Diagnosis of Venous Access Port–Related Infections

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The accumulation of infected clots under the silicone septum of the reservoir of venous access ports (VAPs) has been reported. We analyzed the relationship between these deposits and the occurrence of VAP-related bloodstream infections (VAP-BSIs) by (1) evaluating the accuracy of paired quantitative blood cultures for diagnosing VAP-BSI before the removal of the device and (2) assessing the accuracy of cultures of the tip and septum (i.e., the internal lumen of the VAP) for diagnosing VAP-BSI after removal of the device. Over a 16-month period, all VAPs removed were prospectively investigated. Before VAP removal, paired quantitative blood cultures were 77% sensitive and 100% specific and had a positive predictive value of 100% and a negative predictive value of 98% for diagnosing VAP-BSI. After VAP removal, tip culture was only 46% sensitive, whereas septum culture was 93.3% sensitive for confirming the diagnosis of VAP-BSI. Thus infected deposits that accumulate under the VAP septum are the source of VAP-BSI.

Venous access ports (VAPs) are currently used in patients with cancer or AIDS. They are also used in patients receiving home parenteral treatments (parenteral nutrition, antiviral drugs, and/or chemotherapy). Catheter-related infections are major complications leading to hospital readmission. Until recently, in cases of suspected catheter-related infection, the general approach has been to remove the central venous catheter (CVC). However, many CVCs may be removed unnecessarily, and there is significant morbidity associated with insertion of a new CVC.

For patients with Hickman CVCs, catheter-related infections may be diagnosed before catheter removal by several methods: targeted quantitative skin cultures [1], hub cultures [2], and paired quantitative [3–8] or qualitative cultures [9] of blood simultaneously sampled from the suspected CVC and a peripheral vein. To diagnose catheter-related bloodstream infection without removal of the suspected CVC, paired quantitative blood culture has been considered by several authors [3–8] to be a reliable method. According to various studies [7, 8], this method has a specificity of 100% and a 100% positive predictive value for diagnosing catheter-related bloodstream infection, as well as sensitivity of 83–94%.

Catheter-related infections may also be confirmed after CVC removal by culturing various CVC segments: tip, hub, and subcutaneous catheter portions. Several methods (semiquantitative and quantitative) for segment culture have been described [10–14]. The problem of catheter-related infection is more difficult to resolve with totally implanted access ports, for two reasons. First, paired quantitative blood cultures have not been evaluated for diagnosing VAP-related bloodstream infections. Second, skin cultures cannot be used for patients with such implanted devices.

There have been various reports of fibrin and drug deposits below the silicone septum of infected patients [15, 16]. In a previous study of patients with VAP-related bloodstream infections, we found that systemic antimicrobial treatment combined with the antibiotic lock technique [17] was not effective [18]. This was probably because of the presence of fibrin and drug deposits (including clusters of bacteria) in the internal lumen of the ports, under the silicone septum of the reservoir. The incidence and significance of these deposits under the septum of infected and uninfected ports are unclear.

The aim of this prospective study was to analyze the relationship between these deposits and the occurrence of VAP-related bloodstream infections, with use of two approaches: (1) evaluation of the accuracy of paired quantitative cultures of blood collected in pediatric Isolator 1.5-mL tubes (Oxoid, Basingstoke, UK) for diagnosing VAP-related bloodstream infection before removal of the device and (2) assessment of the accuracy of two-specimen VAP cultures (of catheter tip and VAP septum) for patients with confirmed VAP-related bloodstream infection, after removal of the device.

Methods

Over a 16-month period, all VAPs removed in our unit were clinically and microbiologically examined by the following procedures.

Clinical investigations of the patient’s condition. For each catheterization a form was completed, recording the patient’s clinical diagnosis, underlying conditions (age, sex, weight, and Karnofsky
performance status), date of VAP insertion and removal, all significant events during treatment, and the reasons for removal of the device. The total duration of implantation of the VAP and the number of days in use were recorded. The incidence of infection was calculated by dividing the number of VAP-related infections by the number of days for which the VAP was implanted (rate per 1,000 days). Since in situ VAP treatment was found to be ineffective in a previous study, no antibiotic lock was attempted before device removal [17, 18].

