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Clinical Paper

# The incidence and significance of bacteremia in out of hospital cardiac arrest☆

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ABSTRACT

*Background:* The most common etiology of cardiac arrest is presumed of myocardial origin. Recent retrospective studies indicate that preexisting pneumonia, a form of sepsis, is frequent in patients who decompensate with abrupt cardiac arrest without preceding signs of septic shock, respiratory failure or severe metabolic disorders shortly after hospitalization. The contribution of pre-existing infection on pre and post cardiac arrest events remains unknown and has not been studied in a prospective fashion. We sought to examine the incidence of pre-existing infection in out-of hospital cardiac arrest (OHCA) and assess characteristics associated with bacteremia, the goal standard for presence of infection.

*Methods and results:* We prospectively observed 250 OHCA adult patients who presented to the Emergency Department (ED) between 2007 and 2009 to an urban academic teaching institution. Bacteremia was defined as one positive blood culture with non-skin flora bacteria or two positive blood cultures with skin flora bacteria. 77 met pre-defined exclusion criteria. Of the 173 OHCA adults, 65 (38%) were found to be bacteremic with asystole and PEA as the most common presenting rhythms. Mortality in the ED was significantly higher in bacteremic OHCA (75.4%) compared to non-bacteremic OHCA (60.2%, $p < 0.05$). After adjustment for potential confounders, predictive factors associated with bacteremic OHCA were lower initial arterial pH, higher lactate, WBC, BUN and creatinine.

*Conclusions:* Over one-third of OHCA adults were bacteremic upon presentation. These patients have greater hemodynamic instability and significantly increased short-term mortality. Further studies are warranted to address the epidemiology of infection as possible cause of cardiac arrest.



## 1. Introduction

Over 250,000 patients per year present in cardiac arrest to the Emergency Department (ED) throughout the United States. The etiologies of cardiac arrest are presumed cardiac irrespective of the presenting rhythm.[1] However it should also be considered that there may be other reasons for a patient to present with cardiac arrest.[2] An analysis of community acquired pneumonia patients in the PORT study[3] found the incidence of cardiac complications to be 26.7%.[4] Cardiac events were diagnosed within the first week, most commonly within the first 24 h after hospital admission including complete cardiovascular collapse.[5] Carr et al. reported that within 72 h following hospital admission for pneumonia; 12.1% of patients had in-hospital cardiac arrests (IHCA). The bacteremic IHCA patients were more frequently hypotensive requiring vasoactive drugs or assisted ventilation compared to even the pre-existing pneumonia cardiac arrest patients.[5] Causes of increased morbidity and mortality include the development of infection during

*Abbreviations:* ACLS, advanced cardiac life support; CVC, central venous catheterization; CVP, central venous pressure (mmHg); $DO_2$, systemic oxygen delivery (mL/min/m$^2$); ED, Emergency Department; EGDT, early goal directed therapy; $FiO_2$, fraction of inspired oxygen (%); GPU, general practice unit; ICU, intensive care unit; IHCA, in-hospital cardiac arrest; MAP, mean arterial pressure (mmHg); MET, medical emergency teams; MSOF, multi-system organ failure; OHCA, out of hospital cardiac arrest; $PaO_2$, partial pressure of arterial oxygen (mmHg); SAPS II, simplified acute physiologic score; SBP, systolic blood pressure (mmHg); $ScvO_2$, central venous oxygen saturation (%); $SvO_2$, mixed venous oxygen saturation (%); SOFA, sequential organ failure assessment; SSC, surviving sepsis campaign; $VO_2$, systemic oxygen consumption.

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**Table 1**
Demographics characteristics of patients with OHCA presenting to the emergency department and disposition from the emergency department.

