Original Article

Can we predict which patients with community-acquired pneumonia are likely to have positive blood cultures?

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BACKGROUND: Blood cultures (BC) are commonly ordered during the initial assessment of patients with community-acquired pneumonia (CAP), yet their yield remains low. Selective use of BC would allow the opportunity to save healthcare resources and avoid patient discomfort. The study was to determine what demographic and clinical factors predict a greater likelihood of a positive blood culture result in patients diagnosed with CAP.

METHODS: A structured retrospective systematic chart audit was performed to compare relevant demographic and clinical details of patients admitted with CAP, in whom blood culture results were positive, with those of age, sex, and date-matched control patients in whom blood culture results were negative.

RESULTS: On univariate analysis, eight variables were associated with a positive BC result. After logistic regression analysis, however, the only variables statistically significantly associated with a positive BC were WBC less than $4.5 \times 10^9/L$ [likelihood ratio (LR): 7.75, 95% CI=2.89-30.39], creatinine $>106 \mu\text{mol/L}$ (LR: 3.15, 95%CI=1.71-5.80), serum glucose $<6.1 \text{ mmol/L}$ (LR: 2.46, 95%CI=1.14-5.32), and temperature $> 38^\circ\text{C}$ (LR: 2.25, 95% CI =1.21-4.20). A patient with all of these variables had a LR of having a positive BC of 135.53 (95% CI=25.28-726.8) compared to patients with none of these variables.

CONCLUSIONS: Certain clinical variables in patients with CAP admitted to hospitals do appear to be associated with a higher probability of a positive yield of BC, with combinations of these variables increasing this likelihood. We have identified a subgroup of CAP patients in whom blood cultures are more likely to be useful.

KEY WORDS: Community-acquired pneumonia; Blood cultures

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INTRODUCTION

In the management of infectious disease believed to be of bacterial cause, the culturing of blood samples drawn from the patient may identify the causative organism and guide the treating physician to prescribe the most appropriate antimicrobial regimen. With increasing incidences of bacteria resistant to common

antibiotics, and rising costs of more powerful, broader spectrum antibiotics, the identification of the offending organism is considered to be of increasing importance in the management of infectious disease.^[1-3]

In the United States of America, pneumonia results in more deaths than any other infectious disease, and is the sixth leading cause of death in that country.^[4] Elderly

patients, especially those with co-morbidities or immune suppression, are especially vulnerable.^[5] In Halifax County, Nova Scotia, the community-acquired pneumonia (CAP) hospital admission rate for people greater than 74 years of age was reported as 11.6/1000/year (with a rate of 33/1 000 in nursing home patients), compared to 0.54/1 000/year in those aged 35 to 44 years.^[6] We can expect the incidence of CAP to continue to rise as our population ages, and as more people suffer from immune suppression as a result of organ transplantation medication, AIDS or cancer chemotherapy, and CAP will cause a greater proportion of sufferings and consume more and more health care dollars.^[6]

Blood cultures (BC) have traditionally been recommended as part of the work-up of patients admitted to hospitals for CAP in contemporary clinical practice guidelines.^[7-14] The timing of initiation of antimicrobial therapy for CAP is crucial in determining the outcome of the illness.^[15-18] A study of pneumonia in elderly patients showed that a delay of greater than eight hours was associated with a fifteen percent higher mortality at thirty days than those in whom treatment was started before eight hours. In this same study a full 25% of patients waited over eight hours to start antimicrobial treatment.^[5] Other studies have shown that performing BC after antibiotic treatment has greatly decreased the chance of the BC yielding positive results.^[17,19] These realities dictate that emergency practitioners need to be astute in rapidly determining the indications for initial interventions (like the ordering of BC).

