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Recurrent bacteremia: A 10-year retrospective study in combat-related burn casualties

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ABSTRACT

Introduction: Surviving the first episode of bacteremia predisposes burn casualties to its recurrence. Herein, we investigate the incidence, mortality, bacteriology, and source of infection of recurrent bacteremia in military burn casualties admitted to the U.S. Army Institute of Surgical Research Burn Center over a 10year period.

Methods: Bacteremia was defined as the growth of Gram-positive or Gram-negative organisms in a blood culture that excluded probable skin contaminants. Recurrent bacteremia was defined as a subsequent episode of bacteremia ≥7 days after the first episode. Polymicrobial bacteremia was the presence of more than one pathogen in the same blood culture. Bacteremia was attributed to UTI, pneumonia, or wound sepsis. All other bacteremias were considered non-attributable bloodstream infections. Univariate and multivariate analyses determined factors predictive of clinical outcome.

Results: Out of 952 combat-related burn casualties screened, 166 cases were identified; 63% (non-recurrent) and 37% (recurrent) with median time to recurrence of 20 days. Univariate and multivariate analysis showed that the mortality rate was two and nine-fold, respectively, higher with recurrent bacteremia. Univariate analysis found that except for urinary tract infection, large burn size (>20%), 3rd degree burns, increased injury severity, perineal burns, and mechanical ventilator days were independent factors predictive of recurrence of bacteremia as well as increased mortality in the recurrent bacteremia cohort. *Acinetobacter baumannii* complex (63%) was prevalent in the non-recurrent group, while *Klebsiella pneumoniae* (46% vs. 30%) and *Pseudomonas aeruginosa* (35% vs. 26%) were prevalent in recurrent bacteremia. Half of the recurrent bacteremia cases were polymicrobial, compared to 9% in non-recurrent bacteremia. Pneumonia was prevalent in non-recurrent bacteremia (38%) and a combination of pneumonia and wound sepsis (29%) in recurrent bacteremia casualties.

Conclusions: Recurrent bacteremia increases mortality in military burn casualties. Additional research is needed to address and mitigate the underlying causes, thereby improving survival.

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1. Introduction

The frequent use of improvised explosive devices in recent U.S. conflicts has led to severe tissue damage and perineal burn injuries of combat casualties [1]. Advances in Tactical Combat Casualty Care including rapid evacuation of combat casualties from point of injury to Role 2 facilities (Forward Surgical Hospital) have increased survival rates. That is to say, the mortality rate of casualties who otherwise would have deemed "killed in action" has decreased suggesting a reciprocity between "killed in action" and "died of wounds" rates [2]. Although reduced mortality rates are encouraging, they are often accompanied by concomitant increase in co-morbidities, the treatment of which is cumbersome and expensive.

Burn injuries break down the skin barrier allowing for colonization of burn wounds with microorganisms. With increasing time from injury, evacuation along echelons of care, and exposure to local environmental pathogens, there is a transition from Gram-positive microorganism colonization to increasing rates of Gram-negatives (including nosocomial and increasingly resistant pathogens) [3–5]. Compared to civilian burns, military burn casualties are more severe indicated by higher percent total body surface area burned (%TBSA) and higher injury severity scores (ISS). Additionally, military burn casualties are more frequently accompanied by inhalation injury and have a longer transport time prior to definitive care making them prone to infectious complications [6,7]. An autopsy study conducted at our burn center showed infection to be the common cause of mortality in military burn casualties [7]. Advances in burn wound care and management have reduced burn related mortality; however, it is accompanied by concomitant longer periods of hospitalization and increased use of invasive catheters, making burn casualties increasingly susceptible to infectious complications.

Bacteremia (or blood-stream infection) is a life-threatening infectious complication commonly noted in burn casualties. In civilian burn casualties, bacteremia is a risk factor for increased length of hospital stay and mortality [8–12]. The open nature of burn wounds allows for a point of entry for pathogens to access the blood stream. Other routes of entry of pathogens into the bloodstream include translocation of organisms from the gastrointestinal tract due to burn related damage to mucous membranes, mechanical ventilation, and the extensive use of invasive catheters [11,13]. Surviving the first episode of bacteremia predisposes burn casualties to its recurrence. In the case of military burn casualties, recurrence of bacteremia may be due the exposure of varied environmental pathogens during medical evacuation from the point of injury to the Burn Center at the United States Army Institute of Surgical Research (USAISR) for definitive care [14–18]. Although recurrent bacteremia has been documented in non-burn casualties [14,17,19], its incidence in burn casualties remains largely unknown. Herein, we investigate the incidence, mortality, bacteriology, and source of infection associated with recurrent bacteremia in military burn casualties who were admitted to the Burn Center at USAISR over a 10-year period.

2. Methods

2.1. Study design and patient population

After Institutional Review Board approval, we conducted a retrospective study of U.S. military service members burned during Operation Iraqi Freedom/Operation Enduring Freedom/ Operation New Dawn combat operations and admitted to the USAISR Burn Center from March 2003 to December 2013. A total of 952 electronic medical records of service members with combat-related burn injuries were reviewed that met the aforementioned inclusion criteria. For each admission, the following information was extracted: patient demographics, length of stay (LOS) in the hospital and burn intensive care unit (ICU), %TBSA burned (total and third-degree), ISS, and discharge status (dead or alive). Additionally, the electronic microbiological database was queried for culture results of blood, bronchoalvelolar lavage fluid, urine, and wound cultures for the same 10-year period.

