

Coagulase Negative Staphylococci from Blood Cultures Contaminants or Pathogens?

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ABSTRACT

Detailed clinical data, underlying conditions, inflammatory indices and microbiological parameters in 60 patients who had pure growth of coagulase negative staphylococci from their blood culture specimens at the University Hospital of the West Indies, Jamaica, were analyzed and the clinical significance of the isolates ascertained using standard criteria. This study was undertaken between April and September 2003. The isolates were true pathogens of bloodstream infections in only 5 of the 60 patients (8.4%). In the vast majority ie 44 of 60 (73.3%) they were mere blood culture contaminants and in 11 (18.3%), the clinical significance could not be ascertained. Fifteen of the 44 patients (34%) with contaminating coagulase negative staphylococci were treated with specific anti-staphylococcal antibiotics; 5 (11.4%) with vancomycin. Although there has been a relative increase of coagulase negative staphylococcal infections including bloodstream infections in recent years, the organisms still remain the most common contaminants in blood cultures. Over 70% of isolates were contaminants in this study which is similar to that in a number of such studies in other parts of the world. The findings underline the need for careful evaluation of coagulase negative staphylococci isolated from blood cultures before instituting therapy to avoid unnecessary use of antibiotics, especially vancomycin, and the consequent increase of antibiotic resistance in hospitals.

Estafilococos Coagulasa-Negativos de Cultivos de Sangre: ¿Contaminantes o Patógenos?

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RESUMEN

Los datos clínicos detallados, las condiciones subyacentes, los índices inflamatorios así como los parámetros microbiológicos de 60 pacientes que presentaron crecimiento puro de estafilococos coagulasa-negativos de sus cultivos de sangre en el Hospital Universitario de West Indies, Jamaica, fueron sometidos a análisis. De este modo, se pudo determinar la significación clínica de los aislados, usando criterios estándar. En sólo 5 de los 60 pacientes (8.4%), los aislados resultaron ser realmente patógenos de infecciones del torrente sanguíneo. En la gran mayoría, a saber 44 de 60 (73.3%), se trataba tan sólo de contaminantes en el cultivo de la sangre, y en 11 (18.3%) no pudo determinarse la importancia clínica. Quince de los 44 pacientes (34%) con estafilococos coagulasa-negativos contaminantes, fueron tratados con antibióticos antiestafilocócicos específicos, y 5 (11.4%) con vancomicina. Aunque en años recientes ha habido un aumento relativo de infecciones por estafilococos coagulasa-negativos – incluyendo infecciones del torrente sanguíneo – los organismos siguen siendo todavía los contaminantes más comunes en los cultivos de sangre. Más del 70% de los aislados resultaron ser contaminantes en este estudio: un resultado similar al obtenido en una serie de estudios de este tipo realizado en otras partes del mundo. Los hallazgos apuntan a la necesidad de realizar una evaluación cuidadosa de los estreptococos coagulasa-negativos aislados en los cultivos de sangre antes de proceder a instituir la terapia, a fin de evitar el uso innecesario de antibióticos – en especial la vancomicina – y el consiguiente aumento de la resistencia antibiótica en los hospitales.

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INTRODUCTION

Coagulase negative Staphylococci, hitherto considered to be common contaminants are being increasingly recognized as nosocomial pathogens (1, 2). The organisms have been and continue to be known pathogens in urinary tract infection, prosthetic valve endocarditis, patients with intravenous catheters and indwelling foreign devices, peritoneal dialysis catheter associated peritonitis, cerebrospinal fluid shunt infections in neonates, especially when they are premature (1). They are also common opportunistic pathogens in patients who are immunocompromised (1). However, there are a number of recent reports which state that coagulase negative staphylococci are the most common pathogens of bloodstream infections (3, 4). Such reports have stirred controversy (5). On the other hand, there are others who after careful clinical evaluation of isolates of coagulase negative staphylococci from blood cultures suggest that although there is a relative increase of coagulase negative staphylococcal infections including bloodstream infections in recent years, the organisms still remain the most common contaminants in blood cultures (6–9).

There is no doubt that coagulase negative staphylococci are the most common isolates from blood cultures. But are they the most common pathogens as is reported? If not, how often are the coagulase negative staphylococci isolated from blood cultures, the true pathogens of bloodstream infections and how often are they mere blood culture contaminants? These are the questions for which there are no clear cut answers and the points which continue to be debated (10).