| Patient characteristics | Bacteremic OHCA ($n = 65$) | Non-bacteremic OHCA ($n = 108$) | $p$ |
|---|---|---|---|
| Age, years | 65.5 ± 15.1 | 64.6 ± 18.5 | 0.74 |
| Male | 55.4% (36) | 59.3% (64) | 0.62 |
| Race | | | |
| African American | 88% (57) | 83% (90) | 0.86 |
| Caucasian | 9% (6) | 13% (14) | |
| Other | 3% (2) | 4% (4) | |
| Preexisting comorbid conditions | | | |
| Diabetes mellitus | 34% (22) | 31% (31) | 0.81 |
| Hypertension | 52% (40) | 48% (52) | 0.63 |
| Congestive heart failure | 23% (15) | 23% (25) | 0.55 |
| Coronary artery disease | 29% (19) | 31% (33) | 0.98 |
| Chronic renal failure on hemodialysis | 8% (5) | 6% (6) | 0.78 |
| Chronic renal failure without hemodialysis | 5% (3) | 13% (14) | 0.07 |
| Chronic obstructive pulmonary disease | 22% (14) | 29% (31) | 0.28 |
| ED survival | 25% (16) | 40% (43) | 0.042 |
| 28 days mortality | 94% (61) | 93% (100) | 0.75 |
| Overall mortality | 97% (63) | 95% (103) | 0.66 |

ED indicates emergency department. Continuous variables are presented as mean ± SD. Categorical variables are presented as percentages and absolute numbers ($n$).

the post-resuscitation period and the delays in and inappropriate antibiotic therapy for infections particularly in severe sepsis and septic shock.[6,7] Little is known regarding the prevalence of bacteremia in cardiac arrest patients arriving to the ED. It has been shown that early diagnosis and interventions in infection significantly improves morbidity and mortality.[1] The purpose of this study was to examine the incidence of bacteremia in out of hospital cardiac arrest (OHCA) and identify the characteristics associated with bacteremia.

## 2. Methods

This was a prospective observational convenient sampling study of OHCA adult patients seen at an urban academic teaching institution during the period of August 2007 to August 2009. The diagnosis of cardiac arrest was defined by the American Heart Association (AHA) and the International Consensus Conference on Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC) definitions.[8] All resuscitations were directed by board certified ED physicians and nurses using the most contemporary AHA/advanced cardiac life support (ACLS) guidelines with no involvement of the research team. The institutional review board for human research approved the study with wavier of informed consent.

The study was designed to obtain blood cultures near time of cardiac arrest event in patients 18 years and older during ACLS therapy or return of spontaneous circulation (ROSC) on presentation to the ED without interfering with clinical decision-making. Aerobic and anaerobic blood cultures (10 mL per bottle) were collected through venous or arterial access catheters by personnel not associated with the ED treatment team. OHCA patients without initiation or continuation of ACLS therapy on ED arrival were not considered for enrollment and no data was collected on this group. The excluded were all trauma cardiac arrest victims, pregnant patients, and patients found younger than 18 years. Bacteremic OHCA group had a minimum of two blood culture bottles with skin flora pathogens or one blood culture tube with non-skin flora pathogens. Non-bacteremic OHCA group had no bacterial growth after at least 5 days of incubation. Skin-indigenous bacteria in only one of two blood samples were considered as contamination and categorized as non-bacteremic OHCA.

The primary objective of the study was to identify the incidence of bacteremia in OHCA adults. Secondly, to describe the patient characteristics, the early post-arrest hospital courses and hospital mortality of the bacteremic OHCA compared to the non-bacteremic OHCA group, particularly in those ED survivors. ED survivors were defined as cardiac arrest patients with ROSC in the pre-hospital setting or in the ED who survived hospital admission to the intensive care unit for continuity of medical care.

## 3. Statistical methods

All statistical analyses were performed using commercially SAS software Version 9.2 of the SAS System for MS Windows (Copyright 2002–2008 SAS Institute Inc., Cary, MC, USA). Discrete and continuous variables were compared using Chi-square test and 2-sample $t$-test, respectively.

Univariate analyses were first performed to select potential risk factors. Univariate statistical significant ($p < 0.05$) or clinically relevant risk factors were selected and analyzed using multiple logistic regression to estimate the adjusted effects in cardiac arrest. Two sided $p$ values of 0.05 or less were considered to indicate statistical significance.

## 4. Results

From 2007 to 2009, 250 OHCA cardiac arrest patients had 2 sets of blood cultures obtained. 77 (31%) met exclusion criteria for either trauma victims, pregnant or less than 18 years of age. Of the remaining 173 patients, 71 had positive blood cultures of which 6 cultures were defined as contaminants (skin flora) and included for analysis in the non-bacteremic OHCA group.