Sampling procedures. In cases of suspected VAP-related bloodstream infection, samples of peripheral blood for standard qualitative blood cultures were taken before removal of the device. In cases of local infection and purulence of the skin pocket around the device, the pus was sampled and microbiologically analyzed; a standard qualitative peripheral blood culture was also performed. Thereafter, the procedure was identical for all VAPs, whatever the reason for removal.

Samples were collected as follows. Paired quantitative blood culture specimens were simultaneously obtained from the VAP and a peripheral vein [3–8]. For explantation of the VAP, the tip (distal 4 cm of the catheter) was cut and sent to the laboratory in a dry sterile tube.

We looked for debris under the silicone septum of the VAP by removing the septum of the port and examining the internal lumen of the reservoir. The septum, clots, and drug deposits were immediately sent to the laboratory in a sterile dry tube.

Two CVC segment cultures were performed for VAPs by means of the Brun-Buisson technique [12], which involved quantitative culture of the distal 4 cm of the catheter (tip) and of the septum.

Microbiological analysis. In qualitative blood cultures, 4.25 mL of blood was used to inoculate equally each of 2 Vital blood culture media (Vital AER and Vital ANA; bioMérieux SA, Marcy l’Etoile, France). Vials were incubated at 37°C for 5 days in a Vital system (bioMérieux SA).

In quantitative blood cultures, 1.5 mL of blood was added to a pediatric 1.5-mL Isolator tube. The pediatric Isolator tube technique does not involve centrifugation or dilution. The contents of the Isolator 1.5-mL tube were mixed by vortexing. All of the medium was removed with a 2.5-mL syringe, and 0.2 mL was then applied, in a straight line, across the surface of the two agar plates (Columbia plus 5% sheep blood and chocolate plus PolyVitex agar plates; bioMérieux SA) and distributed evenly with a sterile Pasteur pipette.

In VAP segment cultures, both the tip and the septum of each device were cultured by means of the quantitative Brun-Buisson technique [12]. In brief, sterile water (1 mL) was dripped onto the VAP fragment (tip or septum) and each tube was vortexed for 1 minute. An aliquot (0.1 mL) of each suspension was sampled with a calibrated pipette and spread over the surface of a 90-mm-diameter plate (containing 5% sheep blood and chocolate plus PolyVitex agar) with a U-shaped Pasteur pipette.

If deposits were present in the internal lumen of the reservoir, they were ground and homogenized in a sterile pestle and mortar with 1 mL of sterile water. A sample (0.1 mL) of the suspension was cultured as described above [12].

All plates for quantitative blood cultures and quantitative VAP segment cultures were incubated for 5 days; blood agar plates were held at 37°C in anaerobic Gaspak jars (BBL Microbiology Systems, Cockeysville, MD), and chocolate plus PolyVitex agar plates were held at 35°C in a humid (5% CO2/95% air) atmosphere. All plates were examined each day for 5 days, and the number of colonies was recorded.

Microorganisms were identified by standard laboratory methods. Staphylococci were biotyped with the API 32 Staph System (bioMérieux SA). Pseudomonas aeruginosa isolates were serotyped with O antisera (Sanofi Diagnostic Pasteur, Marnes-la-Coquette, France). Antibiotic susceptibility was tested by the disk-diffusion method with Müller-Hinton agar (Sanofi Diagnostic Pasteur). Strains were identified by a combination of biotyping or serotyping with antibiotic susceptibility profiling.

Definitions. There are no widely accepted definitions for VAP-related infections, so the definitions used in this study were adapted from the definitions of catheter-related infection used by other authors [20, 21]. Systemic VAP-related bloodstream infection was the diagnosis if there was no detectable focus of infection except the VAP and if one of the following criteria was satisfied: (1) presence of local purulence (tunnel infection and/or induration extending at least 3 cm from the insertion port) associated with concordant microbial growth in cultures of port-site exudate and standard cultures of peripherally drawn blood, and/or (2) presence of clinical symptoms of VAP-related infection (body temperature of >38°C or <36°C and shivering after VAP handling) associated with positive quantitative culture of a VAP segment (tip and/or reservoir internal lumen, i.e., septum) and isolation of the same microorganism from the VAP segment and the bloodstream. In Brun-Buisson quantitative culture, a cutoff point of 103 cfu/mL is used to define catheter-related infection [12].