This study was conducted under a protocol reviewed and approved by the U.S. Army Medical Research and Materiel Command Institutional Review Board and in accordance with the approved protocol. The USAISR Burn Center serves as the sole referral center in the U.S. Department of Defense for burn injuries of military service members and provides definitive care for burned military personnel, including rehabilitation and reconstruction.

2.2. Microbiological methods and definitions

All blood cultures were processed in the clinical microbiological laboratory using standard microbiological techniques; organism identification was performed using Vitek1 or 2 (bioMerieux Vitek, Durham, NC). Bacteremia was defined as the growth of Gram-positive or Gram-negative organisms in a blood culture that excluded coagulase-negative staphylococci, *Corynebacterium* spp., and *Propionibacterium* spp. as these were considered probable skin contaminants. If two subsequent cultures were negative for organisms, it indicated that the bacteremic episode had been resolved. The onset of bacteremia was confirmed as the time of the first positive blood culture for each episode. Recurrent bacteremia was defined as the occurrence of a subsequent episode of bacteremia of any organism $\geq$7 days after a prior episode of bacteremia [18]. The occurrence of recurrent bacteremia included organisms that may not have been isolated in the initial episode. Polymicrobial bacteremia was defined as the occurrence of two or more bacterial pathogens in one or more blood cultures during the same bacteremia episode, but excluding the aforementioned skin contaminants. At our burn center blood is drawn for blood cultures at the discretion of the attending clinician.

The probable source of bacteremia was determined using classification criteria defined by the Centers for Disease Control and Prevention (CDC) for asymptomatic bacteremic urinary tract infection (UTI), pneumonia, and wound sepsis. Pneumonia, wound sepsis, and UTI were identified as the source when an organism identified in the patient's blood culture was also present in bronchoalvelolar lavage fluid, wound cultures, or urine, respectively. For example, if organism A was present in the blood as well as wound culture, it was deemed that wound sepsis was a probable source of bacteremia. Infections not classified according to the aforementioned criteria were considered non-attributable blood stream infection (NABSI). The presence of organisms in the wound were evaluated by taking wound culture (predominantly wound swabs) as per discretion of the attending clinician.

2.3. Statistical analysis

Bacteremic burn casualties were categorized into two groups: non-recurrent and recurrent bacteremia. Descriptive statistics were performed for demographics, clinical characteristics, and morbidities (i.e., hospital and ICU LOS, and days on ventilator). Continuous variables were described as the mean with standard deviation (SD), or median with interquartile range (IQR), and tested using either t-test or Mann–Whitney test, as appropriate. Categorical variables were expressed as frequencies and percentages and tested for association with the Chi-square or Fisher's exact test, where appropriate. Logistic regression was used to determine risk factors and calculate the likelihood (odds ratio) of increasing risk of mortality or recurrent bacteremia. The outcome measures were in-hospital mortality and recurrent bacteremia. Statistical significance was determined at $p<0.05$ level. Statistical analyses were performed using SAS, Version 9.4 (SAS Institute Inc., NC).

3. Results

3.1. Study population

The records of U.S. military service members with burn injuries were reviewed in this study. Of the 952 records reviewed, 51 of these burn casualties were excluded due to incomplete data or isolated fungemia. Of the remaining 901 burn casualties, 735 burn casualties were excluded either due to no bacteremia (727 burn casualties) or presumed contaminants (8 burn casualties; Fig. 1). The final study sample comprised of 166 burn casualties that developed bacteremia, accounting for 18.4% of the study population (166/901). Of 166 burn casualties with bacteremia, 105 burn casualties (63.2%) had non-recurrent bacteremia, and the remaining 61 burn casualties (36.8%) had at least one episode of recurrent bacteremia and accounted for 6.4% of all military burn casualties. The median time to recurrence of bacteremia was 20 days (IQR: 13–316).

Table 1 describes burn casualties by bacteremia status. The majority of burn casualties that developed bacteremia were young male (98.2%) adults with a median age of 24 years (IQR: 21–30). More than half of burn casualties with bacteremia were Caucasian Americans (55.4%), had fought in the Iraq War (82.5%), served in the U.S. Army (76.5%), and were predominantly battle injury (88.5%) due to explosion (88.6%) and non-battle injuries accounted for 11% of injuries (n=19). Burn was the dominant injury (n=86; 51.8%) followed by blunt trauma (n=69; 41.6%) and penetrating injury (n=11; 6.6%). Thermal burn with inhalation injury accounted for 45.8% of injuries (n=76). The casualties in this population had 41% TBSA (IQR: 24–58%). Approximately 81% casualties had TBSA ≥20%, 88% had ISS >16, and 93% of casualties had 3rd degree burns (Table 1).

