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Simple Clinical Information may Guide Treatment of Bloodstream Infections

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Abstract

Background: Early appropriate antibiotic therapy improves the prognosis of patients with bloodstream infection (BSI). Our goal was to define the use of antimicrobial agents active against Enterococcus species; we explored the possibility that simple clinical and laboratory parameters may be able to identify those individuals at high risk of suffering BSI caused by Enterococcus species.

Methods: Total of 165169 blood culture bottles from 27360 patients were screened. Patients with blood cultures positive for Gram positive cocci in chain were identified (n=365) and they were classified as having hospital acquired infection (HAI) or community acquired infection (CAI) according to the Centers for Disease Control and Prevention (CDC) criteria. We recorded simple clinical and laboratory parameters (plasma C-reactive protein (CRP) concentration, blood white cell count (WBC), data of systolic and diastolic blood pressure, heart rate, and body temperature) at the time when the blood cultures were drawn.

Results: It was found that CAI cases were most often (86%) caused by Streptococcus species but the majority (73%) of HAI episodes were caused by Enterococcus isolates ($p<0.001$). We also found that combining the data of origin of the infection, age of the patient, and plasma CRP concentration could help to predict the bacterial finding within the CAI category: blood cultures positive for enterococci were mostly encountered among the elderly (>60 years) exclusively with low CRP values. In the HAI category, the bacterial finding was not associated with these parameters.

Conclusion: Our study demonstrates that basic clinical observations and laboratory parameters may effectively guide antibiotic treatment early during the course of BSI caused by Gram positive cocci in chain. These parameters are extremely simple to perform and are readily available in most hospitals. We conclude that clinical evaluation should not be overlooked despite the emergence of novel microbiological methods.

Keywords Blood; Infection; Antimicrobial agent

Introduction

Timely and accurate antibiotic treatment early during the course of suspected Bloodstream Infection (BSI) has been shown to improve a patient's prognosis [1,2]. Blood cultures should be collected before the initiation of empiric antibiotic treatment and thus a conventional Gram staining result may be available within a few hours. Although rapid advance are being made in bacterial identification methodology, the Gram stain of a positive blood culture still has an important role to play. The Gram stain is very accurate and the result may help decide quickly on the early appropriate antimicrobial treatment [3-5]. Combining the stain results with information on whether the infection is hospital- or community-acquired may further assist in coming to the decision about the best antimicrobial treatment for BSI [6,7].

Blood culture Gram staining result of positive cocci in chains may indicate the presence of either Streptococcus or Enterococcus species in the bloodstream of the patient. While the majority of the Streptococcus isolates remain sensitive to penicillins and cephalosporins, there are now a substantial number of resistant Enterococci [8-10]. BSI attributable to Enterococci is associated with a high incidence of the Systemic Inflammatory Response Syndrome (SIRS) [11] and a significant mortality rate [12]. It has been shown that any delay in the initiation of antimicrobial agents active against Enterococci may influence the clinical course of the illness or even lead to increased mortality [12,13]. It is evident that the early identification of BSI patients would be advantageous since the provision of antibiotics active against Enterococci should improve their prognosis.

The most typically prescribed first line antibiotics to treat a suspected BSI are in general those active against the Streptococcus isolates. The efficacious treatment of Enterococci, however, may require choice of alternative drugs. Our current study aims to clarify the early use of agents active against Enterococci; we have evaluated simple clinical, physiological, and laboratory parameters that could possibly be used to identify patients with BSI caused by Enterococcus species.

Materials and Methods

Blood cultures and classification

A total of 165169 blood culture bottles from 27360 patients were screened for bacterial and yeast growth in Oulu University Hospital

(Oulu, Finland) between January 1, 2004 and December 31, 2008. In all, 6880 (4.2%) bottles from 2653 (9.7%) patients yielded positive for growth. All samples from patients older than 18 years of age were included into this study. Blood cultures were carried out by an automated continuous-monitoring screening system supplied by BacT/ALERT (BacT/Alert, (bioMerieux SA, Lyon, Marcy-l´Etoile, France) for at least five days for bacteria or for two weeks for yeasts. The blood culture sets included both aerobic and anaerobic BacT/ALERT bottles. All positive samples were first analyzed by Gram staining (and by acridine orange staining, if necessary) and the result was immediately reported to the clinician by phone. The final identification of the streptococcal and enterococcal species was carried out by the rapid ID 32 Strep test (bioMerieux SA, Lyon, Marcy-l´Etoile, France). Antimicrobial susceptibility of each strain was tested according to Clinical Laboratory Standard Institute (CLSI) guidelines. The bacterial isolates were divided into two categories according to their in vitro penicillin sensitivity; this result was considered to indicate whether or not the patient would benefit from administration of antibiotic active against the Enterococci.