The yield of clinically significant positive results of BC, however, is consistently low, and the routine use of blood cultures for patients admitted with CAP has been questioned.^[20-33] A study of patients with CAP admitted to one of 19 different Canadian hospitals showed that of 760 patients in whom BC was performed, only 43 (5.7%) yielded clinically significant results.^[33] A positive result, however, when it is obtained, can be of great assistance to the clinician in optimizing the management of pneumonia and in ensuring that the most cost effective regimen is being chosen, and experts have warned against omitting BC from the work up of CAP.^[34-36] Negative results of BC do not necessarily indicate less severe disease, nor a better prognosis than positive results.^[31,33,37] Furthermore BC do increase the cost of management, and increase blood loss and discomfort of patients.^[4,7-9] The most recent North American CAP guidelines have listed the use of BC as "optional" in all but a sub-segment of admitted patients.^[38] This recommendation is based more on expert opinion than evidence. Attempts to identify

clinical indicators of bacteremia have thus far not yielded any firm or reliable recommendations, and generally are restricted to retrospective evaluation of the population with *Streptococcus pneumoniae* identified as the causative organism, as opposed to the patients presenting with undifferentiated CAP.^[39,40]

In their review of blood culture contamination, Hall and Lyman suggest that "reducing the use of blood cultures in patients with a very low likelihood of bacteremia will result in a higher positive predictive value and reduced costs associated with contamination".^[41]

It is clear that the sub-group of patients most appropriately served by BC needs to be further clarified. This study aimed to identify demographic and clinical factors that will identify patients in whom blood cultures are more likely to yield a clinically significant result and those in whom a positive result is less likely.

METHODS

A structured retrospective systematic chart audit was performed to compare relevant demographic and clinical details of patients admitted with CAP, in whom blood culture results were positive, with those of date-matched control CAP in patients in whom blood cultures were drawn, but from which no organisms were identified.

The hospital charts of all patients admitted to the Queen Elizabeth II Health Sciences Center with CAP between January 1, 2007 and January 1, 2009 and in whom BC results were positive were audited with regard to their clinical and demographic characteristics, with the information entered a standardized computer database. The "relevance" of clinical variables related to community-acquired pneumonia included those used in the PORT criteria,^[42] with further items decided by group consensus (Table 1). Blood cultures that grew organisms felt likely to be contaminants were excluded from analysis. The control charts of two times the number of CAP patients in whom BC were negative were audited using the same format.

Three medical student data abstractors performed the audits according to the standards described by Gilbert et al.^[43] After instruction on specific and explicit abstraction protocols, defining important variables precisely, the abstractors were trained on a set of "practice" medical records before the start of the study in order to ensure the accuracy of the data gathered and the consistency in which clinical details are recorded. Frequent meetings were held with the abstractors and study coordinators to resolve disputes, and review

Table 1. Variables examined with regard to association with a positive BC

Historic variables	Clinical variables	Laboratory variables
Age	Respiratory rate (RR)	Anion gap
Gender		Chloride
Residence in a nursing home		Venous CO ₂
Whether the patient had been on antibiotics at the time of admission.		Creatinine
A history of:		Glucose
Asthma	Systolic blood pressure (SBP)	Hemoglobin
Congestive heart failure	Heart rate (HR)	Potassium
COPD	Temperature	Sodium
Other respiratory illness	Oxygen saturation (SaO ₂)	Urea
Diabetes	The presence of altered mental status	WBC
Ischemic heart disease	X-ray variables	WBC
Hepatic disease	Lobar consolidation (one lobe)	PaO ₂
Renal disease	Lobar consolidation (>one lobe)	pH
Current malignancy/within previous 6 months	Bronchopneumonia	
Previous malignancy (>6 months)	Pleural effusion	
Other co-morbidity		

coding rules. The abstractors were blinded as to the hypothesis being tested (ie. whether there are factors that would predict a positive BC or not), and to whether the patient's BC results were positive or negative. To reduce the incidence of transcription errors, data were entered directly (concurrent with abstraction) onto a computerized data abstraction form developed by the Dalhousie Emergency Database Manager, and tested and refined in a previous study involving over 800 patients with pneumonia.^[44]

Statistical analysis of our data was performed using the SAS statistical software. Each variable was explored to determine whether it correlated with a higher likelihood that a patient owning the variable would have a positive blood culture. A logistic regression procedure was then performed with the stepwise selection option to select the most important exploratory variables.

RESULTS

A total of 89 patients with positive BC were identified for auditing, and each one was matched with two control patients with similar age and gender, admitted for CAP, who had had negative BC results (after having two or more BC drawn within 24 hours of admission).