The overall incidence of bacteremia was 38% (65 patients) over the two-year study period. There was no significant difference in age, sex, race and past medical history between bacteremic and non-bacteremic OHCA groups (Table 1). The 28-day mortality for bacteremic and non-bacteremic groups was similar at 93.8% and 92.6%, respectively ($p > 0.05$). However, ED survival was significantly lower in the bacteremic (25%) compared to the non-bacteremic (40%) group ($p < 0.042$) (Table 1).

Asystole was the most common presenting rhythm for bacteremic and non-bacteremic OHCA followed by PEA and VF ($p > 0.05$). The presenting location or origin of cardiac arrest, the pre-hospital and ED CPR duration and time to ROSC were similar between the two groups ($p > 0.05$) (Table 2).

Seventeen bacterial species were isolated from the 65 bacteremic OHCA patients (Table 3). Some blood cultures had more than one bacterial species isolated, noting the percent summation

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**Table 2**
Resuscitation Profile of the Bacteremic and Non-bacteremic OHCA groups.

| | Bacteremic OHCA ($n=65$) | Non-bacteremic OHCA ($n=108$) | $P$ |
|---|---|---|---|
| Resuscitation profile | | | |
| Cardiac arrest location | | | |
| Home | 49% (32) | 51% (55) | 0.94 |
| Nursing home | 8% (5) | 9% (10) | |
| Public place | 18% (12) | 16% (17) | |
| Emergency Department | 6% (4) | 8% (9) | |
| Unknown | 18% (12) | 16% (17) | |
| Presenting rhythm | | | |
| Asystole | 65% (42) | 62% (67) | 0.45 |
| PEA | 26% (7) | 22% (24) | |
| VF | 9% (6) | 16% (17) | |
| CPR time | | | |
| Pre-hospital CPR time (m) | 24.49 ± 12.4 | 20.6 ± 12.6 | 0.06 |
| ED CPR time (m) | 16.9 ± 15.7 | 17.2 ± 14.2 | 0.35 |
| Time to ROSC (m) | 13.12 ± 9.8 | 14.65 ± 12.8 | 0.66 |
| Total CPR time (m) | 40.8 ± 21.7 | 35.9 ± 20.4 | 0.15 |

PEA indicates pulseless electrical activity; VF, ventricular fibrillation; CPR, cardiopulmonary resuscitation; ED, emergency medicine; ROSC, return of spontaneous circulation; m, minutes. Continuous variables are presented as mean ± SD unless stated otherwise. Categorical variables are presented as percentages and absolute numbers ($n$).

greater than 100%. The most common gram-positive bacteria species identified were *Staphylococcus epidermidis* and *Streptococcus non-pneumoniae*. The most common gram-negative bacteria were *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis*.

There were 16 bacteremic and 43 non-bacteremic OHCA ED survivors (Table 4). On ROSC, bacteremic and non-bacteremic ED survivors physiologic parameters such as temperature, SBP, MAP, HR, RR and $O_2$ saturation were similar ($p > 0.05$) (Table 4). There was no statistical difference between the bacteremic OHCA and non-bacteremic OHCA ED survivors for hospital length of stay, overall and 28-day mortality ($p > 0.05$) (Table 4).

Of the 16 bacteremic OHCA ED survivors, 94% required vasopressor therapy compared to 74.4% non-bacteremic OHCA ED survivors ($p > 0.05$) (Table 4). Part of the ED medical management included initiation of antibiotics in 11 (69%) bacteremic OHCA ED survivors and 13(30%) non-bacteremic OHCA ($p = 0.01$) (Table 4). Clinically relevant variable discrepancies in the bacteremic OHCA ED survivors were lower arterial pH, higher lactate, higher $pCO_2$ and higher base excess compared to non-bacteremic OHCA ED survivors ($p < 0.05$) (Supplemental Table 1). Other laboratory discrepancies were significantly higher potassium, BUN, creatinine, magnesium and phosphate ($p < 0.05$) (Table 4). There was a trend for lower troponin I and CK-MB in the bacteremic OHCA ED survivors compared to the non-bacteremic OHCA ED with no significance observed ($p = 0.15$) (Table 4).

Lactate, arterial pH, BUN and creatinine showed marginal significant association with bacteremic OHCA ED patients, we studied their joint effect adjusting for white blood cells using multiple logistic regression analysis. Table 5 shows that the adjusting effects were not significant at 0.05. However, we found that an increase in creatinine by 1 mg/dL increased the odds of being bacteremic by 38% in OHCA ED survivors after adjusting for the other relevant risk factors with a cutoff significance at 0.1.