At the University Hospital of the West Indies (UHWI) in Kingston, Jamaica, about 5000 blood cultures are performed per year. Coagulase negative staphylococci are the most common isolates accounting for nearly one-third of all the blood culture isolates encountered in this hospital (unpublished data). This study examines the clinical data, laboratory indices and other characteristics of patients with pure growth of coagulase negative staphylococci from blood cultures, ascertains the clinical significance of isolates and try to answer the question, 'How often is a coagulase negative staphylococcus isolated from blood culture a pathogen in this hospital?' The results are compared with those of similar studies done in various parts of the world and the relevance of the findings to the day-to-day clinical management of bloodstream infections in this hospital is discussed.

METHODS

Clinical data, laboratory indices, microbiological parameters and patient characteristics in 60 patients who had pure growth of coagulase negative staphylococci in their blood cultures were analyzed. This study was undertaken between April and September 2003. The data were collected using a protocol designed by the authors which was similar to that used by Weinstein *et al* (6) in their study on bloodstream infections. The detailed protocol is shown in the appendix and the salient features of the protocol are outlined in Table 1.

Table 1: Salient features of the protocol used to ascertain the clinical significance of the isolates

The clinical significance of the isolates was determined using criteria after Weinstein *et al* (6). These included, among others, elevated body temperature, abnormal haematological indices (leucocyte and differential count), raised erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) if available, hypotension and evidence of shock if any, low urine output, and isolation of the same strain (antibiotype) in multiple blood cultures. Other criteria were presence of a predisposing factor such as intravenous catheter or indwelling foreign device and correlation with culture results from such a device if any, duration of incubation to detect growth, results of culture of specimens from some other sites and clinical course and response to antibiotic therapy (See appendix).

The vast majority of patients (44) were adults, 31–78 years, mean age 61 years. There were nine paediatric patients aged 1–8 years. In seven patients, the age was not known.

The specimens of blood were cultured using Bactec 9240 blood culture system (Becton Dickinson and Company, Maryland) and the isolates of coagulase negative staphylococci were identified by standard methodology including Gram reaction, catalase and coagulase test (11).

RESULTS

Table 2 presents data on clinical significance of coagulase negative staphylococci isolated from blood cultures in 60 patients at the UHWI. As is seen, the vast majority, *ie* 44 out of 60 (73.3%) were contaminants. In 5 patients (8.4%), the isolates were true pathogens of bloodstream infection. The authors could not ascertain the significance of the isolates in 11 (18.3%).

Table 2: Clinical significance of pure growth of coagulase negative staphylococci isolated from blood cultures in 60 patients at the UHWI, Kingston, Jamaica

Category	Number	Per cent
Significant (True pathogen)	5	8.4
Contaminant	44	73.3
Indeterminate*	11	18.3

*In 11 patients, we were unable to accurately ascertain the clinical significance

Table 3 shows the antibiotic therapy in 44 patients who had contaminating coagulase negative staphylococci in their

Table 3: Antibiotic therapy in 44 patients with contaminating coagulase negative *Staphylococci* from blood cultures at UHWI

Antibiotic therapy	Number of patients	Per cent
No antibiotic	9	20.5%
Specific Antistaphylococcal Antibiotic	15	34%
Vancomycin	5 (11.4%)	
Cloxacillin	5 (11.4%)	
Others	5 (11.4%)	
Other Antibiotics	20	45.5%

blood cultures. Antibiotics were not given to nine patients (20.5%) (probably the clinicians recognized that the isolates were contaminants). An anti-staphylococcal antibiotic was

given to 15 patients (34%); vancomycin to 5 (11.4%), cloxacillin to 5 (11.4%), and others to 5 (11.4%). The remaining 20 patients (45.5%) received various other antibiotics. Overall, nearly 80% of the patients with contaminating coagulase negative staphylococci from their blood cultures received antibiotics.

DISCUSSION

The results were similar to those obtained in studies done in hospitals in United States of America, United Kingdom and Sweden, where the contamination rate of coagulase negative *Staphylococci* encountered from blood cultures was high ranging from 72% to 90% (Table 4).

