increasing mortality based upon the severity of sepsis [13]. Sites of infection are primarily the bloodstream, lungs, wound, and urinary tract with either lung or wound being the most common depending upon the diagnostic definitions used [13,18 21]. The role of viral infections is not clearly elucidated in patients with burns. The mode of acquisition of CMV, HSV and varicella zoster virus includes reactivation or primary infection though the relative frequency is undetermined [22]. The pre mortem diagnosis of viral infections remains a challenge and may result in the underestimation of viral induced morbidity and mortality in burn patients. In this review of attributable mortality in patients with severe burns, we noted that bacteria were a cause of death in 28% of 97 autopsy cases and viruses in 5%.

The primary bacteria responsible for death in this series were *P. aeruginosa*, followed by *S. aurues*, *E. coli*, and *K. pneumoniae*. Bloodstream infection was the most common cause of bacteria related death (50%), followed by pneumonia (44%) and wound infection (6%). The origin of bacteremia could not be determined though undiagnosed wound infection or

Table 3 – Demographics of patients with attributable mortality from bacterial and non-bacterial causes.

	Mortality attributable to bacteria	Mortality attributable to other causes	P value
Total #	27	70	
Age (year)	45 (2 95)	51 (2 91)	0.052
% Male	74	71	0.079
% Total body surface area (TBSA)	43 (2 81)	59 (1 96)	0.272
% Full thickness burn	32 (0 84)	38 (0 91.5)	0.384
# Days from injury to death	14 (4 89)	14 (1 124)	0.444
% Inhalational injury	33	24	0.379

Median (range).

Table 4 – Organisms associated with mortality due to bacterial infection.

Bacteria	Numbers[a]
Gram negative organisms	21
Pseudomonas aeruginosa	10 (34.5%)*
Escherichia coli	4 (13.8%)*
Klebsiella pneumoniae	3 (10.3%)*
Enterobacter spp.	2 (6.9%)
Serratia marcescens	1 (3.4%)
Acinetobacter spp.	1 (3.4%)
Gram positive organisms	8
Staphylococcus aureus	7 (24.2%)*
Enterococcus faecalis	1 (3.4%)

% is reflective of total number of isolates.
[a] Number of organisms exceeds number of patients as some patients had mixed infections.
* $P < 0.05$ for organism as an independent cause of mortality.

simply the presence of open wounds that enable bacterial invasion are the most likely sources. Death due to bacteria occurred in less than 21 days in 67% of cases in contrast to fungus in which death typically occurred after 28 days [4]. The relative importance of the identified pathogens appears to be evolving with time. A recent retrospective study performed in this burn unit found that *P. aeruginosa*, *K. pneumonia*, *A. baumannii*, and *S. aureus* are the most common cause of bacteremia in burn patients after 2003 [23]. This study noted *K. pneumonia* to be significantly associated with mortality and, in contrast to our study, *P. aeruginosa* was not. A separate study, also performed after 2003, found *A. baumannii* to be a common cause of infection in burn patients, though this was not associated with attributable mortality [24]. In contrast, our review identified only one infection with *A. baumannii*. The differences may be partially explained by the fact that the autopsy data from this study pre dates the data from the two recent retrospective studies noted above. It is therefore, not inclusive of the time period associated with combat opera tions currently underway in Iraq and Afghanistan.

This study also demonstrates that bacteremia and bacterial pneumonia are a more common cause of death than bacterial wound infections. The systematic use of topical anti micro bials coupled with early excision and grafting may explain the relative decline in bacterial wound infection [25,26]. In addition, the utilization of strict histopathologic definition for wound infection may underestimate the true occurrence. The prominence of bacterial bloodstream infection and pneumonia as causes of death indicates a need to focus on the prevention of these infections. The factors that have been reported to decrease the risk of bloodstream infection in critically ill, non burn patients include tight control of blood glucose as well as the use of enteral nutrition over parenteral nutrition [27]. Modifiable factors that have been found to decrease the risk of pneumonia in critically ill, non burn patients include maintaining head of bed elevation >30 45°, continuous sub glottic suctioning of secretions and the use of daily interruptions in sedation in order to avoid prolonged, heavy sedation which may result in depression of cough reflex [27,28]. The role for these interventions in the burn patient population has not been critically examined and warrant further investigation.

As previously noted, BAMC and the USAISR burn unit relocated to a new facility with a modern infection control infrastructure in 1996. It seems reasonable to assume that these environmental changes would have a positive impact on the incidence of nosocomial bacterial infections. Analysis of the data revealed no statistically relevant difference in the number of deaths attributed to bacterial pathogens though the total number of patients evaluated was likely insufficient to detect a difference if one actually existed. Interestingly, a previous study found no difference in the incidence of methicillin resistant *S. aureus* colonization of hospitalized patients before and after the 1996 relocation [29]. However, the study included medical and surgical wards and intensive care units but not the USAISR burn unit.

