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Results of antibiotic treatment of Hickman-catheter-related infections in oncological patients

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Abstract A group of 330 oncological patients were supported throughout a 7-year period with central venous catheters (Broviac/Hickman catheters) and underwent standard oncological chemotherapy, because of hematological malignancies or solid tumors (156 children), or a myeloablative conditioning regimen followed by bone marrow transplantation because of leukemia or lymphoma (174 patients: 110 adults, 64 children). Of these, 17 patients (8 after bone marrow transplantation) developed a catheter-related bacteremia and were treated by at least two antibiotics according to the sensitivity of the bacteria. In 1 patient the catheter (infected by *Bacillus cereus*) was removed on day 25 of antibiotic treatment because of persistent high fever and further positive blood cultures. After bone marrow transplantation, 2 other patients, with a *Pseudomonas* or a *Staphylococcus* infection respectively, did not respond to the combined antibiotic treatment and died 1 week and 7 weeks later, respectively, from transplant-related severe graft-versus-host disease. In the other 14 patients antibiotic treatment was successful and removal of the central-vein catheter could be avoided.

Key words Antibiotics
Hickman catheter
Catheter-related infections
Oncology · Bone marron transplantation

Introduction

The ethiopathogenesis of central-venous-catheter (CVC)-related infection is multifactorial and this could explain why prevention and therapy of this kind of infection are so debated. The main causes include contamination of the hub, contamination from cutaneous entry of the skin and endogenous colonization of the CVC [5]. The incidence of CVC-related infections is mainly dependent on the duration of implantation, the underlying disease and the type of catheter [3, 4, 7, 11]. Long-term CVC are much more frequently infected (on average 0.1 infections/100 catheter days) than catheters used for short periods [8, 10, 13, 15]. With tunneled catheters bacteremia occurs more often in neutropenic patients (0.6 infection/100 catheter days) than in patients without a malignancy who experience an infection rate of 0.2/100 catheter days [3, 6, 9]. We report our experience with catheter-related bacteremia from 330 consecutive patients with malignancies in whom Hickman catheters were inserted to facilitate antineoplastic treatment. The results of antibiotic treatment in these patients are described and an attempt is made to answer the question of how often removal of the infected central vein catheter may be avoided.

Materials and methods

For antineoplastic treatment 330 oncological patients were supported with Hickman catheters in our clinic from January 1986 until December 1991. Within this group 156 children were treated because of hematological malignancies or solid tumors and, in ad-

dition, 174 patients (110 adults, 64 children) underwent bone marrow transplantation because of leukemia or lymphoma. All patients were supplied with Hickman catheters for a minimum period of 140 days.

While staying in hospital during the first 6–8 weeks after the catheter insertion, all patients were evaluated according to a standard protocol for oral temperatures of more than 38.2° C. Outpatients were advised to return to the hospital immediately if the oral temperature exceeded 38.2° C. When patients presented with fever, every effort was made to determine whether a catheter-related intravascular or extravascular infection existed or whether another source of infection was present. This evaluation included physical examination by a physician, culture of urine, throat culture, fungal and bacterial blood cultures drawn both peripherally and through the catheter and relevant roentgenograms. If indicated, cultures were obtained of sputum, stool, cerebrospinal fluid, mucosal ulcers and skin lesions. Cultures were classified as representing contaminants, colonisation or true infection. Infections were classified as a definite catheter-related infection if there was pus or an exudate at the insertion site and if blood cultures drawn both at a peripheral site and through the catheter yielded the same organism as that found at the insertion site. Probable catheter-related infection was identified if patients had sepsis and at least one positive blood culture drawn from the catheter without another infection site being identified.

Cure of a catheter-related infection was confirmed by clinical improvement, abatement of fever and a negative blood culture drawn from the catheter after antibiotics had been stopped for a minimum period of 24 h. Failure to erradicate a catheter-related infection was defined as either removal of the catheter because the infection had not been controlled by antibiotics or recurrence of bacteremia with the same bacterial strain after a course of appropriate antibiotic treatment had been given.

Catheters were removed electively at the end of chemotherapy when intravenous support with blood products was no longer needed and intervals for drawing blood for diagnostic purposes broadened. This was approximately the case 4 weeks after the end of the last cycle of chemotherapy except for bone marrow recipients in whom the catheter was removed around days +100 after bone marrow transplantation. For this procedure, children below the age of 8 years were subjected to general anaesthesia while, in older patients, local anaesthesia was used. The catheter was removed by preparation of the Dacron inserting cuff followed by gentle manual pulling. The same procedure was used if the catheter was removed because of suspected or proven catheter-related sepsis.