Of these, the charts of 83 patients in the positive BC group and 169 of the 178 control patients were available for auditing. Organisms cultured from the BC group are listed in Table 2.

The variables found on univariate analysis to be associated with a higher likelihood of positive BC are shown in Table 3.

Table 2. Organisms cultured from blood

Organism	Total	%
Acinetobacter lwoffii 2	1	1.1
Afermentive Gram negative rod	1	1.1
<i>Corynebacterium Jeikeium</i>	1	1.1
<i>Enterococcus Faecalis</i>	1	1.1
<i>Escherichia Coli</i>	10	11.2
Gemella species	1	1.1
Gram negative coccobacilli	1	1.1
Gram negative rods	6	6.7
<i>Haemophilus influenzae</i>	1	1.1
<i>Klebsiella oxytoca</i>	1	1.1
<i>Klebsiella pneumoniae</i>	2	2.2
<i>Leuconostoc species</i>	1	1.1
<i>Peptostreptococcus productus</i>	1	1.1
<i>Propionibacterium SP</i>	1	1.1
<i>Proteus mirabilis</i>	3	3.4
<i>Pseudomonas aeruginosa</i>	3	3.4
<i>Staphylococcus aureus</i>	11	12.4
<i>Stenotrophomonas maltophilia</i>	1	1.1
<i>Streptococcus mitis</i>	1	1.1
<i>Streptococcus mitis</i> (2)	1	1.1
<i>Streptococcus mutans</i>	1	1.1
<i>Streptococcus pneumoniae</i>	34	38.2
<i>Streptococcus sanguis</i>	1	1.1
Streptococcus, group B	1	1.1
Streptococcus, group G	3	3.4
Total	89	

Table 3. Likelihood of positive BC on univariate analysis

Variables	LR of +ve BC	95% CI	Patients meeting the criteria
WBC<4.5×10 ⁹ /L	8.96	2.87-27.98	19/246
Anion gap>16	4.27	1.04-17.52	9/244
Systolic BP<90 mmHg	3.87	1.46-10.25	19/247
Creatinine>106 µmol/L	2.87	1.65-5.00	117/242
Urea>9.3 mmol/L	2.49	1.40-4.42	139/242
Glucose<6.1 mmol/L	2.18	1.09-4.35	194/234
No antibiotics on admission	2.01	1.02-3.98	193/252
Temperature>38 °C	2.00	1.16-3.46	135/247

Table 4. Variables significantly associated with positive BC results after logistic regression analysis

Variable/combination	LR of + ve BC	95% CI	Patients meeting the criteria
WBC<4.5×10 ⁹ /L	7.75	2.31-26.00	19/230
Creatinine>106 μmol/L	3.15	1.71-5.80	110/230
Glucose<6.1 mmol/L	2.46	1.14-5.32	190/230
Temperature>38 °C	2.25	1.21-4.20	126/230
Combination of all four variables	135.53	25.28-726.8	2/230

After logistic regression analysis, only four variables remained statistically associated with positive BC results (Table 4). The most parsimonious model including all of these four variables yielded a LR of 135.53 (95% CI=25.28-726.8).

DISCUSSION

Blood cultures in patients with CAP admitted to the hospital are recommended in many clinical practice guidelines for CAP.^[7-14] They are also used as an indicator for the quality of care in patients with CAP.^[45,46] The yield of the cultures, however, is very low, and many researchers have demonstrated the low clinical utility of the test,^[20-33, 47-51] the excessive cost per case that changes practice, and the inappropriateness of their use to measure quality.^[46,52] Even for epidemiological purposes, blood cultures have severe limitations because of the inability of standard methods to culture many common causes of CAP (viral and "atypical" pathogens), and the fact that resistant strains (of utmost importance in epidemiologic studies) are frequently under-represented in blood-culture identified series because of lower rates of bacteremia in many resistant strains. Furthermore, the combination of low pretest probability and high false positive rates due to contamination^[41,50] often leads to a situation in which clinicians are not sure how to interpret positive results.