**Table 3**
Bacterial species isolated from the Bacteremic OHCA group.

| Bacterial species | $n$ (%) |
|---|---|
| *Other Streptococcus species* | 12 (18.5%) |
| *Staphylococcus epidermidis* | 11 (17%) |
| *other Staphylococcus species* | 9 (14%) |
| *Corynebacterium* | 5 (7.7%) |
| *Staphylococcus aureus* | 4 (6%) |
| *Streptococcus pneumoniae* | 4 (6%) |
| *Klebsiella pneumonia* | 3 (4.6%) |
| *Enterococcus faecalis* | 3 (4.6%) |
| *Propinebacterium* | 3 (4.6%) |
| *Escherichia coli* | 3 (4.6%) |
| *Clostridium species* | 3 (4.6%) |
| *Gram positive bacilli NOS* | 2 (3%) |
| *Enterococcus species* | 2 (3%) |
| *Streptoccus agalacteae* | 2 (3%) |
| *Clostridium cadaveris* | 2 (3%) |
| *Proteus mirabilis* | 2 (3%) |
| *Enterobacterium* | 1 (1.5%) |
| *Enterococcus faecacium* | 1 (1.5%) |
| *Actinomices* | 1 (1.5%) |
| *Bacteriodes (Prevotella)* | 1 (1.5%) |
| *Aerococcus viridans* | 1 (1.5%) |

NOS indicates not otherwise specified. All bacterial species isolated were reported and on occasion more than one bacterial species were isolated noting percent summation greater than 100%. Categorical values are shown as absolute numbers and percentages (%).

## 5. Discussion

Within this prospective convenient sampling of OHCA patients presenting to the ED, we found a 38% incidence of bacteremia which to date has not been reported in the literature. The presence of bacteremia was associated with a significant decrease in ED survival compared to non-bacteremic patients. While multiple studies have examined the presence and impact of infection during the post resuscitation period, no study to date has examined it as a precipitating cause or confounder in undifferentiated cardiac arrest.[9]

### 5.1. Bacteremia: incidence and significance

Leibovici et al.[10] noted that the failure to appropriately treat bacteremia was associated with higher short-term mortality and worse long term prognosis, particularly evident in patients with low functional capacity, low serum albumin, high serum creatinine, nosocomial infections, malignancy, septic shock and in elderly patients. Risk factors contributing significantly to mortality in bacteremic patients were increasing age, underlying ultimately fatal disease, presence of severe sepsis, shock and gram-positive pathogen infections excluding coagulase-negative staphylococci.[11]

The incidence of bacteremic complications in early post resuscitation after OHCA was first reported by Gaussorgues et al. at 8%.[12] They hypothesized that a low flow shock state post cardiac arrest along with mesenteric ischemia led to diarrhea and septicemia with gut flora bacteremia in blood cultures obtained 12 h after ROSC.[12,13] Our most common pathogens identified were not of intestinal origin rather *Staphylococcus* and *Streptococcus* species, less common

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**Table 4**
Baseline physiologic and laboratory parameters of the Bacteremic and Non-bacteremic OHCA ED survivors as well as ED disposition.

