

## Short Communication

# Value of Surveillance Blood Cultures in Neutropenic Patients - A Pilot Study

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**SUMMARY:** In this prospective pilot study we evaluated the efficacy of blood cultures (BC) in detecting bacteremia and fungemia prior to the occurrence of infectious signs. Between February 2003 and July 2003, BC were performed twice weekly in neutropenic hematological patients using blood drawn from central venous catheters. Microbial growth prior to the onset of infectious symptoms was detected in 3 of 45 neutropenic episodes in 39 patients and led to modifications in patient management. These results suggest that further prospective studies are warranted to determine the clinical usefulness of surveillance with BC in neutropenic patients.

In the past two decades, the prognosis of hematological patients with acute leukemia, non-Hodgkin's lymphoma or other diseases requiring intense chemotherapy has become more favorable, mainly due to increases in the dose-intensity of chemotherapy. Infectious complications during neutropenia account for about 70% of fatal complications in patients with acute leukemia (1). Hence an even better prognosis could be achieved by improving the diagnosis and therapy of infectious complications. Bacteremia and fungemia are the most commonly documented infections in hematological patients undergoing chemotherapy and stem cell transplantation; they thus have great clinical and prognostic significance (2,3). In recent years, numerous clinical studies have shown a benefit of empirical broad-spectrum antimicrobial therapy at the onset of clinical signs of bloodstream infections (1). Despite such an immediate approach, serious infectious complications (e.g., septic shock and multi organ failure) occur too often and cause considerable mortality. The use of specific antimicrobial agents even prior to the onset of clinical symptoms may improve outcome. We performed a prospective pilot study on the efficacy of blood cultures (BC) to detect bacteremia and fungemia prior to the occurrence of infectious signs.

Between February 2003 and July 2003, BC (at each time point a pair of aerobic and anaerobic cultures; Vital, bioMérieux, Paris, France) using blood drawn from central venous catheters (CVC) were performed twice weekly in neutropenic hematological patients, who had received intense chemotherapy regimens with an expected duration of neutropenia exceeding 1 week. At baseline patients were examined for existing clinical signs of infection (physical examination, chest x-ray, abdominal ultrasound, and mucosal and skin smears). Two pairs of BC (peripheral, CVC) were taken at the onset of neutropenic fever. The timing of the BC test (twice a week) was determined to reach the best possible results, to exclude patients hazards such as phlebotomy-induced anemia, and to be able to include blood sampling into the clinical routine (3). BC was performed according to

the manufacturer's current recommendations to differentiate true pathogens from contaminants. All patients were examined physically for infective foci every day (e.g., mucositis, lung infection, or infection at the CVC insertion site). Skin and mucosal smear cultures were performed when infection was suspected.

Forty-five neutropenic episodes (median 13.5 days, range 4-53 days) in 39 patients (median age 53.3 years, range 19-77 years; acute leukemia 19, lymphoma 10, multiple myeloma 5, other 5) were evaluated. Twenty-one patients had undergone stem cell transplantation (15 autologous, 6 allogeneic). Altogether, 195 BC pairs were examined. Fifteen of 39 patients developed neutropenic fever ( $>38.5^{\circ}\text{C}$ ). The BC of 12 patients were negative prior to onset of fever and those in 3 patients showed microbial growth after 24 h of incubation prior to fever. In all 3 patients the detected bacterium in the BC test was considered to have caused the fever due to the clinical presentation and because the same pathogens were detected in BC taken at the onset of fever. Case I: A coagulase-negative *Staphylococcus* was detected 2 days prior to fever and CVC-related bacteremia was diagnosed. At onset of fever we started treatment specifically adjusted to the in vitro sensitivity of the detected *Staphylococcus*. This therapy (vancomycin) differed from the empiric regimen that would otherwise have been administered (piperacillin/tazobactam, gentamycin). Fever and bacteremia subsided immediately after removing the CVC and commencing antibiotic therapy with vancomycin. Because the BC taken prior to fever and at the onset of fever, and the cultural examination of the CVC tip revealed growth of a coagulase-negative *Staphylococcus* with similar in vitro sensitivity, we considered this to be the causative pathogen. Case II: Bacteremia with *Pseudomonas aeruginosa* that showed in vitro sensitivity to imipenem/cilastin and resistivity to piperacillin/tazobactam-gentamycin was detected in a patient 1 day prior to clinical symptoms of urosepsis. At onset of fever and septic symptoms the patient was started on imipenem/cilastin, and the infection was completely eradicated over the subsequent 3 days. Without the BC result the patient would have received piperacillin/tazobactam-gentamycin, a probably fatal combination in this situation. Case III: *Candida crusei* grew in BC taken from a patient with acute myeloid leukemia. Due to the BC result a computed tomography of the chest was performed and

