15. Hawkins JM, Craig JM, Secker-Walker LM, et al. Ewing's sarcoma t(11;22) in a case of acute nonlymphocytic leukemia. Cancer Genet Cytogenet 1991;55:157–162.
16. Rosoff PM, Hatcher S, West DC. Biphenotypic sarcoma with characteristics of both a Ewing's Sarcoma and a Desmoplastic Small Round Cell Tumor. Med Pediatr Oncol 2000;34:407–412.
17. Maitra A, Weinberg AG, Schneider N, et al. Detection of t:11;22) (q24;q12) translocation and EWS-FLI1 fusion transcript in a case of solid pseudopapillary tumor of the pancreas. Pediatr Dev Pathol 2000;3:603–605.
18. Colpi GM, Contalbi GF, Nerva F, et al. Testicular function following chemo-radiotherapy. Eur J Obstet Gynecol Reprod Biol 2004;113:S2–S6.
19. Cicognani A, Pasini A, Pession A, et al. Gonadal function and pubertal development after treatment of a childhood malignancy. J Pediatr Endocrinol Metab 2003;16:321–326.
20. Kenney LB, Laufer MR, Grant FD, et al. High risk of infertility and long term gonadal damage in males treated with high dose cyclophosphamide for sarcoma during childhood. Cancer 2001; 91:613–621.

# Continuous Antibiotic Infusion for Salvage Therapy of Partially Implanted Central Venous Catheter Tunnel Infections Due to Staphylococci

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Tunnel infection is an uncommon but serious complication observed in patients with partially implanted central venous catheters. International guidelines suggest that should include antibiotics and catheter removal. A success rate of only 5–20% was reported without catheter removal. We treated 13 episodes of tunnel Gram-positive bacterial infection occurring in pediatric patients with cancer or serious blood disorders with 24-hr intra-catheter antibiotic continuous infusion. This approach led to a 69% success rate. Continuous infusion might be an attractive option to treat tunnel Gram-positive bacterial infections when catheter removal might not be feasible or advisable. Pediatr Blood Cancer 2007;49:1010–1012. © 2006 Wiley-Liss, Inc.

**Key words:** central venous catheter; children; therapy; tunnel infection

## INTRODUCTION

Partially implanted central venous catheters (CVCs) play an essential role in atraumatic, long-term venous access for chemotherapy and for supportive care in patients with cancer or hematological diseases. Unfortunately, intravascular catheters are an important risk factor for local and systemic infections [1] among which tunnel infection is an uncommon, but serious complication [2]. International guidelines advise therapy in tunnel infections with antibiotics and catheter removal [3]. However, this procedure might not always be feasible in patients in life-threatening clinical conditions, or with limited vascular access sites such as in young children with cancer, or with conditions that make catheter withdrawal impossible or at least very difficult.

Continuous infusion of beta-lactam antibiotics or vancomycin might provide a constant and effective drug level, and represents an efficacious treatment of severe infections due to susceptible pathogens [4,5]. Moreover, it has been demonstrated that in the treatment of staphylococcal infections the continuous infusion of vancomycin has equal efficacy and also a lower cost than intermittent infusion [6]. Our report retrospectively evaluated the efficacy of continuous infusion of antibacterials with a time-dependent killing curve to treat partially implanted CVC tunnel infections.

## PATIENTS AND METHODS

We retrospectively evaluated the episodes of tunnel infection treated with antibiotic continuous infusion from January 2000 to October 2004 at "Regina Margherita" Children's Hospital, Turin, and "G. Gaslini" Children's Hospital, Genoa, Italy. Tunnel infection was defined by the presence of tenderness, erythema, and induration extended more than 2 cm beyond the CVC exit site, along the subcutaneous tract of the tunneled catheter, with a positive exudate swab culture and/or concomitant bloodstream infection [3]. Continuous antibiotic infusion consisted in the intra-catheter administration of antibiotics by a 24-hr infusion, at a maximum daily dose calculated according to patient weight (40 mg/kg/day vancomycin, 100 mg/kg/day cefuroxime, and 320 mg/kg/day piperacillin/tazobactam). The success of the procedure was defined by general and local improvement, negative cultures, and no infectious relapse in the first month after the end of treatment.