| | Bacteremic ED survivors ($n=16$) | Non-bacteremic ED survivors ($n=43$) | $P$ |
|---|---|---|---|
| Vital signs | | | |
| Temperature (°C) | 35.9 ± 1.5 | 35.5 ± 1.6 | 0.48 |
| HR, beats per min | 104 ± 27 | 105 ± 28 | 0.90 |
| RR, breath per min | 14 ± 4 | 18 ± 8 | 0.25 |
| Systolic BP (mmHg) | 125 ± 51 | 136 ± 52 | 0.58 |
| Diastolic BP (mmHg) | 70 ± 34 | 79 ± 33 | 0.50 |
| MAP (mmHg) | 89 ± 37 | 98 ± 38 | 0.51 |
| $O_2$ Saturation (%) | 96% ± 6.8 | 95% ± 14 | 0.54 |
| Shock Index | 0.89 ± 0.47 | 0.86 ± 0.34 | 0.83 |
| Vasopressors dependent (%) | 93.8% (15) | 74.4% (32) | 0.055 |
| Laboratory values | | | |
| White blood cells (K/μL) | 14.08 ± 7.8 | 12.5 ± 7.7 | 0.49 |
| Hemoglobin (g/dL) | 11.3 ± 1.8 | 11.5 ± 2.4 | 0.69 |
| Hematocrit (%) | 34.9 ± 6.5 | 34.7 ± 6.7 | 0.91 |
| Lactate (mmol/L) | 13.4 ± 7.3 | 8.8 ± 5.5 | 0.01 |
| Arterial pH | 7.03 ± 0.2 | 7.17 ± 0.17 | 0.01 |
| Arterial $pCO_2$ (mmHg) | 67.3 ± 28.2 | 52.6 ± 23.1 | 0.05 |
| Arterial $pO_2$ (mmHg) | 133.2 ± 118 | 192.2 ± 114 | 0.16 |
| Base excess (mmol/L) | 14.8 ± 8.3 | 10.5 ± 6.0 | 0.04 |
| Sodium (mmol/L) | 144.6 ± 10.1 | 142.4 ± 8.4 | 0.41 |
| Potassium (mmol/L) | 5.2 ± 1.3 | 4.1 ± 2.4 | 0.005 |
| Chloride (mmol/L) | 104.9 ± 7.7 | 107 ± 8.5 | 0.39 |
| Bicarbonate (mmol/L) | 18.5 ± 5.3 | 20.1 ± 8.6 | 0.49 |
| BUN (mg/dL) | 48.8 ± 31.1 | 27.8 ± 19.6 | 0.02 |
| Creatinine (mg/dL) | 3.7 ± 2.2 | 2.4 ± 1.7 | 0.02 |
| Glucose (mg/dL) | 253 ± 162 | 249.7 ± 121 | 0.93 |
| Magnesium (mg/dL) | 2.7 ± 0.6 | 2.1 ± 0.6 | 0.01 |
| Phosphorus (mg/dL) | 10.3 ± 4.6 | 7.4 ± 3.7 | 0.01 |
| Troponin I (ng/mL) | 1.23 ± 1.98 | 3.34 ± 8.17 | 0.15 |
| CK-MB (ng/mL) | 7.8 ± 0.14 | 30.1 ± 42.36 | 0.13 |
| PT (s) | 22.3 ± 5.0 | 22.7 ± 28.8 | 0.93 |
| INR | 1.94 ± 0.57 | 2.21 ± 4.5 | 0.71 |
| Hospital disposition | | | |
| ICU LOS, d | 3.50 ± 5.34 | 5.49 ± 7.99 | 0.36 |
| Hospital LOS, d | 4.25 ± 7.15 | 6.63 ± 8.88 | 0.34 |
| 28 day mortality | 81% (13) | 81% (35) | 0.65 |
| Overall mortality | 88% (14) | 84% (36) | 0.25 |
| Antibiotics initiated in the ED | 69% (11) | 30% (13) | 0.01 |

ED indicates emergency department; °C indicates Celcius; HR, heart rate; RR, respiratory rate; BP, blood pressure; MAP, mean arterial pressure; $O_2$, oxygen. Continuous variables are presented as mean ± SD unless stated otherwise. BUN indicated blood urea nitrogen; CKMB, creatine kinase myocardial band; PT, prothrombin time; INR, international normalized ratio and LOS, length of stay. Categorical variables are presented as percentages and absolute numbers ($n$). Continuous variables are presented as mean ± SD unless stated otherwise.

were gram-negative bacteria. The discrepancy in pathogens identified was likely related to the timing of blood culture sampling immediately upon arrival to the ED.

In post cardiac arrest resuscitation, Mongardon et al.[14] reported bacteremia and catheter related infections as the second and third most common infectious complications in hypothermia treated cardiac arrest survivors. Most common identified pathogens were *E. coli*, *Staphylococcus aureus*, *Streptococcus species*, and *S. epidermidis*.[14] They described the isolation of *Streptococcus* species and *S. epidermidis*, skin-indigenous pathogen, to have significant potential in causing bacteremia and should not be disregarded as mere contamination if found in more than one bottle sample.[14] There was no comment whether the presence of bacteremia or other infectious complications existed prior to initiation of hypothermia post cardiac arrest.

In this study, the incidence of bacteremia in OHCA is higher than any previously reported and has significant therapeutic implications. Friedman et al. described a classification system for bloodstream infections that aids in identifying the potential source of infection, pathogen and susceptibility patterns, various comorbid conditions, mortality rates and the implications for empirical antibiotic therapy.[15] In this study, the ED medical team initiated empiric antibiotic therapy in 69% of bacteremic OHCA ED survivors.