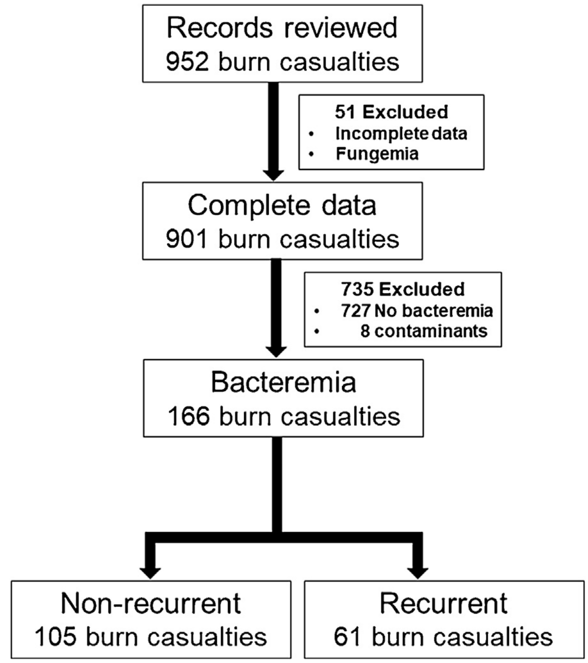

Fig. 1 – Study design.

Compared to non-recurrent bacteremia cohort, casualties with recurrent bacteremia were associated with severe burn (% TBSA ≥20%; 95.1% vs. 72.4%; p=0.0002), severe injury (ISS >16, 95.1% vs. 83.8%; p=0.0006), and higher Baux scores (84.0 vs. 58.8; $p<0.0001$), respectively. However, no association was noted in the demographic factors (i.e., gender, age, military service), injury classification (Battle Injury vs. Non-Battle Injury), injury characteristics (i.e., mechanisms of injury, dominant type of injury, and mechanism of burn), and time from admission to the development of first episode of bacteremia (Table 1).

3.2. Risk of recurrent bacteremia

Univariate analyses for the likelihood of developing recurrent bacteremia (Table 2) showed that casualties with %TBSA ≥20% had 7.4 times higher risk of developing recurrent bacteremia compared to casualties with <20% TBSA (OR: 7.38; 95%CI: 2.14–25.41). The risk of recurrent bacteremia was 7% (OR: 1.07; 95% CI: 1.04–1.09) higher in casualties with 3rd degree burns for each 1% increase in 3rd degree burn. Each 1-unit increase in ISS was associated with a 16% (OR: 1.16; 95%CI: 1.06–1.27) higher risk of recurrent bacteremia. Perineal burns and UTI were significantly associated with a 3.2-fold (OR: 3.15; 95%CI: 1.48–6.74) and 6.7-fold (OR: 6.66; 95%CI: 3.00–14.41) higher risk of recurrent bacteremia, respectively. We also found that each 1 day increase in ventilator use was associated with a 5% higher risk of recurrent bacteremia (OR: 1.05; 95%CI: 1.03–1.07). Compared to non-recurrent bacteremia casualties, the median (IQR) hospital LOS [99 (64–146) vs. 42 (17–64)], ICU LOS [66 (38–100) vs. 14 (7–28) days], and days on mechanical ventilation [36 (9–70) vs. 5 (2–11) days] were longer in casualties with recurrent bacteremia ($p<0.0001$) (Fig. 2A–C).

Table 1 – Characteristics of combat burn casualties treated at United States Army Institute of Surgical Research (USAISR) Burn Center that developed bacteremia during the 10 year period from 2003 to 2013. Interquartile range (IQR); total body surface area (TBSA); injury severity score (ISS).

Variable	All bacteremia	Non-recurrent	Recurrent	p Value
Number of patients, no. (%)	166 (100)	105 (63.2)	61 (36.8)	
Male, no. (%)	163 (98.2)	103 (98.1)	60 (98.4)	0.90
Age, median (IQR), Yr.	24 (21–30)	24 (21–32)	23 (21–27)	0.23
Race/ethnicity, no. (%)				0.41
Caucasian American (White)	92 (55.4)	62 (59.1)	30 (49.2)	
Black	17 (10.2)	10 (9.5)	7 (11.5)	
Hispanic	19 (11.5)	9 (8.6)	10 (16.4)	
Other	38 (22.9)	24 (22.9)	14 (22.9)	
Theater, no. (%)				0.48
Operation Enduring Freedom (OEF)	29 (17.5)	20 (19.1)	9 (14.8)	
Operation Iraqi Freedom (OIF)/Operation New Dawn (OND)	137 (82.5)	85 (80.9)	52 (85.2)	
Military service				0.51
Air Force	1 (0.6)	0 (0.0)	1 (1.6)	
Army	127 (76.5)	80 (76.2)	47 (77.1)	
Marine	36 (21.7)	23 (21.9)	13 (21.3)	
Navy	2 (1.2)	2 (1.9)	0 (0.0)	
Injury classification, no. (%)				0.32
Battle injury	147 (88.5)	91 (86.7)	56 (91.8)	
Non-battle injury	19 (11.5)	14 (13.3)	5 (8.2)	
Mechanism of injury				0.51
Explosion	147 (88.6)	91 (86.7)	56 (91.8)	
Fire/flame	11 (6.6)	9 (8.6)	2 (3.3)	
Other	8 (4.8)	5 (4.8)	3 (4.9)	
Dominant type of injury				0.62
Blunt	69 (41.6)	41 (39.1)	28 (45.9)	
Burn	86 (51.8)	56 (53.3)	30 (49.2)	
Penetrating	11 (6.6)	8 (7.6)	3 (4.9)	
Mechanism of burn, no. (%)				0.73
Thermal alone	90 (54.2)	58 (55.2)	32 (52.5)	
Thermal & inhalation	76 (45.8)	47 (44.8)	29 (47.5)	
Time from injury to 1st bacteremia, days	8 (4-16)	8 (4-14)	8 (6–19)	0.31
TBSA, median (IQR), %	41 (24–58)	31 (17–44)	59 (47–75)	<0.0001
TBSA >20.0%, no. (%)	134 (80.7)	76 (72.4)	58 (95.1)	0.0002
3rd-Burn, no. (%)	154 (92.8)	94 (89.5)	60 (98.4)	0.06
Median (IQR) 3rd-burn, %	35 (17–54)	23 (10–38)	52 (40–65)	<0.0001
Injury severity score, median (IQR)	33 (25–45)	29 (17–42)	38 (29–50)	0.0006
ISS ≥16, no. (%)	146 (88.0)	88 (83.8)	58 (95.1)	0.03
Baux score mean (SD)	68 (51–85)	58.8 (19.9)	84.0 (20.8)	<0.0001
Discharge status, death, no. (%)	39 (23.5)	17 (16.2)	22 (36.1)	0.004