## RESULTS

During the study period, 13 episodes of CVC tunnel infections were treated with antibiotic continuous infusion. Table I summa-

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Received 19 October 2005; Accepted 14 March 2006


DOI 10.1002/pbc.20864

**TABLE I. Patients' Characteristics, Etiology, Treatment, and Outcome of Tunnel Gram-Positive Bacterial Infections**

| Pt. | Age | Underlying disease | HSCT | Neutropenia | Bacteria | Therapy | | Outcome |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Drug | Days of treatment | |
| 1 | 1 year | Histiocytosis | NO | YES | *S. aureus* | Vancomycin | 16 | Failure |
| 2 | 3 years | Neuroblastoma | YES | NO | CNS | Vancomycin | 10 | Failure |
| 3 | 2 years | Aplastic anemia | NO | NO | *S. aureus* | Cefuroxime | 18 | Failure |
| 4 | 18 months | Hemophilia | NO | NO | *S. aureus* | Vancomycin | 10 | Failure |
| 5 | 10 years | ALL | YES | NO | *S. aureus* | Piperacillin/tazobactam | 11 | Success |
| 6 | 2 months | Neuroblastoma | NO | NO | *S. aureus* | Cefuroxime | 12 | Success |
| 7 | 14 years | Ewing sarcoma | NO | NO | *S. epidermidis* | Vancomycin | 12 | Success |
| 8 | 6 years | AML | YES | YES | *S. hominis* | Vancomycin | 24 | Success |
| 9 | 3 years | ALL | NO | NO | *S. aureus* | Vancomycin | 12 | Success |
| 10 | 4 years | ALL | NO | NO | CNS | Vancomycin | 11 | Success |
| 11 | 14 years | NHL | YES | YES | *S. aureus* | Vancomycin | 14 | Success |
| 12 | 7 years | Neuroblastoma | NO | NO | *S. epidermidis* | Vancomycin | 14 | Success |
| 13 | 2 months | RMS | NO | NO | *S. aureus* | Vancomycin | 14 | Success |

HSCT, hematopoietic stem cell transplant; ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; NHL, non-Hodgkin's lymphoma; RMS, rhabdomyosarcoma; CNS, coagulase-negative staphylococci.

rizes patients' age and underlying disease, presence of granulocytopenia (absolute granulocyte count $<1 \times 10^9$ cells/L) at time of diagnosis, etiology, treatment, and outcome of tunnel infection. The infections were due to *Staphylococcus aureus* (*S. aureus*) in eight cases and to coagulase-negative staphylococci in the other five. Ten episodes were due to oxacillin-resistant strains and were treated with vancomycin. The remaining three cases, all due to oxacillin-susceptible bacteria, were treated with beta-lactam antibiotics. Continuous infusion with vancomycin or beta-lactams antibiotics was administered for a median of 12 days (range 10–24) on the basis of clinical/microbiological response and recovery of absolute granulocyte count. This treatment procedure was successful in nine cases (69%). In four patients the catheter was removed because of the persistence (three cases) or relapse (one case) of the local infection (*S. aureus* in three cases and a coagulase-negative Staphylococcus in the other). No significant differences were noted between the rate of failure with the use of vancomycin (3/10, 30%) and beta-lactam antibiotics (1/3, 33%). There were no deaths or other complications related to the infection. The treatment was well tolerated by all patients. In particular, creatinine serum levels, checked three times weekly, remained within the normal range for age.

## DISCUSSION

Catheter-related infections are often difficult to treat because they are caused by organisms embedded in a biofilm layer on the catheter surface that allows the bacteria to survive despite host defenses. Moreover, antibiotics do not easily penetrate the biofilm. The bactericidal activity of vancomycin and beta-lactam antibiotics is time-dependent. The important determinant of their efficacy is the period when the serum concentration is above the minimal inhibitory concentration (MIC). Continuous intravenous administration produces a relatively constant concentration of antibiotic which can be maintained above the MIC, thereby improving the pharmacodynamic properties [6], without evidences of increased bacterial resistance [7]. Furthermore, it has been suggested that a continuous exposure may be an effective alternative against Staphylococcus strains with reduced susceptibility to vancomycin [7]. In our patients with tunnel Gram-positive bacterial infections the use of continuous antibiotic infusion led to a 69% (9/13) success rate, while historical data report a success rate of 5–20% with medical therapy without catheter removal [8]. Although these results may be biased because of their retrospective nature, they suggest an improvement in outcome with this approach. Catheter removal probably remains the ''golden standard'' to treat tunnel infections in partially implanted CVCs [3]. However, our experience suggests that continuous antibiotic infusion, for at least 10–14 days, is effective, safe, and easy to administer. This approach should be studied prospectively.

## ACKNOWLEDGMENT

We are grateful to Mr. Andrew Martin Garvey BA (Hons) LTCL for editorial assistance.

## REFERENCES

1. Viscoli C, Castagnola E. Factors predisposing cancer patients to infection. Cancer Treat Res. 1995;79:1–30.
2. Beekman SE, Henderson DK. Infections caused by percutaneous intravascular devices. In: Mandell GL, Bennett JE, Doolin R, editors. Principles and practice of infectious diseases. Philadelphia: Churchill Livingstone; 2005. pp 3347–3361.
3. Mermel LA, Farr BM, Sherertz RJ, et al. Guidelines for the management of intravascular catheter-related infections. Clin Infect Dis 2001;32:1249–1272.
4. Amsden GW, Ballow CH, Bertino JS Jr., et al. Pharmacokinetics and pharmacodynamics of anti-infective agents. In: Mandell GL, Bennett JE, Doolin R, editors. Principles and practice of infectious diseases. Philadelphia: Churchill Livingstone; 2005. pp 271–280.
5. Kasiakou SK, Sermaides GJ, Michalopoulos A, et al. Continuous versus intermittent intravenous administration of antibiotics: A meta-analysis of randomised controlled trials. Lancet Infect Dis 2005;5:581–589.