Moler et al.[16] recently identified multiple factors during and early post-pediatric OHCA with return of circulation associated

**Table 5**
Logistic analysis based on predictors for Bacteremic OHCA ED survivors.

| | Estimate | Std error | Odds ratio | 90% CI | $p$ |
|---|---|---|---|---|---|
| Predictor | | | | | |
| Arterial pH | −2.390 | 2.491 | 0.092 | (0.002, 5.516) | 0.337 |
| Lactate (mmol/L) | 0.072 | 0.078 | 1.074 | (0.945, 1.221) | 0.358 |
| WBC (K/μL) | −0.017 | 0.047 | 0.983 | (0.913, 1.058) | 0.696 |
| BUN (mg/dL) | 0.019 | 0.015 | 1.020 | (0.995, 1.045) | 0.199 |
| Creat (md/dL) | 0.323 | 0.193 | 1.381 | (1.006, 1.897) | 0.094 |

CI indicates confidence interval; WBC, white blood cells; BUN, blood urea nitrogen; Creat, creatinine. Significance noted for $p$-value < 0.1.

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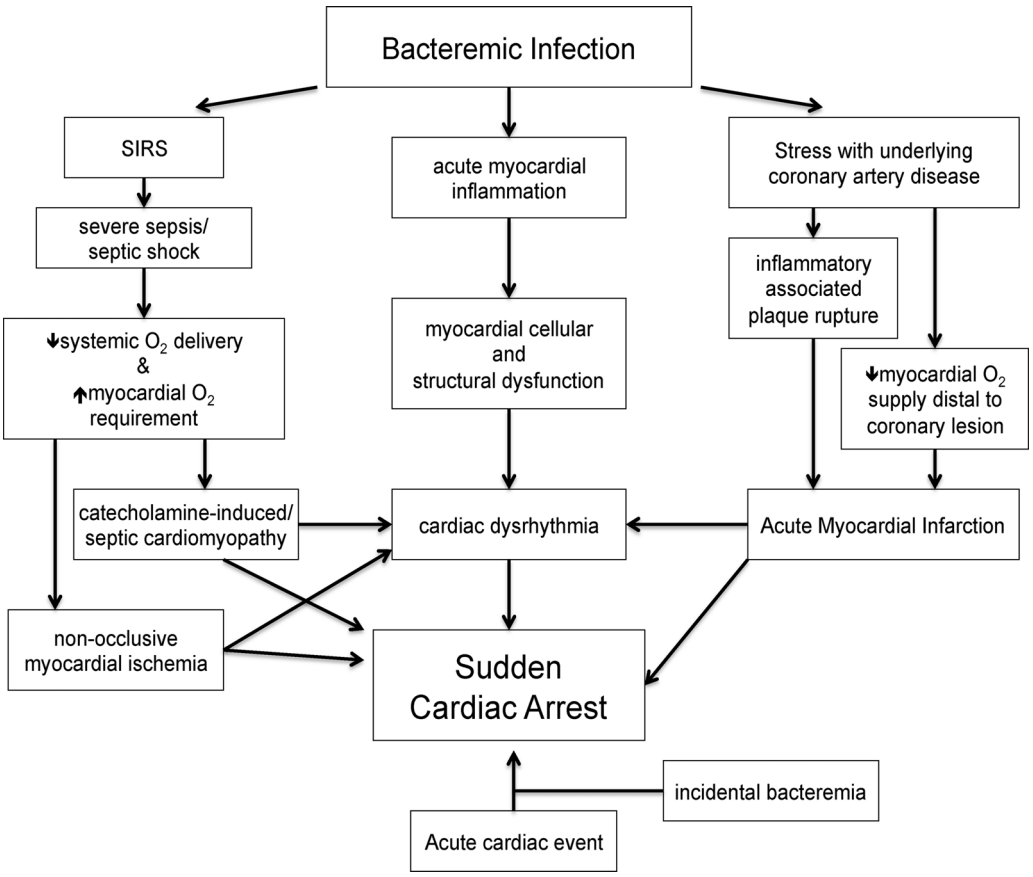


**Fig. 1.** Proposed association between bacteremic infection and sudden cardiac arrest.

with non-survivorship. These factors include asystole, long duration of CPR, presence of any vasopressor or inotropic agent, higher lactate and lower pH.[16] Similarly, our bacteremic OHCA group had significantly higher lactates, a lower pH and the use of vasopressors. Because of the high mortality, our study was not powered to compare survivability rather to identify the prevalence of bacteremia in OHCA adults.