3.3. *Risk of mortality in casualties with recurrent bacteremia*

Univariate analyses for the likelihood of mortality (Table 2) demonstrated that thermal burn with inhalation injury more than doubled (OR: 2.66; 95%CI: 1.26–5.60) the risk of mortality compared to thermal burn alone. Casualties with burn size ≥20% TBSA conferred a 3.6-fold higher risk of mortality compared to burns <20% TBSA [OR: 3.55 (1.02–12.37)]. Depth of burn injury also increased the risk of mortality by 4% for each 1% TBSA increase in 3rd-degree burn [OR: 1.04 (1.02–1.06)]. Each 1-unit increase in ISS, presence of perineal burns, and use of mechanical ventilation were also associated with a higher risk of mortality by 27% [OR: 1.27 (1.15–1.41)], 4.3-fold [4.27 (1.67–11.66)], and 3% [1.03 (1.02–1.05)], respectively compared to those with no perineal burns, and no mechanical ventilator exposure.

Univariate analysis indicated mortality was nearly three-fold higher in recurrent bacteremia casualties (p=0.004) compared to non-recurrent bacteremia casualties (Table 2 and Fig. 2D). After adjusting for cause of burn, % TBSA, ISS, perineal burns, and ventilator use, multivariate analysis demonstrated that recurrent bacteremia was an independent risk factor for mortality, increasing the risk of mortality by 9-fold [9.12 (2.72–30.62)] (Table 2).

3.4. *Bacteriology*

We characterized the occurrence of Gram-positive and Gram-negative bacteria in the non-recurrent and recurrent bacteremia groups (Fig. 3). Gram-negative bacteria were the predominant (~85%) microorganisms in both groups (Fig. 3A). Of the Gram-positive bacteria, *Staphylococcus aureus* was the predominant organism in both non-recurrent (22 casualties; 22%) and recurrent bacteremia casualties (18 casualties; 29%) (Fig. 3C). Streptococci were detected only in non-recurrent bacteremia casualties (14 casualties; 14%). Twelve casualties (19%) in the recurrent bacteremia group developed

Table 2 – Likelihood of recurrent bacteremia and mortality. Multivariate analysis has been adjusted for cause of burn, overall total body surface area (%TBSA), perineal burn, central line catheter, urinary catheter, injury severity score (ISS), time from point of injury (POI) to discharge or 240 days, and ventilator use. Urinary tract infection (UTI); Operation Iraqi Freedom (OIF); Operation Enduring Freedom (OEF); Operation New Dawn (OND).

	Recurrent bacteremia		Mortality	
	Odd ratio OR (95%CI)	p Value	Odd ratio OR (95%CI)	p Value
Battle vs. non-battle Injury	1.72 (0.59-.04)	0.32	1.73 (0.48-6.28)	0.40
Theater: OEF vs. OIF/OND	0.74 (0.31–1.74)	0.48	1.30 (0.53-3.23)	0.57
Mechanism of injury				
Explosion vs. fire/flame	2.77 (0.58-13.28)	0.21	1.46 (0.30-7.07)	0.64
Other vs. fire/flame	2.70 (0.33-22.0)	0.35	0.64 (0.05-8.62)	0.74
Type of injury				
Blunt vs. burn	1.28 (0.66-2.45)	0.47	1.34 (0.64-2.79)	0.43
Penetrating vs. burn	0.70 (0.17–2.84)	0.62	0.35 (0.04-2.93)	0.33
Penetrating vs. blunt	0.55 (0.13-2.25)	0.41	0.26 (0.03-2.20)	0.22
Cause of burn				
Thermal/inhalation vs. thermal alone	1.12 (0.59-2.11)	0.73	2.66 (1.26-5.60)	0.01
Time from POI to MTF, each 01 day of increase	0.97 (0.78-1.20)	0.76	1.05 (0.83-1.33)	0.68
Time from POI to 1st bacteremia, each 01 day increase	1.00 (0.98-1.02)	0.76	1.02 (0.99-1.04)	0.13
TBSA burnt, %	1.07 (1.05-1.09)	<0.0001	1.05 (1.03-1.07)	<0.0001
Overall TBSA burnt, ≥20% vs. <20%	7.38 (2.14-25.41)	0.002	3.55 (1.02-12.37)	0.047
TBSA 3rd burn, each increase of 1%	1.07 (1.04-1.09)	<0.0001	1.04 (1.02-1.06)	<0.0001
ISS, each 01 score increase	1.16 (1.06-1.27)	0.001	1.27 (1.15-1.41)	<0.0001
Perineal burn, yes vs. no	3.15 (1.48-6.74)	0.003	4.27 (1.67–11.66)	0.005
Central line catheter, yes vs. no	4.95 (0.60-40.56)	0.14	2.55 (0.31-21.08)	0.38
Urine catheter, yes vs. no	4.28 (0.51-35.66)	0.18	2.22 (0.26-18.59)	0.46
Mechanical ventilator, yes vs. no	1.05 (1.03-1.07)	<0.0001	1.03 (1.02-1.05)	<0.0001
UTI, yes vs. no	6.66 (3.00 –14.41)	<0.0001	1.12 (0.49-2.55)	0.80
Univariate model				
Recurrent vs. non-recurrent bacteremia	–	–	2.92 (1.40-6.10)	0.004
Multivariate model				
Recurrent vs. non-recurrent bacteremia	–	–	9.12 (2.72-30.62)	0.0004