6. Dalle JH, Gnansounou M, Husson MO, et al. Continuous infusion of ceftazidime in the empiric treatment of febrile neutropenic children with cancer. J Pediatr Hematol Oncol 2002;24:714–716.
7. Wysocki M, Delatour F, Faurisson F, et al. Continous versus intermittent infusion of vancomycin in severe staphylococcal infections: Prospective multicenter randomized study. Antimicrob Agents Chemoter 2001;45:2460–2467.
8. Fatkenheuer G, Buchheidt O, Cornely OA, et al. Central venous catheter (CVC)-related infections in neutropenic patients. Ann Hematol 2003;82:S149–S157.

# Clinical Appearance of Neuroblastoma 10 Years After Screening

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A follow-up study was performed for children with previous repeated positive results by neuroblastoma mass screening and negative clinical results (30 out of 439,128 children screened in Austria between 1991 and 2003, median follow-up 113 months). Four children had continuously elevated urine catecholamines for more than 6 months. One of these patients was diagnosed with pelvic neuroblastoma and multiple metastases 10 years after the first positive screening result. In the light of a 'wait and see' strategy for localized neuroblastomas, our observation suggests that these patients should be further observed even after normalization of urine catecholamines. Pediatr Blood Cancer 2007;49:1012–1014.


**Key words:** late presentation; mass screening; neuroblastoma

## INTRODUCTION

Neuroblastoma is the most common solid tumor in childhood, affecting 1 out of 6,000 children [1]. Despite new and developing treatment options, the prognosis of advanced disease remains very poor [2,3]. In order to detect neuroblastoma at earlier disease stages, nationwide urinary mass screening was introduced in Japan in 1985 with the aim to detect neuroblastomas in a subclinical stage and thus to improve the prognosis [4]. Encouraging results concerning survival rate [5] prompted other countries or regions to introduce similar screening programs [6]. In Austria, screening was introduced in 1991 and continued until 2003 [7]. Infants (439,128) were screened and 62 neuroblastomas were detected by screening. Since the early nineties, there was, however, increased concern that screening might increase neuroblastoma incidence without reducing disease related mortality [8,9]. Finally, two large-scale controlled trials confirmed this assumption [10,11]. As a consequence, worldwide screening programs and studies were discontinued even in Japan [12]. The aim of this study was to evaluate the further course in previous screening-positive cases classified as 'false-positive' to possibly detect any late presentations of neuroblastoma.

## METHODS

A follow-up study was performed of 30 children previously classified as 'false-positive' by neuroblastoma mass screening. Three-step evaluation consisted of analysis of the records of the national neuroblastoma registry, data analysis of the screening center which performed all catecholamine analyses for Austria since 1990, and personal information provided by parents. For this purpose, parents of previously screening-positive children were contacted by phone and 27/30 cases were evaluable in this way.

## RESULTS

Median follow-up time was 113 months. In 26 patients, urine catecholamines returned to normal within 6 months; none of these patients developed neuroblastoma in the further course. Four children had elevated urine catecholamines for more than 6 months. Characteristics of these cases are shown in Table I.

A thorough clinical examination, including blood cell count, serum analysis, ultrasound, MIBG and CT scan, was performed for all four children; no visible tumor was detected. In two children without any clinical or other lab abnormalities, urine catecholamines returned to normal 16 and 45 months after the first screening test, respectively.

In one female patient, moderate signs of dysmorphia were observed (discrete muscle hypotonia, discrete hyperpigmentation, strabismus, brittle hair, growth retardation, deep husky voice). However, chromosomal analysis and endocrinological tests, as well as screening for inborn metabolic disorders, were all normal. In follow-up, celiac disease was diagnosed in this patient. Despite gluten restriction, urine catecholamines (mostly dopamine) continued to be elevated, and at a follow-up time of 113 months, are still clearly above normal. There is, however, no hint of neuroblastoma. In one case a neuroblastoma was diagnosed almost 10 years after the first positive screening result, and a further description is provided for this patient.

## CASE REPORT

In February 1994, at the age of 8 months, the female infant tested positive for urinary mass screening. Two other urine samples were

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Grant sponsor: Styrian Government; Grant sponsor: Styrian Children's Cancer Fund; Grant sponsor: Children's Cancer Research Institute, Vienna (CCRI).

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Received 20 October 2005; Accepted 8 February 2006


DOI 10.1002/pbc.20828