All catheters were cultured and examined for clots at the time they were removed. The catheter tip cultures were performed as described elsewhere [14]. Briefly, the proximal catheter segment was trimmed to pieces of 5 cm with sterile scissors and the segments were rolled back and forth over the surface of a blood agar plate. After incubation at 37° C for 48 h the agar plates were inspected daily for microbial growth.

Results

From 330 patients a total of 680 blood cultures were analyzed during febrile episodes: 140 of these were positive for various strains of bacteria or fungi. Out of this group bacteremia was judged to be catheter-related in 9 out of 156 children (5.7%) with a malignancy, and 8 (6 adults, 2 children) out of 174 patients (4.5%) undergoing bone marrow transplantation. High fever was the first and in most cases the only symptom of bacteremia. Bacteria repeatedly found in the 9 children with a malignancy were coagulase-negative staphylococci (methicillin-resistant) (four times), *Streptococcus viridans* (twice), *Bacillus cereus* (twice) and *Alcaligenes* (once). In the 8 patients after bone marrow transplantation, coagulase-negative staphylococci (methicillin-resistant) were assayed in 4 patients, *Pseudomonas aeruginosa* in 3 patients and *S. viridans* in 1 patient. Combined antibiotic treatment was performed in all patients according to the kind of bacteria and the sensitivity testing.

In the group of 9 children with a malignancy (Table 1) antibiotic treatment of a *B. cereus* infection with cefotaxime plus piperacillin failed in 1 patient and the central-vein catheter had to be removed after 25 days because of persistent high fever and positive blood cultures. In this patient the same bacilli were isolated from the catheter tip after removal of the CVC as from the blood. The second patient with a *B. cereus* infection responded well on the same antibiotics given for 12 days, and no signs of infection recurred after the end of treatment. In the other 7 patients antibiotics also led to defervescence and disappearance of the bacteria from the blood. Staphylococcal infections were successfully treated according to the sensitivity testing with vancomycin plus another antibiotic in 3 patients and with cefotaxime plus piperacillin in 1 patient. Cefotaxime plus piperacillin plus gentamicin to tobramycin, respectively, cured a *S. viridans* infection in 2 children and an *Alcaligenes* infection in 1 child during 10–12 days of treatment. The CVC could be maintained after antibiotic treatment. In 2 patients the CVC was removed during antibiotic treatment on day 12 for other reasons but was not infected at that time.

In the group of 9 patients treated by conventional chemotherapy for solid tumor or leukemias, blood from the venous catheter contained at least ten times as many bacteria (more than 2000/ml) as that obtained by peripheral venepuncture. The same ratio was found in the group of 8 patients with CVC infection after bone marrow transplantation. Since removal of the infection CVC and reimplantation of a new one in the latter group of patients was considered too dangerous, because of the complete absence of leukocytes in conjunction with transfusion demanding thrombocytopenia, prolonged antibiotic therapy was performed. In 6 out of 8 patients repeated blood cultures became negative within 3 days of treatment, the fever disappeared and the catheter was removed as planned 100 days after bone marrow transplantation (Table 2). Only 2 patients did not respond to the antibiotic treatment and died from severe graft-versus-host disease after 1 and 7 weeks respectively. In these 2 patients *Staphylococcus epidermis* or *Ps. aeruginosa*, respectively, could not be eradicated from the catheter (despite sensitivity to the antibiotics used) and blood cultures remained positive.

Table 1 Results of antibiotic treatment in 9 oncological patients with catheter-related bacteremia

Patient no.	Bacteria in blood cultures	Antibiotic treatment	Duration and result of antibiotic treatment	Catheter removed
1	*Strep. viridans*	Cefotaxime + piperacillin + gentamicin	11 days, cure	No
2	*Strep. viridans*	Cefotaxime + piperacillin + tobramycin	10 days, cure	No
3	*Staph. epidermidis*	Vancomycin + rifampicin	7 days, cure	No
4	*Staph. epidermidis*	Vancomycin + cefotaxime	11 days, cure	No
5	*Staph. epidermidis*	Vancomycin + cefotaxime + piperacillin	9 days, cure	Yes (day 9)
6	*Staph. epidermidis*	Cefotaxime + piperacillin	12 days, cure	No
7	*B. cereus*	Cefotaxime + piperacillin	12 days, cure	Yes (day 9)
8	*B. cereus*	Cefotaxime + piperacillin	25 days, no response	Yes (day 25)
9	*Alcaligenes*	Cefotaxime + piperacillin + tobramycin	12 days, cure	No