bacteremia due to enterococci, compared to 2 casualties (2%) in the non-recurrent bacteremia group.

Acinetobacter baumannii complex (ABC) was more frequently isolated in non-recurrent (64 casualties; 63%) than recurrent bacteremia casualties (23 casualties; 37%) (Fig. 3B). ABC was the predominant pathogen isolated in 35% of all bacteremia related deaths in the non-recurrent bacteremia casualties (6/17 deaths). *Enterobacter* spp. isolation was also more prevalent in non-recurrent (21 casualties; 21%) than recurrent bacteremia casualties (7 casualties; 11%). *Klebsiella pneumoniae* (46% vs. 30%) and *Pseudomonas aeruginosa* (35% vs. 26%) were more prevalent in recurrent than non-recurrent bacteremia population. The proportion of *Serratia marcescens*, *Escherichia coli*, and *Stenotrophomonas maltophilia* isolates were not statistically different on a per-species basis between the two groups (Fig. 3D).

3.5. Polymicrobial bacteremia

Our study identified *S. aureus*, ABC, *K. pneumoniae*, *P. aeruginosa*, *Enterobacter aerogenes*, and *Enterobacter cloacae* as the most prevalent pathogens that caused bacteremia at our burn center. We identified 83 patients with non-recurrent bacteremia and 55 patients with recurrent bacteremia that developed bacteremia with aforementioned microorganisms. Half of the recurrent bacteremia population had polymicrobial infection compared to 9% in the non-recurrent bacteremia cohort (Fig. 3B). The most common combinations in polymicrobial bacteremia were ABC+*K. pneumoniae* (7 patients), *K. pneumoniae*+*P. aeruginosa* (5 patients), ABC+*P. aeruginosa* (4 patients) *and K. pneumoniae*+*P. aeruginosa*+*S. aureus* (4 patients), *and K. pneumoniae*+*S. aureus* (3 patients).

3.6. Source of infection

In non-recurrent bacteremia casualties, 38% developed bacteremia due to pneumonia, wound sepsis (14%), UTI (1%), and combination of pneumonia and wound sepsis (4%). In the recurrent bacteremia group, pneumonia was a source of infection in 15% of casualties, wound sepsis and UTI in 8% each, respectively, and, 29% of recurrent bacteremia casualties had a combination of pneumonia and wound sepsis as a source of infection. In both, the non-recurrent and recurrent bacteremia populations, 40% of casualties developed bacteremia without pneumonia, wound, or urinary sources (NABSI) (Fig. 4A and B).