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revealed pulmonary infiltrates suspicious of fungal infection. Therapy with amphotericin B was started, but unfortunately the patient died due to pulmonary hemorrhage the day fungal infection was diagnosed.

In hematological patients undergoing chemotherapy and stem cell transplantation, major sources of infection are the mucous membranes of the oropharyngeal and gastrointestinal tract, which are frequently damaged by the intensive treatment modalities. In the literature we found various studies evaluating the usefulness of surveillance cultures (stool, urine, sputum, skin, mucous membranes) in predicting clinically significant infection (4-6). However, these studies did not deal with surveillance of BC. Microbial evidence of bloodstream infections is regularly obtained by BC, which are drawn at the onset of fever (7,8). Under these conditions, bacteremias are reported in 20-70% and fungemias in 20-40% of cases (9). As bacteria are the most frequently detected causative pathogens, antibacterial prophylaxis has become a standard procedure in patients at high risk for bloodstream infections. This has led to a profound decline in the incidence of Gram-negative bacteremia (*Enterobacteriaceae*, *P. aeruginosa*) due to translocation from the intestinal tract. In contrast, Gram-positive bacteremia (*Streptococci*, *Enterococcae*, *Staphylococcus aureus*) with its increasing incidence due to the use of CVC continues to be a therapeutic challenge (10). Fungemia is also closely related to the use of CVC and severe mucositis, and *Candida* spp. are most commonly detected in such cases (11).

To our knowledge, no study thus far has evaluated the efficacy of BC as a means of microbiological surveillance of neutropenic patients in the absence of clinical signs of infection. In our pilot study, microbial growth in BC prior to the onset of infectious symptoms was detected in 3 of 45 neutropenic episodes. Importantly, the results of surveillance of BC lead to modifications in patient management. One concern about using BC as a surveillance method in neutropenic patients is the possibility of false-positive results, which would lead to over-diagnosis of infections, particularly CVC-related infections (12,13). Interestingly, we did not observe any false-positive BC results in our study, since the three patients who had positive BC in the absence of clinical infectious signs became symptomatic shortly after the BC were obtained, and the same pathogens were detected in repetitive BC. However, one should bear the possibility of false-positive results in mind and interpret positive BC results with caution, always examining for the presence of clinical infectious signs. We do not recommend the use of antibiotic therapy in patients with positive BC in the absence of clinical signs of infection, but rather the use of targeted therapy instead of empirical therapy at the onset of fever.

Our observations and previous data suggest that the BC test prior to onset of clinical infectious signs is less useful for early detection of fungal infection than for early detection of bacterial infection. Possible reasons include the poor prognosis of patients with fungemia, difficulties in culturing fungal pathogens, and the lower incidence of invasive fungal infections (1,7,13).

Our study provides interesting data supporting the usefulness of surveillance of BC in neutropenia. Since the surveillance of BC can be integrated into the clinical routine of drawing blood samples, it causes very little additional effort for the patients or the hospital staff. Furthermore, surveillance by BC twice weekly is inexpensive compared to other diagnostic and therapeutic procedures in neutropenic

hematological patients. Taken together, our results warrant further prospective studies to determine the usefulness of surveillance with BC in neutropenic patients in larger patient cohorts. A particularly interesting issue is whether patient management modifications, based on BC results, may improve outcome.

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