Coagulase negative staphylococci are important causes of infections associated with biomaterials such as intravenous catheters and various indwelling foreign devices. Some strains of coagulase negative staphylococci produce some virulence factors. These include, among others, a surface Polysaccharide Adhesin (PS/A) and an Extracellular Slime Substance (ESS) which are responsible for biofilm formation on the surface of the biomaterial. The first step in the formation of such biofilm is adhesion of the organisms to the biomaterial. This is mediated by PS/A, then the biomaterial and bacterial cells become coated with a variety of serum and tissue fluid components such as fibronectin, fibrinogen, vironectin which influence further binding. The next step involves the production of ESS which ultimately brings about the biofilm formation. The biofilm thus formed includes en-

Table 4: Clinical significance of coagulase negative *Staphylococci* isolated from blood cultures. A review of some published data and comparison with data obtained at the University Hospital of the West Indies.

Institution/ Setting	Number of patients/coagulase negative <i>Staphylococci</i> evaluated	Results No (%)			Reference
		Pathogens,	Indeterminate	Contaminants	
Duke University Med Center, Durham, NC, Robert Wood Johnson University Hospital, NJ, and Salt Lake City, Veteran Admin Med Centre, Salt Lake City USA	703 isolates	87 (12.4%)	41 (5.8%)	575 (81.9%)	6
Oxford Public Health Laboratory UK	129 patients	13 (10%)		116 (90%)	7
Deaconess Med Center and Sacred Heart Med Center Spokane, Washington USA	81 patients	20 (24.7%)	10 (12.3%)	59 (72.8%)	8
Malmo General Hospital, University of Lund, Sweden	73 patients	3 (4.1%)	4 (5.5%)	66 (90.4%)	9
Present study UHWI	60 patients	5 (8.4%)	11 (18.3%)	44 (73.3%)	

cased multiple layers of bacteria which are protected from phagocytic activity and also function as penetrating barrier to antibiotics. The growing increase of patients with biomaterials and those who are severely immunocompromised are some of the factors responsible for the relative increase of coagulase negative staphylococcal infections including blood stream infections.

Ascertaining the clinical significance of an isolate of coagulase negative staphylococcus from blood culture is difficult (12, 13). Unlike isolates such as *Escherichia coli*, *Klebsiella pneumoniae*, *Streptococcus pyogenes* and *Staphylococcus aureus*, which are encountered often as pathogens and diphtheroids and bacillus species which invariably are contaminants, coagulase negative staphylococci could be either pathogens or contaminants when encountered in blood cultures. Furthermore, because of their low virulence, they may not evoke sufficient inflammatory response and thus a number of patients with coagulase negative staphylococcal bloodstream infection may not have typical clinical manifestations and laboratory indices of infection (12). In addition to standard criteria of infection, certain other criteria have to be taken into account to ascertain the significance of the isolate in such a situation. Some of these are:

1. Isolation of the organism in multiple blood cultures.

Same strain of coagulase negative *staphylococcus* isolated in pure growth in multiple blood cultures taken from different body sites or at different times is more likely to be a pathogen than a contaminant (14). However, it should be borne in mind that it is not an absolute indicator of infection (7, 14). Interpretation of the clinical significance should not be based solely on this criterion. It should be used in conjunction with other parameters in ascertaining the significance. There are a large number of species and strains of coagulase negative staphylococci (1). To ascertain that multiple isolates encountered from a patient are of the same type requires strain typing. Many laboratories in developing countries cannot afford to do speciation and strain typing routinely. Comparison of antibiotic susceptibility pattern (antibiotype) is an alternative in such a situation. Antibiotype comparison, however, may not be as accurate as speciation and strain typing.

2. The nature of the patient involved.

Coagulase negative staphylococcus rarely ever causes bloodstream infection in a healthy immunocompetent young adult without any predisposing factor. Hence a predisposing factor such as central venous catheter, indwelling foreign devices, the very young or old (especially premature neonates), immunocompromised and undernourished state, a ventriculo-venous shunt or any other predisposing factors (1) should be looked for and correlated in the evaluation.

3. Duration of incubation to detect growth.

In general, pathogenic bacteria grow in a shorter time than contaminants in blood cultures (15, 16). This may be applied

in case of coagulase negative staphylococci. Isolates which grow within a few hours or in the first day of incubation are more likely to be pathogens compared to those which grow late, especially after 48 hours (15, 16).

All these clearly illustrate the difficulties in ascertaining the clinical significance of an isolate of coagulase negative staphylococcus from blood culture. Despite detailed evaluation, the authors were unable to accurately ascertain the clinical significance in nearly one fifth of the patients (Table 2). This has been the experience of a number of others who have undertaken similar studies (Table 4).