Bacteremia or other confirmed source of infection in post cardiac arrest patients has been associated with hemodynamic instability, worse neurologic outcome and increased mortality.[17–19] Herlitz et al. reported clinical presentation immediately prior to death to be 45% congestive heart failure and 30% infectious complications, 12% aspiration pneumonia and 18% other infections.[20] Simons et al. reported emesis in one third of patients with OHCA. These patients may be associated with the development of pneumonia and had a decreased chance of survival.[21]

### 5.2. Association of bacteremic infection with sudden cardiac arrest

A recent study by Carr et al.[5] examined the characteristics of in-hospital cardiac arrest diagnosed with pre-existing pneumonia. The incidence of pre-existing pneumonia was 12.1% (5367 of 44,416) from a multicenter cardiac arrest registry. A subset of patients developed abrupt cardiac arrest without signs of hypotension, overt shock, respiratory failure or severe metabolic derangements. Comparing patients with preexisting pneumonia to patients with bacteremia, more than half the patients with cardiac arrest in the bacteremic group were hypotensive requiring vasoactive drugs, needing assisted ventilation and more likely found in the ICU compared to the pneumonia group.[5] This highlights the impact of infection (pneumonia) prior to abrupt cardiac arrest and life-threatening arrhythmia irrespective of being monitored in the ICU or the non-monitored GPU.

One proposal for possible association of bacteremia and cardiac arrest was described by Gaussorgues et al. as translocation of gut-flora bacteria after identifying a high incidence of gram-negative bacteria 12 h following CPR.[12] The proposal for translocation bacteremia immediately post cardiac arrest may be consider if the following conditions exist. First condition requires the presence of pathogenic or nonpathogenic bacteria that can easily cross into the blood barrier once disruption occurs during cardiac arrest or ROSC. Second requires the bacteria to regenerate rapidly enough to ensure a high bacterial load throughout the bloodstream into two blood culture vials immediately during ACLS resuscitation irrespective of ROSC. The timing of blood cultures drawn during ACLS resuscitation or ROSC while in the ED was designed to minimize time for bacteria regeneration within the blood. Compared to Gaussorgues et al. findings, this study identified a higher incidence of gram-positive bacteria compared to gut flora unlikely supports immediate bacteria translocation.

Fig. 1 describes four proposed pathways associating bacteremia with sudden cardiac arrest given that the above two conditions of translocation were unlikely in this study setting. It is well established that critically ill diseases including sepsis can be symptomatic up to 24 h prior to hospital arrival.[22] The clinical progression from infection to severe disease can be slow, insidious or abrupt and catastrophic.[23] Cardiovascular insufficiency is the most frequent and important organ dysfunction impacting mortality more than any other organ failure in the first 24 h in patients with infections.[11,24] Three pathways describe the impact of bacteremia leading to a common pathway of sudden cardiac arrest.

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The fourth pathway describes the incidental finding of bacteremia during an acute cardiac event.

One proposed pathway to sudden cardiac arrest is sepsis related bacteremic infection (Fig. 1). Sepsis is a complex disease process where the body's response to a pathogen is amplified far beyond the initial site of infection.[25] Progression to organ dysfunction and cardiovascular compromise in severe sepsis and septic shock is associated with an average mortality of 30–46%.[26] Severe sepsis with cardiac dysfunction has a reported mortality of 70–90%. A common feature in the presentation of patients with severe sepsis and septic shock are arrhythmias such as sustained tachycardia, atrial fibrillation and ventricular arrhythmias.[26–28] These new onset arrhythmias in conjunction with sepsis induced global tissue hypoxia may lead to pathologic cardiac dysrhythmias.[4] Sepsis-related cardiomyopathy involves the endogenous or exogenous catecholamine exposure along with global tissue hypoxia compromising the myocardium leading to massive myocardial infraction or global right and left ventricular dysfunction.[29,30] Postmortem macroscopic findings of the myocardium in septic shock observed high incidence of coronary artery sclerosis and right heart hypertrophy/dilation and a lower incidence of left heart hypertrophy/dilation and myocardial ischemia.[31]