Local VAP-related infection was defined as a microbiologically confirmed site infection (or skin induration above the silicone septum that measured <2 cm) in the absence of concomitant bloodstream infection (i.e., peripheral standard blood cultures were sterile).

VAP colonization was defined as the growth of a microbial pathogen (positive but nonsignificant culture results: <103 cfu/mL) in either the catheter tip culture or septum culture, in the absence of clinical symptoms of infection and in the absence of positive standard blood cultures.

Statistics. The number of VAP-related infections is expressed as the number of infections per 1000 days of VAP placement, as in most studies. Results are presented as mean ± SD and as medians (Statview 4.5; ABACUS Concepts, Berkeley, CA).

Results

From August 1996 to the end of December 1997, 170 VAPs were removed from 170 patients (aged 50.7 ± 12 years; median, 51 years; range, 16–78 years). All were examined and cultured. These patients had cancer (117 cases), AIDS (10 cases), and hematologic disorders (42 cases); 1 patient had cystic fibrosis.

The median duration of implantation of the VAPs was 228 days (range, 13–1826 days). VAP-related bloodstream infection was observed in 15 patients (8.8%), 73% of whom had hematologic disorders or AIDS (table 1). The overall incidence of VAP-related bloodstream infection was 0.28/1000 VAP-days. Twenty-three VAPs (13.5%) were removed from 23 patients...
because of suspected VAP-related bloodstream infection, and 15 VAPs were removed from 15 patients (8.8%) because of confirmed VAP-related bloodstream infection (table 1). Patient 13 had a systemic VAP-related bloodstream infection associated with a local subcutaneous port infection, whereas 14 other patients had VAP-related bloodstream infection with no local subcutaneous port infection. The microorganisms present were as follows: coagulase-negative staphylococci (5 patients), methicillin-susceptible Staphylococcus aureus (3), gram-negative rods (4, including 1 each of Stenotrophomonas maltophilia, Pseudomonas aeruginosa, Enterobacter cloacae, and Acinetobacter baumannii), yeasts (1 each of Candida albicans and Torulopsis glabrata), and Bacillus cereus (1).

Eight VAPs were removed from 8 patients (4.7%) because of suspected VAP-related bloodstream infection. However, none yielded significant growth in paired quantitative blood cultures, and cultures of various VAP segments were sterile. These patients remained febrile after VAP removal; 2 had AIDS, 4 had hematologic disorders, 1 had total parenteral nutrition, and 1 had lung cancer.

In 141 cases, VAPs were removed at the end of treatment; except for 2 VAPs, all tip and septum cultures were sterile. Two VAP fragments yielded positive but nonsignificant results (50 cfu/mL in a tip culture and 25 cfu/mL in a septum culture). According to the definitions used in this study, these 2 VAPs were colonized. Six patients had a VAP removed either because of mechanical complications (5) or deep venous thrombosis (1); none had positive VAP segment cultures.

Figure 1 shows the predictive values of paired quantitative blood cultures performed before removal of the device and the predictive ability of segment cultures (tip and septum) for diagnosing VAP-related bloodstream infections.