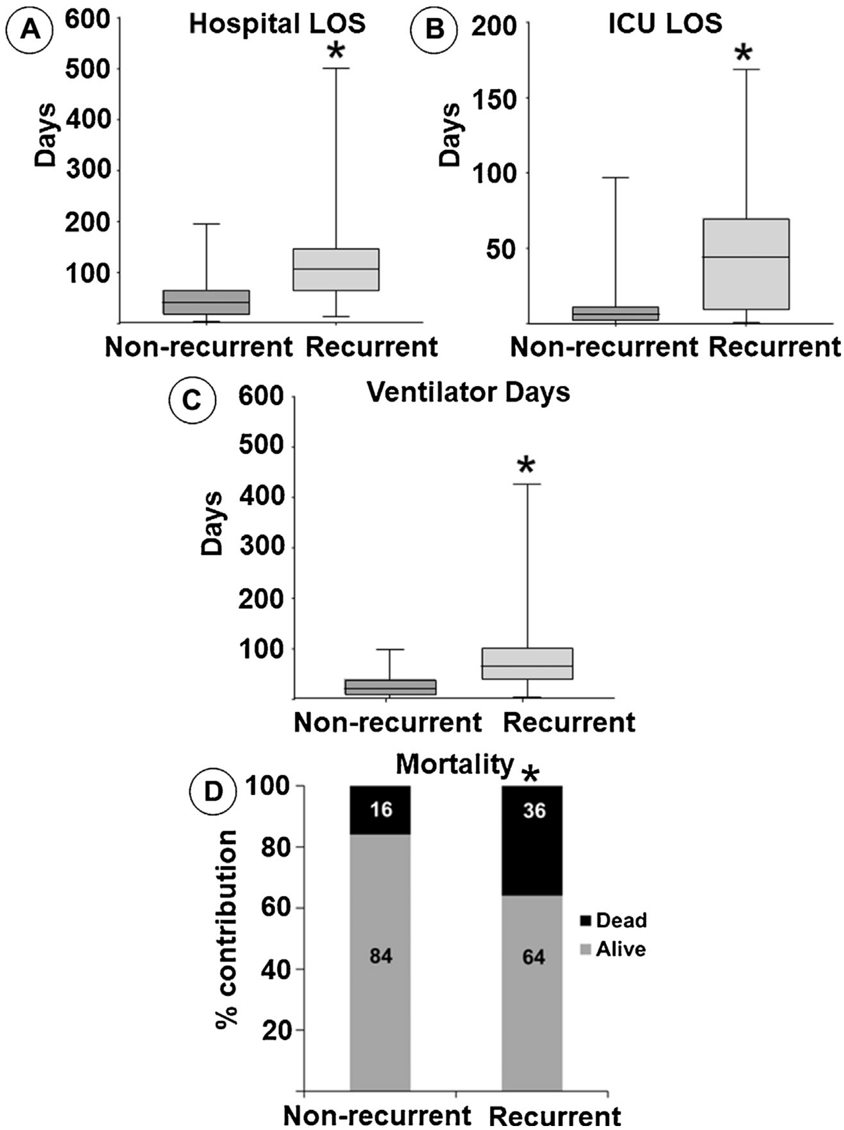

Fig. 2 – (A) Hospital length of stay (LOS), (B) intensive care unit (ICU) LOS, and (C) days on mechanical ventilation, and (D) mortality rate, in non-recurrent and recurrent bacteremia groups is shown. *Significantly different than non-recurrent bacteremia ($p<0.001$).

4. Discussion

The objective of this retrospective study was to examine the incidence, mortality, bacteriology, and the source of infection in military burn casualties with a recurrent episode of bacteremia. Reassuringly, only 6% of all military burn casualties developed recurrent bacteremia; however, recurrence rate was high with 37% of military burn casualties (61/166) with bacteremia developing at least one subsequent episode of bacteremia with a median time to recurrence of 20 days. Multivariate analysis demonstrated that recurrent bacteremia was an independent risk factor for mortality, increasing the risk of mortality by 9-fold. Larger burn size (≥20% TBSA), severity of the burn injury (IS >16), longer days on mechanical ventilation, and the presence of perineal burns were risk factors associated with recurrent bacteremia and mortality. Despite occurring in only 8% of burn casualties with recurrent bacteremia, UTI was an additional risk factor for the recurrence of bacteremia.

In our study, we found that 37% of bacteremic casualties experienced one or more recurrent episodes. Our recurrence rate is strikingly higher than the 9–16% recurrence rates reported in the literature [14,17–21]. We believe that differences in the recurrence rates could be due to differences in study population (burn vs. non-burn casualties) and study design (retrospective vs. case-control). Additionally, the definition of recurrence and follow-up periods are different among studies. The high recurrence rate is also presumably due to the state of relative immunodeficiency associated with severe burn injuries [22–24]. There have been no studies that report the contribution of recurrent bacteremia to mortality in burn casualties; however, the more than 9-fold mortality rate