Table 2 Results of antibiotic treatment in 8 patients with catheter-related bacteremia after bone marrow transplantation

Patient no.	Bacteria in blood cultures	Antibiotic treatment	Duration and result of antibiotic treatment	Catheter removed
1	*Staph. epidermidis*	Vancomycin + imipenem	7 days, no response	No
2	*Staph. epidermidis*	Cefotaxime + piperacillin	42 days, cure	No
3	*Staph. epidermidis*	Flucloxacillin + cefotaxime	12 days, cure	No
4	*Staph. epidermidis*	Cefotaxime + tobramycin	34 days, cure	No
5	*P. aeruginosa*	Cefotaxime + piperacillin + tobramycin	18 days, cure	No
6	*P. aeruginosa*	Cefotaxime + tobramycin	35 days, no response	No
7	*P. aeruginosa*	Cefotaxime + piperacillin + gentamicin	10 days, cure	No
8	*Strep. viridans*	Vancomycin + imipenem	18 days, cure	No

Discussion

Combined antibiotic therapy of central-venous-catheter-related bacteremia succeeded in 8 of 9 children with a malignancy and in 6 of 8 patients after bone marrow transplantation. Similar results were reported by Darbyshire (cure in 62%), Reilly (64%) and Shapiro (71%) [1, 10, 11]. We deduce from this and from our earlier experience [13] that failure of antibiotics after 1–2 weeks of treatment is a strong argument for removal of the CVC. Monitoring with repeated blood cultures during antibiotic treatment at 3-day intervals is necessary. For the treatment of catheter-related septicemia, antibiotics often recommended and used are listed in Table 3. A proven staphylococcal infection is preferably treated with vancomycin plus rifampicin, as rifampicin has the strongest bacteriocidal activity of all antibiotics (acting at extremely low concentrations) but must be combined with another effective antibiotic to prevent secondary resistance. In the case of a catheter infection caused by other gram-positive bacteria, treatment should combine cefazolin plus gentamicin [2, 12]. Against gram-negative bacilli, cefotaxime (or ceftazidime) plus gentamicin (or tobramycin) should be preferred (according to the results of sensitivity testing). For fungal infections (e.g. by *Candida*) the combination of amphotericin B plus flucytosine is advisable [14]. With respect to the underlying disease, persisting fever and bacteremia despite adequate therapy dictate removal of the catheter. This holds especially true in candidemia because of the risk of *Candida endophthalmitis*, as well as seeding to the CNS, liver, heart or kidneys. Removal may also become necessary in the presence of complications such as local cellulitis, organ abscesses, endocarditis or suppurative thrombophlebitis of the great veins. Similar experiences have recently been reported on over 600 patients by Newman et al. [7]. Sporing bacilli and gram-negative nonfermenters, such as *Pseudomonas*, *Acinetobacter* and others, are seldomly eradicated by the administration of antibiotics alone, especially when thrombophlebitis has become established. However, even when the catheter is not the primary source of the bacteremia it may become colonized during a bacteremic infection and become a secondary focus of infection.

Table 3 Recommendations for antibiotic treatment of catheter-related bacteremia according to the causative microorganisms

Against staphylococci	
Vancomycin:	daily 2 g (30 mg/kg) divided into four i.v. infusions over 60 min
Rifampicin[a]:	daily 0.6 g (10 mg/kg) divided into four i.v. infusions; do not mix with vancomycin in the bottle
Against streptococci (except enterococci)	
Cefazolin:	daily 6 g (100 mg/kg) divided into three i.v. infusions over 60 min
Gentamicin[a]:	daily 0.24 g (3 mg/kg) divided into three i.v. infusions over 60 min
Against gram-negative bacilli	
Cefotaxime or ceftazidime:	daily 6 g (100 mg/kg) divided into three i.v. infusions over 60 min
Gentamicin[a]:	daily 0.24 g (3 mg/kg) divided into three i.v. infusions over 60 min
Against *Candida*	
Amphotericin B i.v.:	Low initial dose then subsequent dose increases to maintenance dose of 0.6 mg/kg^{-1} day^{-1}

[a] Flucytosine: daily 6 g (100 mg/kg) divided into four single doses orally, if sensitivity testing is positive

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