Table 1. Data concerning 15 patients whose venous access parts (VAPs) were removed because of VAP-related bloodstream infection.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Disease</th>
<th>Clinical symptomsa</th>
<th>Culture yield: cfu/mL</th>
<th>Clots under silicon septum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>PQBCb Tip Septum</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Leukemia</td>
<td>Fever</td>
<td>400 0 15 × 10⁷</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>AIDS</td>
<td>Fever</td>
<td>10⁴ 10³ 10³</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>AIDS</td>
<td>Fever</td>
<td>4 10³ 10³</td>
<td>−</td>
</tr>
<tr>
<td>4</td>
<td>Lymphoma</td>
<td>Fever</td>
<td>0 0 2 × 10⁶</td>
<td>−</td>
</tr>
<tr>
<td>5</td>
<td>AIDS</td>
<td>Fever</td>
<td>0 0 2 × 10⁶</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>Myeloma</td>
<td>Fever</td>
<td>0 1500 (NS) 5 × 10⁵</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>Leukemia</td>
<td>Fever</td>
<td>10⁷ 0 10³</td>
<td>−</td>
</tr>
<tr>
<td>8</td>
<td>Solid tumor</td>
<td>Fever</td>
<td>ND 10⁷ 10⁷</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>Cystic fibrosis</td>
<td>Septic shock</td>
<td>ND 10³ 10³</td>
<td>−</td>
</tr>
<tr>
<td>10</td>
<td>AIDS</td>
<td>Septic shock</td>
<td>10⁴ 500 (NS) 10³</td>
<td>−</td>
</tr>
<tr>
<td>11</td>
<td>AIDS</td>
<td>Septic shock</td>
<td>10³ 10³ 10³</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>Solid tumor</td>
<td>Fever</td>
<td>10³ 10³ 10³</td>
<td>−</td>
</tr>
<tr>
<td>13</td>
<td>Solid tumor</td>
<td>Local VAP infection</td>
<td>100 15 (NS) 0</td>
<td>−</td>
</tr>
<tr>
<td>14</td>
<td>Lymphoma</td>
<td>Fever</td>
<td>5 × 10⁷ 0 10⁷</td>
<td>−</td>
</tr>
<tr>
<td>15</td>
<td>Lymphoma</td>
<td>Fever</td>
<td>10⁷ 10³ 10³</td>
<td>+</td>
</tr>
</tbody>
</table>

NOTE. CONS, coagulase-negative staphylococci; ND, not done; NS, positive but not significant results; +, yes; −, no.

a Fever: temperature >38.5°C.

b Paired quantitative cultures of blood (PQBCs) from the VAP and a peripheral vein.

c Microorganisms observed in standard peripheral blood cultures, in PQBCs, and in VAP.
d Methicillin-resistant strains.

Figure 1. Sensitivity (black bars), specificity (white bars), positive predictive value (gray bars), and negative predictive value (striped bars) of paired quantitative cultures of blood (PQBC) sampled before the removal of the venous access port (VAP) and of VAP segment (tip and septum) cultures after device removal.

Macroscopic debris and clots were observed in 12 of 15 VAPs removed from patients with proven VAP-related bloodstream infection (sensitivity, 80%). However, they were also observed in 14 of 155 uninfected VAPs (specificity, 91%). Thus the positive predictive value of macroscopic debris for diagnosing VAP-related bloodstream infection was only 46%, whereas the negative predictive value was 98%.

A specimen of residue (infected clots and particulate matter) from below the silicone septum of the reservoir (patient 9) is shown in figure 2.
Discussion

Hickman CVCs and vascular access ports are commonly used to provide vascular access in patients requiring prolonged intravenous treatment. Both devices are inserted beneath the skin, but VAPs differ from other devices in that a reservoir is attached to the most external portion of the CVC. This reservoir makes it possible for VAPs to be completely implanted under the patient’s skin, which probably reduces infection.

Several studies have attempted to compare the infectious complications associated with VAPs and Hickman CVCs [22–24]. In a prospective nonrandomized analysis of 1431 devices in cancer patients, Groeger et al. [22] observed a significantly lower rate of infection with VAPs than with external CVCs (0.21 infections per 1000 VAP days vs. 2.77 infections per 1000 CVC days; P < .001). In children with malignancies treated by intensive chemotherapy, Rubie et al. reported an incidence of port-related infections of 0.5 per 1000 catheter days [24]. Muller et al. noted similar rates of infection for VAPs and Hickman CVCs in a randomized study, but the follow-up period was only 6 months [23].

