Polyclonal Staphylococcus Endocarditis

E. Van Wijngaerden, W. E. Peetermans, S. Van Lierde, and J. Van Eldere

Coagulase-negative staphylococcus (CNS) is the most frequent cause of nosocomial bacteremia and prosthetic valve endocarditis. CNS bacteremia can be polyclonal. No data exist on the clonality of CNS causing endocarditis. We present a case of CNS aortic homograft endocarditis in which at least five different genotypes of CNS were identified in initial blood-culture isolates by genomic macrorestriction enzyme analysis and pulsed field gel electrophoresis. Since the polyclonality was accompanied by differences in antibiotic susceptibility, this observation may have important consequences for the treatment of CNS endocarditis. Because of the parallels in the pathogenesis of CNS prosthetic valve endocarditis and CNS infections of a variety of other prosthetic devices, it might also have consequences for CNS prosthetic device infections in general. We suggest that antibiotic susceptibility testing of just one blood-culture isolate may be insufficient.

Coagulase-negative staphylococcus (CNS) is being increasingly reported as the most common cause of nosocomial bloodstream infection [1]. CNS is also the most frequent cause of prosthetic valve endocarditis [2]. Antibiotic therapy for infective endocarditis due to CNS is usually guided by susceptibility testing of a single isolate, on the basis of the assumption that there is only one infecting strain. However, it is well documented that CNS bacteremia can be caused by a mixture of strains as shown by genotyping and phenotyping methods [3]. Antibiotic susceptibility testing of just one isolate does not necessarily provide an antibiotic susceptibility pattern for all or even the most important strains involved in polyclonal infections.

For an editorial response, see the article by Archer on pages 72–3.

The clinical consequences of incomplete antibiotic susceptibility testing could be particularly important in a difficult-to-treat infection such as infective endocarditis. To our knowledge, no data on the clonality of bacteria causing endocarditis in general or CNS causing endocarditis in particular have been published.

Case Report
A 50-year-old man was admitted to the hospital because of fatigue, low-grade fever, night sweats, and progressive heart failure. A splenectomy had been performed for splenic trauma 5 years earlier, and the patient had been treated for non-Hodgkin’s lymphoma 4 years earlier. At that time, mild aortic valve regurgitation was noted. One year before, his aortic valve was replaced with a homograft valve because of aortic valve endocarditis due to CNS. Six months before, mild aortic valve regurgitation was again noted.

At the time of admission, there were signs of severe aortic valve regurgitation. Transesophageal echocardiography confirmed a grade 4 regurgitation, and several valvular vegetations were visualized. Contrary to the recommendations of the microbiology laboratory, an excessive number (23) of blood specimens for culture were taken in the emergency department and subsequently in the cardiology ward. Twenty-two blood-culture bottles yielded CNS. Pulmonary edema on day 4 of hospitalization prompted urgent surgical intervention with homograft replacement. Antimicrobial therapy with flucloxacillin plus amikacin was administered for 6 weeks. The postoperative period was uneventful.

Twenty-two of 23 culture bottles of blood taken from a peripheral vein at separate times on two consecutive days were positive. All specimens were routinely plated on blood agar on which CNS grew. One isolate was further identified as Staphylococcus epidermidis susceptible to vancomycin, teicoplanin, methicillin, and amikacin but resistant to gentamicin and penicillin. These findings guided antimicrobial therapy. The antibiotic susceptibility pattern for the CNS isolate from a blood specimen obtained 1 year earlier was identical. This particular isolate was not available for genotyping.

In the context of an ongoing prospective study on CNS bacteremia, one colony from each agar plate was inoculated in brain-heart infusion broth (Unipath, Basingstoke, United Kingdom) and grown overnight, inoculated in fresh brain-heart infusion broth and grown for 4 hours, and frozen until further analysis. Genotyping was performed by using Smal digestion (GIBCO BRL, Gaithersburg, MD) of chromosomal DNA, and restriction fragments were separated by pulsed field gel electrophoresis with use of the CHEF Mapper System (Bio-Rad,
glycoside, whereas the others were susceptible to aminoglyco-
side. Susceptibility to erythromycin and clindamycin was vari-
able. All genotypes were susceptible to oxacillin, vancomycin,
teicoplanin, ofloxacin, rifampin, and fusidic acid.

Discussion

The main conclusion of this study is that cultures of blood
from a patient with infective endocarditis due to CNS yielded
a mixture of distinct CNS genotypes with different antibiotic
susceptibility patterns. Because of the retrospective nature
of the analysis, it is impossible to determine how many of
these genotypes were involved in the valve infection and
how many were culture contaminants. Four of five genotypes
were present in at least two blood-culture bottles, a finding
making contamination less likely. Moreover, blood cultures
positive for CNS represent only 10% of the total number of
blood cultures in our microbiology laboratory, which indi-
cates that multiple contaminations are rather unlikely. Since
earlier strains were not available for genotyping, it is not
clear whether polyclonality was a property of the bacteria
causing the endocarditis 1 year earlier or a property of the
bacteria infecting the homograft valve.

The observed polyclonality of CNS causing endocarditis
does not necessarily mean that the infecting bacteria
are polyclonal from the start. In our study, we found five
genotypes, and all of them were different from each other.
This suggests that the infection was polyclonal from the begin-
ing. Our results show that a lack of identity between a single clone
and an isolate from a blood culture and a clone from an infected valve is by
no means evidence against the infected valve being the origin
of the blood-culture isolate.

Polyclonality may also have consequences for the treatment
of CNS endocarditis. The practice of performing detailed anti-
biotic susceptibility testing on a single selected colony may be
inappropriate in the setting of polyclonal infection. Antibiotic

Table 1. Patterns of susceptibility to selected antibiotics according to genotype of coagulase-negative
staphylococcus.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>A1 (6)</th>
<th>B (7)</th>
<th>C (2)</th>
<th>A2 (6)</th>
<th>A3 (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>S (0.19)</td>
<td>S (0.006)</td>
<td>R (&gt;32)</td>
<td>R (&gt;32)</td>
<td>R (&gt;32)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>R (&gt;256)</td>
<td>R (&gt;256)</td>
<td>S (0.02)</td>
<td>R (&gt;256)</td>
<td>R (&gt;256)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>R (&gt;256)</td>
<td>R (&gt;256)</td>
<td>S (0.02)</td>
<td>R (&gt;256)</td>
<td>S (0.032)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>S (0.125)</td>
<td>S (0.125)</td>
<td>R (24)</td>
<td>S (0.094)</td>
<td>S (0.094)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>S (0.5)</td>
<td>S (0.5)</td>
<td>I (2)</td>
<td>S (0.38)</td>
<td>S (0.75)</td>
</tr>
</tbody>
</table>

NOTE. I = intermediate; R = resistant; S = susceptible.
* Susceptibility at the breakpoint concentration determined by an agar dilution method.
† Determined by the Etest.
‡ No. of isolates.
susceptibility testing should be performed on an appropriate number of CNS strains isolated from a patient with CNS endocarditis. Therapy should be guided by the most resistant strain recovered. It is not clear yet what constitutes an appropriate number of strains. Further studies of series of patients with CNS endocarditis are needed to solve this clinically relevant matter.

We have investigated two more cases of CNS endocarditis that turned out to be clonal (data not shown). Recently, it was reported that strain relatedness in isolates from randomly selected patients with cases of CNS bacteremia could be found in only 44.7% of the cases within a 7-day period [3]; these investigators suggested that a high prevalence of contamination was the most likely explanation. From our data, we conclude that true polyclonal infection may occur, but the exact incidence of infection due to multiple CNS strains is still unknown and merits further investigation.

Most foreign-body infections due to CNS are considered to be acquired by a common mechanism of seeding of the device by skin flora from either the patient or a member of the surgical team. This seeding can occur either perioperatively while the device is being inserted or postoperatively secondary to bacteremic spread from wounds, intravascular catheters, and other sources [1, 2, 6]. To our knowledge, no data on the clonality of bacteria causing these infections have been published yet.

Our data suggest that the clonality of CNS causing infections of intravascular devices, joint prostheses, vascular grafts, ventriculoperitoneal shunts, and other prosthetic devices should be studied in detail. These findings could lead to a better interpretation of data obtained from epidemiological studies and a better strategy for susceptibility testing of CNS causing foreign-body infections. Thus, establishing a sufficient and yet feasible number of isolates to be tested is a major concern.

Acknowledgment

The authors thank Mr. J. Vandersmissen for his expert technical assistance.

References