The second proposed common pathway to sudden cardiac arrest involves acute infectious myocardial inflammation and injury. Fernandes et al. described cases of acute infectious myocarditis postmortem that included findings of myocardial interstitial neutrophil infiltration, foci of myocardial necrosis, and formation of abscesses.[32] Experimental studies by intravenous infusion of live bacterial organisms reported myocardial interstitial and intracellular edema, focal mitochondria swelling and subendocardial hemorrhage.[33,34] These cellular and structural changes may lead to significant myocardial damage and global myocardial depression, increasing the risk for cardiac dysrhythmias and complete cardiovascular collapse or sudden cardiac arrest.

Ischemic heart disease remains the predominant cause of sudden cardiac arrest in adults.[35] The last two common pathways to sudden cardiac arrest are primarily related to pre-existing coronary artery disease and the elderly population with underlying comorbidities. The risk factors for sudden cardiac arrest are similar to those seen with coronary heart disease.[36] The most common comorbidities in the bacteremic OHCA group were hypertension, diabetes mellitus, coronary artery disease and congestive heart failure (Table 1). Musher et al.[37] proposed stress from infection particularly pneumonia may rupture a vulnerable plaque leading to significant myocardial infarction in patients with preexisting coronary artery disease.

The final pathway to sudden cardiac arrest may not be related to bacteremic infections. The isolated bacteria found in the bacteremic OHCA group may be an incidental finding given the comorbidities of study population with multiple independent risk factors for sudden cardiac arrest. Carr et al. reported myocardial ischemia/infarction as the small plausible primary cause of in-hospital cardiac arrest in only 6.3% of the pre-existing pneumonia group.[5]

### *5.3. How this paper can change management or current ACLS guideline*

Current 2012 AHA/ACLS post cardiac arrest care guidelines note the importance of cardiopulmonary resuscitation, consideration for therapeutic hypothermia, hemodynamic and ventilation optimization, immediate coronary reperfusion, glycemic control and neurologic care.[14,38] The AHA/ACLS statement on the initial post-cardiac arrest care recommendation includes to "try to identify and treat the precipitating causes of the arrest and prevent recurrent arrest."[8] This study suggests that one major precipitating factor or comorbidity associated with OHCA is unrecognized bacteremia. Furthermore, identified a failure to initiate prompt empiric antibiotic therapy during the post cardiac arrest resuscitation period for the bacteremic OHCA. Further studies are needed to confirm the generalizability of this unexpected high incidence of bacteremia in OHCA than previous reported and the impact of pre-hospital infection on survivability post cardiac arrest.

## 6. Limitations

This study was performed at a single institution with blood cultures randomly drawn with the true number of out of hospital cardiac arrest patients eligible for enrollment unknown possibly underestimating the true prevalence of bacteremia. Given the study design, the likelihood of selection bias is minimized given the similarities in the demographics, laboratory values and resuscitation profiles between the bacteremic and non-bacteremic OHCA groups. The study was not powered to evaluate the impact of bacteremia on survivability and could potentially underestimate the contribution of infection during ACLS resuscitation for cardiac arrest. The study was not designed to determine the infectious causality of cardiac arrest or factors influencing ROSC.

The study was designed to report blood cultures results without requiring specimens from other potential sites of infection. During the study period, the ED medical team initiated empiric antibiotic treatments for both groups. Commonly, empiric antibiotic therapy is initiated for suspicion of infection particular findings on chest X-ray, events prior to cardiac arrest and laboratory results. However, a Hawthorn effect for initiation of empiric antibiotics by the ED medical team knowing that blood cultures were being studied on the cardiac arrest patients is possible. These findings were merely reported with no impact on the incidence of bacteremia in OHCA.

## 7. Conclusion

This study is the first to report over 38% incidence of bacteremia in OHCA adults. The bacteremic OHCA adults had severe metabolic derangements, higher lactates and lower ED survival similar in the characteristic found for severe sepsis and septic shock. Further study is needed to identify the cause and effect relationship between bacteremia and sudden cardiac arrest, whether bacteremia was the immediate byproduct of cardiac arrest or the major contributing factor of unrecognized severe sepsis leading to sudden cardiac arrest.

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## Conflict of interest statement

None.

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