Our rates of infection are higher for cancer patients than those of Groeger et al. [22] (0.28 vs. 0.21 per 1000 VAP days). However, our study concerned only patients whose VAPs were removed between August 1996 and the end of December 1997, rather than the whole population with implanted VAPs treated in our hospital during the same period (486 VAPs, with an incidence of port-related infections of 0.23 per 1000 catheter days). This bias accounts for the higher rate of infection observed in the study.

VAP-related bloodstream infection is difficult to diagnose in the absence of local port infection. Various techniques [1, 2, 10–14] have been described for diagnosing catheter-related infection, but all require catheter removal. Given the acute morbidity associated with insertion of VAPs, it is difficult to recommend the routine removal of the device from all patients with unexplained fever. Therefore several methods that do not require catheter withdrawal have been developed to diagnose catheter-related infections without requiring the unnecessary removal of noninfected devices.

Raad et al. [1] observed in cases of tunneled CVCs that targeted quantitative skin cultures are highly sensitive, specific, and predictive of catheter-related infections. However, this method cannot be used for patients with totally implanted ports. Some studies [3–8] have suggested the use of paired quantitative blood culture of samples drawn through the device and a peripheral vein to avoid the risk of removing unnecessarily a suspect device. The concentration of organisms is greatest near the source of infection, so the number of colonies in cultures of blood obtained from an infected device should be higher than the bacterial count from a peripheral blood sample.

Wing et al. [3], using the pour-plate culture technique, reported a case of catheter-related sepsis diagnosed by the significantly larger bacterial colony count from blood drawn through the suspect CVC than from blood drawn from a peripheral vein. However, Flynn et al. found that 99% of animals with experimental peritonitis had similar colony counts in paired quantitative cultures of blood simultaneously sampled from a CVC and a peripheral vein [5].

A previous study [8] evaluated the accuracy of paired quantitative blood culture specimens collected in pediatric Isolator 1.5-mL tubes for diagnosing catheter-related bloodstream infection in 58 bacteremic adult patients. This method for diagnosing catheter-related bloodstream infection before CVC removal is 83% sensitive and 100% specific (with 78% negative and 100% positive predictive value). Furthermore, the strains of coagulase-negative staphylococci in the various cultures (paired quantitative blood cultures and CVC segment cultures) were identified by genomic DNA fingerprinting by pulsed-field gel electrophoresis. For all these bacteremic patients, the same strains of coagulase-negative staphylococci were identified in paired quantitative blood cultures, standard peripheral blood cultures, and CVC segment cultures [8]. Coagulase-negative staphylococci were not identified by DNA fingerprinting in this study, for economic reasons.

Thus paired quantitative cultures of blood collected simultaneously via a CVC and a peripheral vein are a reliable method for diagnosing catheter-related bloodstream infection before CVC removal. In this study, the differential colony count observed in paired quantitative blood culture (VAP/peripheral vein) was more than 4 : 1. With this threshold, similar to that in other studies [7, 21], paired quantitative blood culture had 77% sensitivity, 100% specificity, 100% positive and 98% negative predictive value.
This study of patients with totally implanted devices confirms the usefulness and the limitations of paired quantitative blood cultures for patients with tunneled CVCs [7, 8]; if the findings of paired quantitative blood cultures are significant (≥4-fold difference in cfu/mL), the device is the source of infection. However, this method is not 100% sensitive, so a nonsignificant differential colony count cannot exclude the possibility that the device is the source of VAP-related bloodstream infection [8].

In a recent but retrospective study, Blot et al. [9] evaluated the differential positivity times of qualitative cultures of blood simultaneously drawn from suspected CVCs and peripheral sites [9]. In this study, all but one of the patients with catheter-related bloodstream infections had a blood culture differential positivity time of >120 min, whereas for all patients with infections of other origins it was <75 min. The cutoff limit of 120 min was highly sensitive and predictive of catheter-related bloodstream infection. However, before this simple and promising procedure becomes widely adopted, its usefulness should be confirmed by prospective studies.