Patients with blood cultures positive for Gram positive cocci in chain were analyzed. The clinical significance of the findings was judged according to the Centers for Disease Control and Prevention (CDC) criteria [14]; those that fulfilled the CDC criteria were included into this study (n=365). BSI was classified as hospital acquired (HAI) when the infection was not suggested or present when the patient was admitted to the hospital. Other cases were considered community acquired (CAI) with the exception of patients in whom the infection had been acquired during some earlier antimicrobial treatment.

Clinical information

Clinical and laboratory parameters are stored in the electronic files of each hospitalized patient and these were collected for analysis. For each blood culture positive patient, we collected data about the plasma C-reactive Protein (CRP) concentration, and blood White Cell Count (WBC). Data of systolic blood pressure, diastolic blood pressure, heart rate, and body temperature at the time when the blood samples were drawn was also collected.

Statistical analysis

The data was analysed with PASW Statistics 18 (SPSS Inc., Chicago, IL., USA). The T-test and Chi-Square test were used to test for the statistical significance between the clinical and laboratory parameters and the blood culture finding. A p-value of <0.05 was considered statistically significant. We searched for prognostic markers to differentiate penicillin sensitive cases from resistant microbes using multivariable analysis of two or more parameters but no useful parameter combination found.

Results

Total of 365 patients with blood cultures positive for Gram positive cocci in chains fulfilled the CDC criteria of true BSI. Community acquired infections (n=245) were more common than the hospital acquired BSI (n=120) (Table 1). Penicillin sensitive Streptococcus species predominates in the CAI category whereas Enterococcus isolates were common among the HAI cases (Table 1). The origin of infection seemed to predict whether the patient had penicillin-sensitive or penicillin-resistant bacteria in his/her blood (Table 1). Community acquired BSI cases were most likely to be penicillin sensitive and majority of HAI episodes were attributable to penicillin resistant bacteria (p<0.001).

	Community acquired BSI n=245	**Hospital acquired BSI n=120**
Streptococcus, viridans group	16	15
Streptococcus, beta haemolytic	85	17
Streptococcus pneumoniae	123	0
Enterococcus species	21	88
All, penicillin sensitive	224	32***
All, penicillin resistant	21	88***

Table 1: Summary of Gram positive cocci in chain found in blood cultures of 365 BSI patients subdivided according to the origin of infection (community or hospital acquired infections) and the major bacterial categories. A summary of the bacteria isolated that displayed penicillin sensitivity is also shown. ***=p<0.001.

	All patients (n)		**CAI patients (n)**		**HAI patients (n)**	
	pen S	**pen R**	**pen S**	**pen R**	**pen S**	**pen R**
CRP	193** (236)	117 (91)	200** (209)	107 (20)	136 (26)	119 (71)
Blood white cells	13,8 ** (240)	10,6 (97)	13,9 (211)	12,3 (21)	13,3 (28)	10,1 (76)
Systolic blood pressure	126 (187)	125 (81)	126 (161)	129 (19)	124 (25)	123 (62)
Diastolic blood pressure	71 (187)	70 (81)	71 (161)	72 (19)	69 (25)	70 (62)
Heart rate	102** (165)	92 (74)	103 (141)	98 (15)	98 (23)	90 (59)
Age	58,9** (256)	64,2 (109)	58,3** (224)	70,6 (21)	62,3 (32)	62,7 (88)
Body temperature	38,2* (163)	37,8 (81)	38,2 (137)	37,9 (16)	38,3* (25)	37,8 (65)

Table 2: Summary of plasma C-reactive protein concentration (CRP, mg/ml), blood white cell count (×10e9), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (beats per minute), age of patient (years), and body temperature (°C) at the time when the blood cultures were drawn divided according to origin of the infection and antimicrobial susceptibility. Penicillin-sensitive (pen S) bacteria represent Streptococcus isolates and penicillin-resistant (pen R) are Enterococcus isolated. *=p<0.05, **=p<0.01. Number of isolates in each condition is shown (n).

Plasma CRP concentration (p<0.01), blood white cell count WBC (p<0.01), heart rate (p<0.01), and body temperature (p<0.05) were

higher in patients with a penicillin-sensitive bacterial finding as compared to those with penicillin-resistant bacteria (Table 2). In addition, the patients with BSI caused by penicillin-sensitive bacteria were younger than those with a resistant isolate ($p<0.01$). If one combines the data of origin of the infection (CAI or HAI), age of the patient, and plasma CRP concentration measured when the blood cultures were drawn seemed to help predict the penicillin sensitivity of the bacterial findings in the CAI patients (Figure 1A).

Discussion

Any delay in provision of empirical antibiotic therapy of an invasive infection is associated with increased mortality [15] and it is known that early adequate treatment of BSI caused by an enterococcus is crucial to patient survival [12]. Our study demonstrates that very basic clinical observations and simple laboratory parameters can be used to help decide on the appropriate antibiotic treatment of BSI caused by Gram positive cocci in chain. For example, 73% of hospital acquired BSI episodes in our study were caused by enterococci and it may be advisable to consider antibiotic treatment against enterococci in all such cases (Figure 1B).