The effect of viral infections on the morbidity and mortality of burn patients is unresolved. Clearly viral agents have the potential to cause end organ disease, as evidenced by the 5 patients with death attributed to CMV or HSV in this review, and the early diagnosis of CMV and HSV infection is challenging. It is possible to detect CMV and HSV reactivation

Table 5 – Organisms associated with specific clinical diagnoses.

	Bloodstream infection	Pneumonia	Wound infection
# of isolates (# of patients)[a]	19 (16)	16 (14)	2 (2)
Gram negative organisms	15	10	2
Pseudomonas aeruginosa	8 (42.1%)*	4 (25.0%)*	2 (100%)
Escherichia coli	3 (15.7%)*	2 (12.5%)	0
Klebsiella pneumoniae	1 (5.3%)	2 (12.5%)	0
Enterobacter spp.	1 (5.3%)	0	0
Serratia marcescens	1 (5.3%)	2 (12.5%)	0
Acinetobacter spp.	1 (5.3%)	0	0
Gram positive organisms	4	6	0
Staphylococcus aureus	3 (15.7%)*	6 (37.5%)*	0
Enterococcus faecalis	1 (5.3%)	0	0

% is reflective of total number of isolates per clinical diagnosis.
[a] Number of organisms exceeds number of patients as some organisms were associated with infections at multiple sites in a single patient.
* $P < 0.05$ for association between organism and clinical diagnosis.

Table 6 – Characteristics of the 5 patients with virus noted as an attributable cause of death.

Age	Gender	% TBSA	Head and neck burn	Inhalational injury	Intubated	Time from burn to death (days)	ARDS	Virus	Site of viral involvement	Bacterial pneumonia on autopsy
27	F	60	Yes	Yes	Yes	25	Yes	HSV	Tracheobronchitis, bilateral interstitial pneumonia, esophagitis	No
32	F	43	Yes	Yes	Yes	23	Yes	HSV	Skin, necrotizing viral tracheobronchitis, bilateral lower lobe pneumonia, esophagitis, vaginitis, endometritis	No
50	M	53	Yes	Yes	Yes	14	No	HSV	Necrotizing tracheobronchitis, bilateral pneumonia	Staphylococcus
88	M	35	Yes	No	Yes	13	Yes	HSV	Skin (perioral and anterior neck), necrotizing traceobronchitis, pneumonia	No
72	M	53	Yes	Yes	Yes	42	Yes	CMV	Tracheobronchitis, pneumonia	Staphylococcus

through the use of molecular techniques and viral culture. However, it is unclear if detection of virus in clinical samples is simply a marker of critical illness and its associated immunosuppression or a prelude to clinical disease. A recent evaluation of cytomegalovirus reactivation in critically ill patients included 20 burn patients [6]. CMV reactivation was determined by PCR based detection of virus in serum. The study found an association between CMV reactivation and prolonged length of stay or death. This association occurred in the absence of CMV disease and there is currently insufficient evidence to recommend routine antiviral prophylaxis or treatment of critically ill patients with a detectable CMV viral load. HSV disease in burn patients has been previously described. HSV involvement of the middle and lower respira tory tract was first reported in 1949 [30]. HSV disease was described by the USAISR in 1970 with a rate of 10%, however, death was attributed to HSV alone in only 2 of the 14 patients [5]. Another autopsy study conducted by Nash in a general population showed the prevalence of herpes tracheobron chitis and bronchopneumonia to be 1% (possibly contributing to death in 3 of 10 patients) [31]. Only 5 of the 10 patients evaluated had burns and the impact of viral infection as a cause of death was not documented. Isolating HSV from critically ill patients, to include burn patients, may be more common than originally thought given that another study notes HSV to be the most frequently isolated organism from the lungs of patients with severe respiratory distress [32]. HSV was more common in patients with burns (7 of 15, 47%). However, autopsy performed on 7 patients with HSV found only 1 with histologic changes suggesting active disease [32]. Overall, the number of cases of HSV or CMV disease diagnosed in patients with severe burns is still somewhat limited, and it is still unclear how they contribute to the overall mortality. The clinical picture is further complicated by the ability to detect these agents in clinical samples in the absence of demonstrable disease. The impact of CMV and HSV reactiva tion in this patient population is unclear. Further studies correlating reactivation of CMV and HSV with invasive disease and examining the role of antiviral therapy or prophylaxis are needed.

This study revealed the ongoing impact of bacterial infections leading to death even during the early days after burn, with the common sources being bloodstream infections and pneumonia primarily with gram negative bacteria, notable *P. aeruginosa*, and *S. aureus*. This occurs even in an era of enhanced infection control, aggressive excision of burned skin, and broad spectrum antimicrobial agents. Continued improvements in the care of burn patients to mitigate the impact of bacterial infections leading to death needs to be undertaken. It appears that viruses might have a direct impact on mortality, especially in the middle and lower respiratory tract, but continued evaluation of their role in immune modulation must be undertaken and their direct impact on outcomes with better diagnostic strategies needs to be defined.

Conflict of interest statement

No conflicts for any of the authors.

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