There is a tendency for clinicians and some clinical microbiologists to overuse antibiotics in patients with coagulase negative staphylococci from blood cultures. One-third of the study patients with contaminating coagulase negative staphylococci were treated with specific anti-staphylococcal antibiotics (Table 3). Souvenir and others in their study found that one-half of the patients with contaminating coagulase negative staphylococci were treated with antibiotics and 34% with vancomycin (8).

Coagulase negative staphylococci from blood cultures were once dismissed as mere contaminants (17, 18). With changes in therapeutic modalities and patient population, there has been some increase of coagulase negative staphylococcal infections including bloodstream infections in recent years (1, 2). However, as is found in this study and that of others (6–9), the vast majority of coagulase negative staphylococci are still encountered as contaminants. This should be borne in mind and patients with isolates of coagulase negative staphylococci from blood cultures should be carefully evaluated before instituting therapy to avoid unnecessary use of antibiotics, especially vancomycin and the consequent increase of antibiotic resistance in hospitals.

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APPENDIX

Detailed protocol used in ascertaining the clinical significance of an Isolate of coagulase negative staphylococcus from blood culture.

Basic Data

Serial # OP/IP Ward Age:

Lab # Sex:

Date of admission Date of Discharge

Duration of Stay

Clinical Diagnosis

Date when 1st blood culture was done Results

Essential general and laboratory indices on admission:

Temp:

WBC: Differential

ESR:

Others:

Platelet count

CRP

Previous admissions: Yes No

Date (s)

Diagnosis

Clinical Features

Presenting Symptoms

Duration

.....

Physical Examinations

General

Temperature (on admission and daily thereafter)

Date/Temp:

Pulse Rate: Resp. Rate

BP: Any other relevant findings

Systemic Examination

CVS

Resp

CNS

Abdomen

Others

Underlying Conditions

Undernourished:

Immunocompromised:What:

Diabetes:Hypertension:

Haematological malignancy (indicate what):

Non-haematological malignancy

Renal failure:

Is the patient on dialysis? From when

Cirrhosis of liver

In neonates:- Complicated labour premature neonate

Does the patient have an IV catheter?

If so, was the culture done

from IV site catheter

results of such culture

Is the patient on any other foreign devices?:

urinary catheter

ventriculovenous shunt

ventilator

other

Results of culture from any of these sites:

.....

Did the patient have a surgery?

What surgery? Date:

Postsurgical infection if any:

Wound:

Other:

Microbiology Data

Blood culture

Date received: Lab #

Culture done by:

venepuncture:

from IV catheter

other

Number of sets/bottles cultured (indicate which particular bottle):

1 bottle only ()

1 set (2 bottles) ()

2 sets (4 bottles) ()

More than 2 sets ()

Results from each of the culture bottles:

Bottle	Isolate	Duration of incubation to detect growth
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Was there any mixed growth (indicate specifically from which bottles)

Bottle	Mixed Isolates (Name)
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Susceptibility data

Other bacteriology culture results, if any:

Throat swab

Nasal swab

Sputum

Urine

CSF

Wound swab

Stool

Others

Other results in microbiology, if any:

Virology

Immunology

Parasitology

Other laboratory findings:

WBC (total differential)

on admission

periodically thereafter (date/value)

.....

ESR

on admission

periodically thereafter (date/value)

.....

Hb

on admission

periodically thereafter (date/value)

.....

Platelet count

on admission

periodically thereafter (date/value)

.....

Liver function tests

Normal Abnormal (expand) Not done

.....

Any other abnormal laboratory findings:

.....

Other diagnostic test results:

X-ray

Ultrasound

CT Scan

Bronchoscopy

Biopsy

Antibiotic Therapy

Was the patient on antibiotic therapy prior to admission or before the blood culture was taken?

Antibiotic Dose Response (Temp, WBC,ESR, other)

.....

Coagulase-Negative *Staphylococci* from Blood Cultures

Initial (empirical) therapy after the blood culture was taken at the hospital..

Antibiotic	Dose	Response (Temp, WBC, ESR, other)
.....

Was there any change in therapy after preliminary results were conveyed to the ward?

Antibiotic	Dose	Response (Temp, WBC, ESR, other)
.....

Therapy after report of culture and sensitivity:

Antibiotic	Dose	Response (Temp, WBC, ESR, other)
.....

Was there any follow-up culture (during or post-antibiotic therapy)?

Date	Results
.....

State of the patient at discharge: