Clinical significance of *Propionibacterium acnes* recovered from blood cultures:

Analysis of 524 episodes

Running title: Clinical significance of *Propionibacterium acnes* bacteremia

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Abstract

Of 522 patients with *P. acnes* bacteremia (PAB), 18 (3.5%) had clinically significant PAB. Of these 18 patients, 10 (55.6%) had hospital-acquired bacteremia and 6 (33.3%) had undergone invasive procedures before development of PAB. One patient with a ventricular septal defect presented with infective endocarditis. After excluding 1 patient whose outcome was not available, the overall mortality rate was 5.9% (1/17).
Propionibacterium acnes is a microaerophilic anaerobic, Gram-positive bacilli, and one end product of bacterial fermentation is propionic acid. The organism is a member of normal flora of the oral cavity, large intestine, conjunctiva, and skin in humans (4). In some patients, however, *P. acnes* can cause severe infections, including endocarditis, intravascular (6, 7), central nervous system infections (11), endophthalmitis (13), and, rarely arthritis (12, 16). Identification of *P. acnes* as pathogen is difficult because anaerobic conditions and a long incubation time are required for the culture. Moreover, *P. acnes* is usually considered a contaminant of blood cultures (5). The exact frequency and the characteristics of clinically significant *P. acnes* bacteremia (PAB) have not been well known. We therefore evaluated the clinical significance and characteristics of *P. acnes* recovered from blood cultures in a tertiary care hospital.

The medical records of all patients, including 151 pediatric patients (less than 16 years old), who gave blood samples of which one or more was positive for *P. acnes* on culture, between January 1997 and August 2009, at the Asan Medical Center (a 2,700-bed tertiary affiliated hospital in Seoul, Republic of Korea) were reviewed. Recommendations for blood culture practices during the study period were as follows; 1) 3 sets of blood culture, 2) sampling from separate venipuncture sites (if a patient has a central venous catheter, 1 set from the central venous catheter), 3) 20 ml blood sampling for each culture set with 10 ml inoculation into 1 aerobic and 1 anaerobic bottle, respectively. 1% chlorhexidine in 70% isopropyl alcohol or 10% povadine (povidone-iodine) were used for skin disinfection as 2% chlorhexidine is not yet available in Korea. Overall blood culture contamination rate of our hospital has been sustained at less than 1% (unpublished data). All blood cultures were processed by the hospital microbiology laboratory using a standard blood culture system (BACTEC 730 or BACTEC 9240; Becton Dickinson, Sparks, Maryland). Clinical isolates were identified using
MicroScan (Dade Behring, West Sacramento, CA) or VITEK 2 (bioMérieux, Maray l’Etoile, France). Antibiotic susceptibilities were not routinely performed. They were only assessed when a physician requested the antibiotic susceptibility information.

*P. acnes* blood isolates were considered significant if two or more separate blood culture sets were positive on the same day and if systemic inflammatory response syndrome (SIRS) was present without any alternate explanation; that is, patients had to be shown to have at least two of the following four criteria: i) body temperature of >38.0 or <36 °C, ii) heart rate >90 beats per minute, iii) respiratory rate of >20 breaths per minute, and iv) peripheral white blood cells counts of >12000/mm³ or >10% bands. Severe sepsis was defined as sepsis with organ dysfunction, hypoperfusion, or hypotension, and septic shock was defined as sepsis-induced hypotension (a systolic blood pressure of <90 mm Hg or a drop in the mean arterial pressure of >40 mm Hg from the baseline) not responsive to an intravenous fluid challenge with signs of peripheral hypoperfusion (1).

Medical records were analyzed to determine underlying disease and medical condition, type of surgery or procedures, choice and duration of antibiotics used to treat *P. acnes*, and outcome at discharge from the hospital.

During the study period, there were 36,369 positive blood culture results, of which 524 blood culture specimens from 522 patients were positive for *P. acnes*, thus accounting for 1.4% (524/36,369) of the positive blood cultures. Two patients were positive for *P. acnes* in each of two separate cultures performed on different days. All 151 positive pediatric patients (<16 years old) were positive in only one blood culture. Forty-six adults (8.8%) were positive in two or more separate blood cultures. Of the 522 positive patients, 20 (3.8%) presented with SIRS, but 2 of these patients were excluded from the study because they had other apparent sources of infection (community-acquired pneumonia). Therefore, clinically significant
bacteremia was identified in 18 patients (3.5%) of 522 patients with PAB. The incidence of clinically significant PAB was 1.72 cases per 100,000 admissions.

The epidemiology and clinical characteristics of the 18 patients with significant PAB are shown in Table 1. Ten patients (55.6%) were male, and median patient age was 59.5 years (range, 30-72 years). Malignancy was the most common underlying disease (13 patients, 72.2%), followed by liver cirrhosis (4 patients, 22.2%) and diabetes mellitus (3 patients, 16.7%). Ten patients (55.6%) had hospital-acquired bacteremia. The sources of bacteremia was identified in only 2 patients (11.1%, both central-venous catheters). Six patients underwent diagnostic or therapeutic invasive procedures, including transarterial embolization, radiofrequency ablation, bronchoscopy, cystoscopy, or pericardiocentesis, before developing PAB. One patient with a ventricular septal defect presented with infective endocarditis following inguinal herniorrhaphy surgery two months earlier. Two patients had polymicrobial bacteremia, in which *P. acnes* was associated with *Peptococcus* species, and *Staphylococcus epidermidis*, respectively. Seventeen patients (94.4%) met the criteria for sepsis, none met the criteria for severe sepsis, and one (5.6%) presented with septic shock. Thirteen patients (72.2%) were treated with antibiotics, 9 (50%) with third-generation cephalosporins. Median duration of antibiotic therapy was 8 days (range, 1-73 days).

Clinical outcomes are summarized in Table 1. The outcome of one patient (number 16) was not available because that patient was transferred to another hospital. Of the 17 remaining patients, 1 (5.9%) died. This patient (number 17) was a 39 year-old male with hepatitis B virus-associated liver cirrhosis and a malignant mesenchymal tumor who had undergone a right posterior segmentectomy of the liver.

*P. acnes*, a common skin organism, belongs to *Propionibacteria* along with *P. granulosum*, *P. avidum*, *P. propionicum*, and *P. innocuum*. Among the *Propionibacteria*, *P. acnes* is the most
frequent cause of human infections. Such infections are usually associated with predisposing factors, such as surgery, the presence of a foreign device, or trauma (10). Because of the increased use of indwelling foreign bodies, such as central venous catheters, prosthetic joints, prosthetic heart valves, ventriculoperitoneal shunts, and intraocular lenses, it is necessary to understand the epidemiology, clinical characteristics, and outcomes of *P. acnes* infection.

Few reports to date have addressed the infection characteristics and outcomes of patients with PAB. Data on such infections are usually reported when series of patients with anaerobic bacteremia are studied (3, 8, 15), although one series included non-bacteremic children (2). To the best of our knowledge, our PAB series is the largest studied to date. We found that *P. acnes* was responsible for 1.4% of all positive blood cultures in our hospital, within the range of previous reports (0.76 ~ 3.0%) (8, 14). The percentages of patients positive for coagulase-negative staphylococci (CoNS), *Bacillus* species, and *Corynebacterium* species, all of which are common blood culture contaminants, were 19.5%, 2.5%, and 1.3%, respectively (unpublished data).

Few studies have addressed the clinical significance of bacteremia caused by *Propionibacterium* spp. One study, of 843 instances of positive blood cultures, regarded all 48 *Propiobacterium* species isolated from blood cultures as contaminants (14). A second study, of 166 patients whose blood cultures yielded anaerobic bacteria, found that none of the 53 patients with *Propionibacterium* bacteremia had clinically significant disease (15). A recent investigation of the clinical significance of anaerobic bacteremia in 140 patients found that, of the 46 *Propionibacterium* species identified, all isolates were contaminants (8). Although we applied more stringent criteria for clinically significant PAB than in previous studies, we found that the incidence of clinically significant PAB was 3.5% (18/522), which was higher than the 0% rate noted in previous studies. The differences may be explained in
several ways. First, because *P. acnes* bacteremia is relatively rare and the numbers of patients
in individual studies have been small, significant bacteremia caused by *Propionibacterium*
spp. may not have been detected earlier. As our study included about 10-fold more patients
with *Propionibacterium* bacteremia than did previous reports, it is more likely that we would
encounter patients with clinically significant PAB. Second, differences in PAB frequency may
be partly attributable to variation in the criteria used to define clinically significant
bacteremia. In previous studies, *P. acnes* may have been considered a contaminant in patients
with SIRS who experienced rapid recovery. We believe it erroneous, however, to regard all
patients positive for *Propionibacterium* bacteremia as having been infected with
contaminants. Several case reports of *Propionibacterium* bacteremia in patients with
endocarditis and osteomyelitis have appeared, in which *Propionibacteria* were indeed the
true pathogens (6, 9).

We were able to identify entry portals in only 2 of the 18 patients with clinically significant
bacteremia; in both instances, central venous catheters were responsible. Seven patients
(38.9%) had undergone invasive procedures or surgery before PAB, suggesting that transient
bacteremia associated with such treatments may explain a substantial proportion of patients
with clinically significant bacteremia. Except for the patient with endocarditis (number 3), the
other six patients recovered quickly.

Among the 17 patients with clinically significant PAB, only 1 (5.9%) died of bacteremia-
associated causes. The mortality rate we observed was similar to that (5%) previously
reported in patients infected with *P. acnes*, including children with bacteremic- and non-
bacteremic *P. acnes* (4).

Our study had several limitations. First, during the study period, we did not routinely assess
the antibiotic susceptibilities of *P. acnes* isolates, making it difficult to determine whether
patients recovered spontaneously or responded to antibiotics. Second, our study was performed on patients in a single large tertiary-care center, and results may thus differ in other settings. For example, the incidence of PAB may be higher in hospitals where prosthetic implantations are frequently performed. Our hospital is one of the largest medical centers in Korea, and many surgeries, including organ transplantations (heart, lung, liver, kidney, etc.) and invasive procedures are being performed. In our hospital, approximately 300 liver transplants, 200 kidney transplants, 50 heart transplants, 450 prosthetic knee arthroplasties, and 180 prosthetic hip arthroplasties have been performed annually. Therefore, our findings may not be generalized to other hospitals.

In summary, our results suggest that \textit{P. acnes} rarely causes significant bacteremia and may be associated with a low risk of mortality. Nevertheless, PAB has pathogenic potential and may play a significant role in some patients with underlying malignancy or hospital acquired infections and especially in those with implanted devices or who have undergone invasive procedures.