Paired (quantitative or standard) blood cultures cannot determine whether the source of the sepsis is the tip or the internal lumen of the VAP of the infected device. The presence of a reservoir in VAPs creates a possible repository of blood products and drug deposits that may serve as an incubation medium for infectious microorganisms. Deswarte [15] described the presence of fibrin and drug deposits below the silicone septum of infected patients. Whitman et al. [16] systematically analyzed these deposits from 29 infected VAPs. They compared the predictive value of line, pocket, tip, and internal specimen cultures and reported that cultures of particulate matter from within the reservoir had perfect scores, with no false-positive or false-negative results.

However, this study was not prospective and was conducted only in patients with sepsis, so no culture specimens were obtained from VAPs explanted for other reasons, such as the end of treatment (in such circumstances, the specificity and negative predictive value of the internal cultures are difficult to evaluate). Nevertheless, this study demonstrated that the internal portion of the reservoir may be the source of VAP-related bloodstream infection.

In our study, all VAPs removed during a 16-month period were systematically opened and examined, whatever the reason for removal: end of treatment, mechanical complications, venous thrombosis, or suspected VAP-related bloodstream infection. Macroscopic observation of residues after the septum was lifted out was 80% sensitive and 91% specific but had a poor positive predictive value (46%). Fourteen patients with no VAP-related bloodstream infection had macroscopic (but sterile) debris and clots under the silicone septum of their devices. Therefore, the clinical observation of debris inside the reservoir is not accurate enough for diagnosis of VAP-related bloodstream infection; cultures of the septum (i.e., the internal lumen of the reservoir) and blood are required.

This study was also designed to evaluate the accuracy of quantitative tip and septum (internal lumen of the reservoir) cultures. The predictive values of tip and septum cultures for diagnosing VAP-related bloodstream infections (figure 1) were calculated: tip culture was not precise enough for diagnosis of VAP-related bloodstream infection (sensitivity, 46% for tip culture vs. 93.3% for septum culture). In our study, septum culture findings were always highly significant. Only one patient (patient 13) had a VAP bloodstream infection associated with a sterile septum culture. This patient had a local port infection due to methicillin-susceptible S. aureus.

We did not attempt to eradicate VAP-related bloodstream infections (keeping the infected device in situ) by a combination of systemic treatment and the antibiotic lock technique described by Messing et al. [17], for two reasons. First, among 8 patients, we noted infections with S. aureus (3 patients), C. albicans (1), T. glabrata (1), A. baumannii (1), P. aeruginosa (1), and S. maltophilia (1). We routinely removed the infected device to prevent more serious complications associated with these microorganisms [25–27]. The removal of these 8 VAPs was associated in each case with systemic antimicrobial treatment [25–27].

Second, to prevent any effects on VAP segment cultures, no antibiotic lock was used before the removal of the infected device. In our unit only VAP-related coagulase-negative staphylococcal infections are treated with the infected device kept in situ.

Nevertheless, in patients with VAP-related infections, Longuet et al. observed limited efficacy (40%) of in situ treatment [18]. They found that infected VAPs treated and left in situ may predispose the patient to new, possibly more serious bloodstream infections caused by resistant microorganisms.

Thus, as with Hickman CVCs, infected VAPs must be removed in cases of septic shock, tunnel tract or periport infection, and vascular thrombosis associated with VAP-related bloodstream infection. Infected VAPs must also be removed in cases of VAP-bloodstream infection caused by S. aureus [25], fungi [26, 27], or species of Bacillus or Corynebacter, and in cases of bacteremia that persists despite 72 hr of specific treatment.

In summary, in the absence of local port infection, the diagnosis of VAP-related bloodstream infection is very difficult, as is the decision to remove or maintain a VAP when a bloodstream infection is suspected. This study shows that paired quantitative blood cultures are a reliable and convenient means for diagnosing VAP-related bloodstream infection before device removal. We also demonstrated the relationship between the internal lumen of the VAP and VAP-related bloodstream infection. If VAP-related bloodstream infection is suspected, a
negative catheter tip culture cannot exclude the diagnosis; in all cases, the internal lumen of the reservoir should be cultured.

References