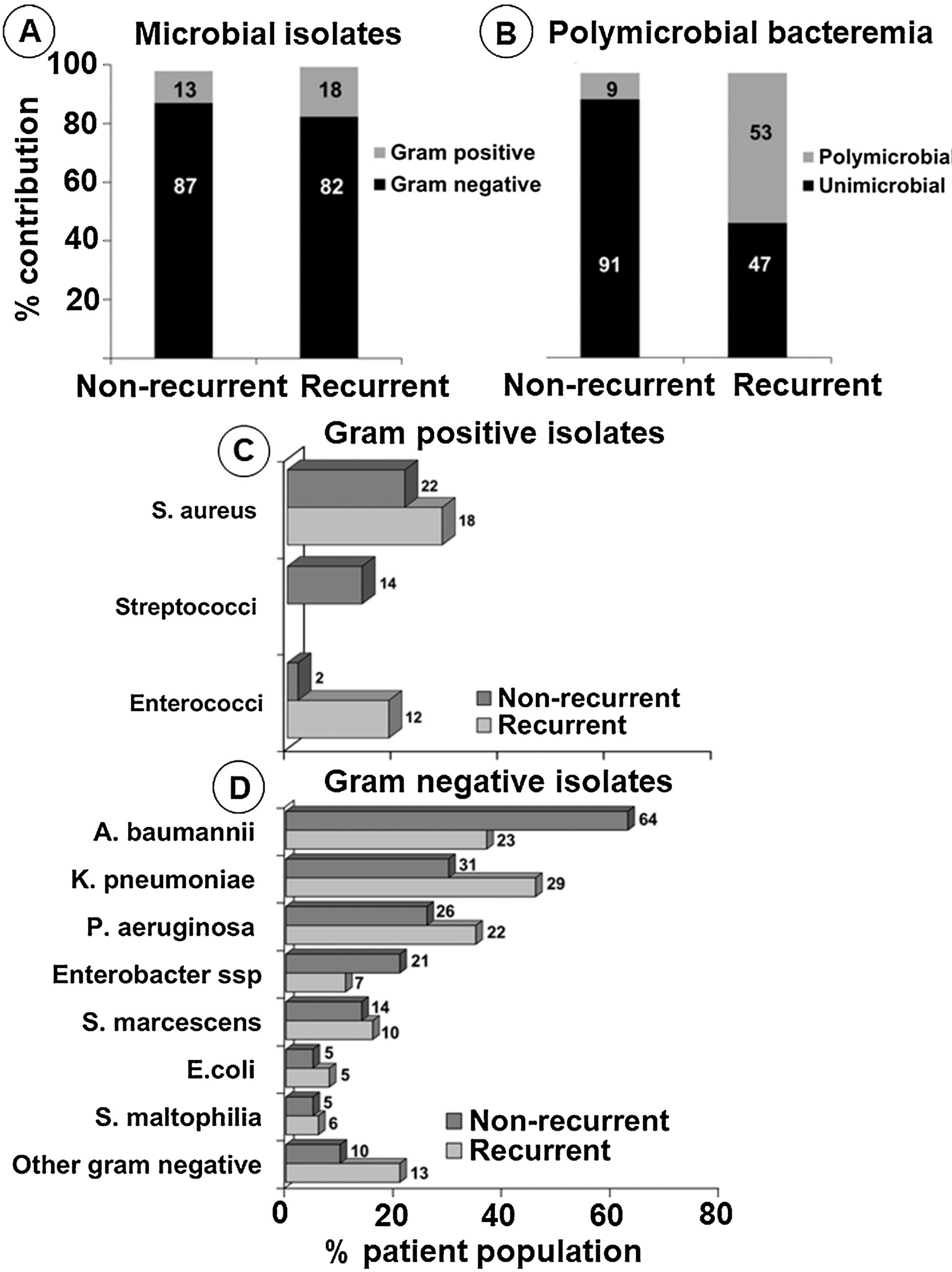

Fig. 3 – (A) Distribution of microbial isolates in the non-recurrent and recurrent bacteremia groups. (B) Incidence of polymicrobial bacteremia in non-recurrent and recurrent bacteremia groups. Distribution of Gram positive isolates (C) and Gram negative isolates (D) in non-recurrent and recurrent bacteremia casualties. The graph gives the number of isolates and the percentage of casualties (in the bar graph) identified with a specific bacteria.

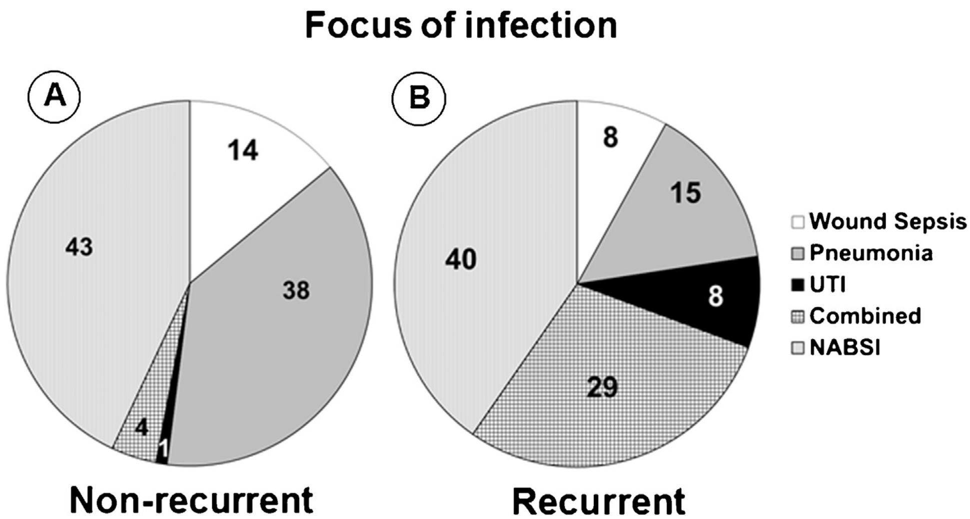

Fig. 4 – Distribution of focus of infection (percent population) in non-recurrent (A) and recurrent bacteremia (B) casualties. UTI: urinary tract infection; NABSI: non-attributable blood stream infection.

of our recurrent bacteremia cohort is comparable to studies that report mortality of 54% [25] and 80% [22] in non-burn casualties with a recurrent episode of bacteremia. The univariate risk factors for increased mortality in our study included larger burn size, higher ISS, perineal burns, and longer periods on mechanical ventilation. Our finding support the work of others that report an association between the aforementioned factors and mortality [1,26]. The higher mortality rate of our recurrent bacteremia cohort is also presumably due the prevalence of *K. pneumoniae* and *P. aeruginosa* as primary pathogens [7,27], and the occurrence of polymicrobial episodes [28], as they have been also reported to increase mortality. Multivariate analysis indicated recurrent bacteremia increased mortality by 9-fold; however, it's difficult to establish causation as the increase in mortality may be also due to burn induced morbidity [11] including the compromised immune system.