There is undoubtedly significant value in identifying causative organisms in patients with CAP, especially sicker patients where discordant treatment has the greatest potential to result in a poor outcome. Indeed, articles demonstrating the limitations of blood cultures are frequently accompanied by editorials or letters citing anecdotal cases where blood cultures "saved the day" for a particular patient.^[34-36] It seems likely that there is a place for blood cultures in CAP management although far less than that prescribed by "expert-opinion" based practice guidelines.^[38] Selective use of BC would

provide us the opportunity to save healthcare resources and patient discomfort. Several authors have suggested that BC be reserved for patients with more severe CAP, co-morbidities,^[26,27] or old age^[52] although the association between more severe illness and positive results has not been consistent^[33] even in the intensive care population.^[53] Several investigators have examined the differences in clinical course and presentation of patients subsequently confirmed to have pneumococcal pneumonia.^[39,40,54,55]

In deriving a model to predict bacteremia in in-patients, Bates et al^[56] found that a temperature of 38.3 °C or higher, the presence of a rapidly (less than 1 month) or ultimately (less than 5 years) fatal disease, shaking chills, intravenous drug abuse, acute abdomen on examination, and major comorbidity were independent multivariate predictors of true bacteremia.

A subsequent study of two prediction rules for bacteremia found that the "low-risk group" of the more reliable of the two rules still had bacteremia in 7% and 8% of patients in the university and community hospital populations, respectively^[57] (rates higher than those reported for undifferentiated CAP patients in most CAP studies).

Studies of BC in general emergency department patients showed that the yield of BC and contribution thereof to patient care is minimal.^[58-60] Our study is the first to assess the association between specific clinical variables on ED presentation in patients with undifferentiated CAP and subsequently positive BC.

We identified features associated with a higher likelihood of a positive BC result in patients admitted to hospital with CAP. Interestingly, a low white blood count (WBC) was associated with a higher likelihood of a positive BC than a normal or high WBC, most likely because the leucocytosis is indicative of an adequate cellular immune response. Surprisingly, we found that hypo- or normo-glycemia was actually associated with a higher yield of positive BC than hyperglycemia. This was surprising, in light of the belief that a blood glucose >13.9 mmol/L is associated with a higher pneumonia severity.^[42] We hypothesize that this finding may be related to the hypothalamic-pituitary-adrenal axis response to infection. Other investigators have found that the use of antibiotics at the time of presentation with CAP is associated with a two-fold lower incidence of positive BC.^[19] In our study, although the non-use of antibiotics was associated with a higher likelihood of positive BC on univariate analysis, this statistical significance was not seen after logistical regression analysis.

Apart from the presence of a low WBC ($<4.5 \times 10^9/L$), the LRs were all less than five. Thus, we are unable to claim that we have developed a strong tool with which clinicians can safely identify patients needing blood cultures with a high degree of sensitivity. When the four factors were still found to be statistically significant after logistic regression analysis (Table 3), the LR rose to 135.53 (95% CI: 25.28-726.8). Although this sounds impressive, only two subjects of the total population studied met all four of the criteria, suggesting the limited clinical use of the identification of this group. However, the data from this study add to our understanding of the issue. A frequent perception is that patients with high WBC are more likely to be bacteremic and are likely to have a poorer prognosis. Austrian and Gold^[61] found that a leukocyte count of 10 000 to 25 000/mm³ was associated with the best chance of recovery, and that mortality was highest in those with the count less than 5 000/mm³.

Other limitations of the study include the retrospective nature. We attempted to mitigate by stringent data abstraction procedures, with abstractors blinded to the hypothesis. Subjects were identified from a laboratory database of patients with CAP who were subjected to BC. We did not identify patients with CAP admitted to hospitals, who were not subjected to BC. Finally the variables chosen for analysis were based on the criteria as well as a few well accepted CAP features because they were most likely to be on the patient chart. Others have used far more extensive lists of variables associated with CAP. Musher et al^[55] found a higher incidence of bacteremia in African-Americans and those with significant alcohol intake, and factors that are generally not available on patient charts.

We may have missed a number of variables that might be useful for estimating the chance of positive BC.

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Contributors: Campbell SG proposed the study and wrote the paper. All authors contributed to the design and interpretation of the study and to further drafts.

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