\textbf{Potential conflicts of interest.} All authors : no conflicts.
References


**Table 1**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex/age (years)</th>
<th>Acquired</th>
<th>Underlying disease(s)</th>
<th>Reason for admission</th>
<th>No. of positive sets/total culture sets</th>
<th>Probable source of bacteremia</th>
<th>Result surgery or guidance</th>
<th>Current defect/feature</th>
<th>Antibiotic therapy (duration, days)</th>
<th>Outcome (cause of death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 F, 39</td>
<td>F/39</td>
<td>Hospital-</td>
<td>Ulcerative colitis</td>
<td>Abdominal pain</td>
<td>2/3</td>
<td>Gram-negative cathereter</td>
<td>None</td>
<td></td>
<td>Piperacillin/tazobactam (7)</td>
<td>Recovered</td>
</tr>
<tr>
<td>2 F, 58</td>
<td>F/58</td>
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<td>Primary central nervous system lymphoma, ventricular septal defect</td>
<td>Sepsis</td>
<td>2/3</td>
<td>None</td>
<td></td>
<td></td>
<td>Cefoperazone/sulbactam + amikacin (14)</td>
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</tr>
<tr>
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<td>Ventricular septal defect</td>
<td>Sepsis</td>
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<td></td>
<td></td>
<td>Peptoococcas</td>
<td>Recovered</td>
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<td>M/64</td>
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<td>Sepsis</td>
<td>2/3</td>
<td>None</td>
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<td></td>
<td>Cefoperazone/sulbactam + amikacin (14)</td>
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</tr>
<tr>
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<td>Sepsis</td>
<td>2/3</td>
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<td></td>
<td>Cefoperazone/sulbactam + amikacin (14)</td>
<td>Recovered</td>
</tr>
<tr>
<td>6 F, 66</td>
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<td>Community-</td>
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<td>Sepsis</td>
<td>2/3</td>
<td>None</td>
<td></td>
<td></td>
<td>Cefoperazone/sulbactam + amikacin (14)</td>
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</tr>
<tr>
<td>7 M, 55</td>
<td>M/55</td>
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<td>Sepsis</td>
<td>2/3</td>
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<td></td>
<td>Cefoperazone/sulbactam + amikacin (14)</td>
<td>Recovered</td>
</tr>
<tr>
<td>8 F/37</td>
<td>F/37</td>
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<td>Lymphoma</td>
<td>Sepsis</td>
<td>2/3</td>
<td>None</td>
<td></td>
<td></td>
<td>Cefoperazone/sulbactam + amikacin (14)</td>
<td>Recovered</td>
</tr>
<tr>
<td>9 M, 35</td>
<td>M/35</td>
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<td>Sepsis</td>
<td>2/3</td>
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<td>Cefoperazone/sulbactam + amikacin (14)</td>
<td>Recovered</td>
</tr>
<tr>
<td>10 M, 67</td>
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<td>Liver cirrhosis</td>
<td>Sepsis</td>
<td>2/3</td>
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<td>Cefoperazone/sulbactam + amikacin (14)</td>
<td>Recovered</td>
</tr>
<tr>
<td>11 F/71</td>
<td>F/71</td>
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<td>Liver cirrhosis</td>
<td>Sepsis</td>
<td>2/3</td>
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<td>Cefoperazone/sulbactam + amikacin (14)</td>
<td>Recovered</td>
</tr>
<tr>
<td>12 M, 67</td>
<td>M/67</td>
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<td>Liver cirrhosis</td>
<td>Sepsis</td>
<td>2/3</td>
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<td>Cefoperazone/sulbactam + amikacin (14)</td>
<td>Recovered</td>
</tr>
<tr>
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<td>Sepsis</td>
<td>2/3</td>
<td>None</td>
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<td>Cefoperazone/sulbactam + amikacin (14)</td>
<td>Recovered</td>
</tr>
<tr>
<td>14 F/58</td>
<td>F/58</td>
<td>Community-</td>
<td>Liver cirrhosis</td>
<td>Sepsis</td>
<td>2/3</td>
<td>None</td>
<td></td>
<td></td>
<td>Cefoperazone/sulbactam + amikacin (14)</td>
<td>Recovered</td>
</tr>
<tr>
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<td>Age</td>
<td>Sex</td>
<td>Type</td>
<td>Condition</td>
<td>Duration</td>
<td>Status</td>
<td>Treatment</td>
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<td>15</td>
<td>37</td>
<td>F</td>
<td>Hospital-acquired</td>
<td>Peripheral T-cell Lymphoma</td>
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<tr>
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<td>72</td>
<td>F</td>
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<td>Unknown</td>
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<td>Not available</td>
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<tr>
<td>17</td>
<td>39</td>
<td>M</td>
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<td>Malignant mesenchymal tumor, s/p Right posterior segmentectomy</td>
<td>2/3</td>
<td>Unknown</td>
<td>None</td>
<td>Septic shock</td>
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<td></td>
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<tr>
<td>18</td>
<td>65</td>
<td>M</td>
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<td>Unknown</td>
<td>None</td>
<td>Ciprofloxacin (14)</td>
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<td></td>
</tr>
</tbody>
</table>

Note: Ceftriaxone (1) and Metronidazole (1) were also administered. P. acnes septic shock led to expired on September 13, 2017.