Gram-negative microorganisms were predominant in both non-recurrent and recurrent bacteremia cohorts. This echoes prior literature that reports Gram-negative bacteria as the dominant causative pathogen in adult burn casualties with bacteremia [29–32]. The high prevalence of ABC infections in non-recurrent bacteremia casualties is not surprising as the pathogen has been frequently isolated from military casualties from the Middle East. Furthermore, the burn casualties included in this analysis were admitted during a multiyear outbreak of ABC in the U.S. military system [33–36]. Burn casualties with bacteremia were more common in OIF/OND compared to OEF. One possible explanation is the increased soldier deployment during OIF/OND. Additionally, these conflicts saw a rise in the use of improvised explosive devices (IED) by insurgents that led to extensive injuries to include burns. The extensive nature of burns allowed inoculation with environmental pathogens that may have led to new infectious complications [2]. *K. pneumoniae* (46%) and *P. aeruginosa* (36%) were the two most common Gram-negative isolates in the recurrent bacteremia cohort. Previously, these pathogens have been associated with increased risk of mortality at our burn center [7]. *K. pneumonia* as the primary pathogen in recurrent bacteremia casualties may be due to the prolonged periods of mechanical ventilation as the pathogen has been shown to colonize ventilator condensate [11]. *P. aeruginosa* being the second most prevalent pathogen in the recurrent bacteremia cohort corroborates studies that report *P. aeruginosa* as the most frequently isolated pathogen from burn autopsies and burn units [37–39]. The higher incidence of polymicrobial infection could be multifactorial to include but not restricted to the possibility of larger burns, occurrence of burn related sepsis, co-morbidities, and infectious complications (e.g., UTI) [40].

Pneumonia as a source of infection was prevalent in both non-recurrent as well as recurrent bacteremia casualties. This finding is not surprising, as pneumonia is a known morbidity in severe burn casualties. Pneumonia, in particular, ventilator-associated pneumonia, is a common infection in casualties on mechanical ventilation for $\geq$48h. Wound sepsis is more pronounced in third degree burns [41–43]. It is likely that a combination of pneumonia and wound sepsis as a source of infection in recurrent bacteremia casualties is likely due to prolonged period of mechanical ventilation and larger burn size (TBSA $\geq$20%) in this patient cohort. The lower rate of wound sepsis (8%) as a possible source of recurrent bacteremia is most likely due to the wound management protocol at our burn center. The protocol involves early debridement, excision, grafting, and application of topical antimicrobials that include alternating silver sulfadiazine (SSD) and 12% mafenide acetate cream or soaks with 5% mafenide acetate solution [44].

The seven-fold higher incidence of UTI as a source of infection in recurrent bacteremia casualties could be attributed to the higher incidence of perineal burns in this cohort. Corroborating this finding is a recent study in the same patient population that showed casualties with perineal burns to have a ten times higher incidence of UTI [1]. Catheter related UTI is ubiquitous and the higher incidence of UTI in recurrent bacteremia cohort may be due the prolonged use of indwelling Foley catheters. At our burn center, urinary catheters are changed every 30 days in burn ICU patients and as needed if infection or colonization has been identified by culture. Together, this suggests that there needs to be strict adherence to bundles, monitoring the duration of catheterization, including frequent changing of catheters in patients with a high risk of recurrent bacteremia.

Intravascular catheters are known to provide a pathway for the entry of pathogens in the blood stream. At our burn center, central venous catheters and arterial lines are changed every five days for wound sizes greater than 20% TBSA. We arrived at this frequency through a performance improvement study conducted at our burn center that showed a five day change frequency to result in the lowest bacteremia rates in combat burn casualties (unpublished data). In this study, in either patient population, NABSI accounted for ~40% of infections. It may well be that this included infections acquired from the use of catheters or from underlying burn associated morbidities. This certainly warrants further investigation of intravascular related bacteremia, but is beyond the scope of this study and may be a possibility of future investigations in the same patient population.

5. Limitations

The retrospective design is a limitation of the study. The small number of casualties with recurrent bacteremia and single-center are other limitations of the study. The study cohort only includes military burn casualties with a high incidence of concomitant trauma, which is a homogenous population. However, the homogeneous nature of the study population is advantageous as it allows us to objectively evaluate recurrent bacteremia as a risk factor for mortality. The study includes casualties injured in operation OEF/OIF where ABC was prevalent, and were evacuated within a system experiencing a multiyear polyclonal outbreak of the organism. Another limitation of the study is that there is no standardized policy at our institution for follow-up blood culture in bacteremia cases so it may well be possible that a recurrent episode may have been missed. Furthermore, intravascular catheters as a probable source of nosocomial bacteremia was not investigated in the study, but may be a possibility of future investigations. Finally, all the univariate and multivariate analyses were carried out in an exploratory fashion. Hence, it is seemingly possible that some risk factors may have not been detected or explored in our study.

6. Conclusion

To the knowledge of the authors, this is the first study to investigate incidence, mortality, bacteriology, and source of infection of recurrent bacteremia in military burn casualties. Reassuringly, only 6% of all military burn casualties developed recurrent bacteremia, but recurrence rate was high (37%), and more importantly recurrent bacteremia resulted in 9-fold increase in mortality. In our study, patients with extensive and severe burns, prolonged ventilator days, and presence of perineal burns were at a higher risk of recurrent bacteremia, which is associated with increased mortality. In these high risk patients, closely monitoring the bacteriology by obtaining early blood cultures may mitigate the recurrence of bacteremia and mortality. Given that UTI was independently associated with recurrent bacteremia, strict adherence to bundles and monitoring the duration of catheterization will be needed to minimize recurrence of bacteremia in our patient population. Future studies will incorporate the timing, type, dosage regimens, and duration of antimicrobial therapy. Additionally, severe burn injuries are accompanied by co-morbidities; therefore, future studies will investigate their impact of mortality in patients with a recurrent episode of bacteremia.

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Disclaimer

All components of this study including the decision to publish and where to publish were the sole discretion of the authors. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense. The authors are employees of the United States Government and this work was prepared as a part of their official duties.

Conflicts of interest

None.

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