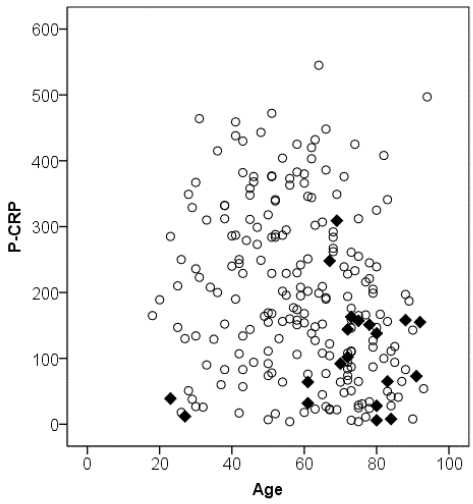

Figure 1: (A) The community acquired BSI cases according to their age (years) and their plasma C-reactive protein (P-CRP) concentration (mg/ml) measured at the time when the blood cultures were drawn. Patients with penicillin-sensitive bacteria (open circle) and penicillin-resistant bacterial findings (solid symbol) are shown.

We also found that the age of the patient, for example, can be used to predict the bacterial finding: empirical treatment directed against enterococcus bacteremia should be provided to elderly patients with community acquired BSI; especially those of advanced age and a low plasma CRP concentration were associated with enterococcus blood culture isolates.

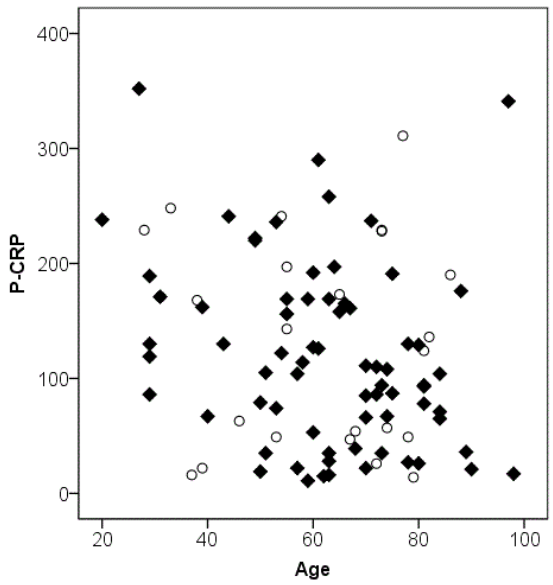

Figure 1B: Hospital acquired BSI cases according to their age (years) and their plasma C-reactive protein (P-CRP) concentration (mg/ml) measured at the time when the blood cultures were drawn. Patients with penicillin-sensitive bacteria (open circle) and penicillin- resistant bacterial finding (solid symbol) are shown.

It is important to identify those patients who do not require antibiotics active against enterococci in order to avoid toxicity and the potential of resistance development. In our study, 86% of community acquired patients had penicillin-sensitive bacteria in their blood cultures. In particular patients with community acquired infection and aged 60 years or below rarely required treatment for enterococcus BSI (Figure 1A). In the patients with hospital acquired infection, however, there was no apparent correlation between the clinical parameters and the blood culture finding. It is possible that other illnesses and conditions such as infection at some other body location, malignant conditions, and surgical procedures may all influence the measured parameters. Unfortunately, simple clinical or laboratory parameters were not able to distinguish whether or not a patient with hospital acquired BSI had an enterococcus bacteremia.

Advanced laboratory techniques based on Mass Spectrometry (MS) or identification of bacterial DNA may help to identify micro-organisms or their resistance properties. However, most typically conventional blood cultures are still required before these methods can be employed [16,17]. Although several Gram negative bacterial species are readily identified by these modern methods, the accurate detection of Gram positive cocci or polymicrobial infections directly from blood cultures using MS remains challenging [18]. In addition, MS is only available in most laboratories during office hours and accessibility may also be restricted in small hospitals or in hospitals operating under resource limited conditions. The simple clinical and laboratory parameters used in our study, however, are cheap and they are readily available in most hospitals. We conclude that none of the current microbiological methods based on bacterial cultures and their identification can replace careful evaluation conducted by experienced clinician at the time when the very early empiric antimicrobial treatment is being selected. Early conventional clinical information

may indeed help to guide the promt treatment and improve the prognosis of a BSI patient.

Basic clinical evaluation should not be overlooked in the era of advanced microbiological technologies. Simple clinical information available at any time is a valuable resource for the busy clinician. We are convinced that hospitals should collect and follow their own statistical data on bacterial findings and employ this information to guide BSI treatment. We believe that additional simple clinical parameters can be found and they can be used to improve the efficacy of the BSI patient care.

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