

Piperacillin-tazobactam in pediatric cancer patients younger than 25 months: a retrospective multicenter survey

A. Simon · T. Lehrnbecher · U. Bode · A. H. Groll ·
L. Tramsen · R. Wieland · E. Molitor · G. Fleischhack ·
H. J. Laws

Published online: 4 September 2007
© Springer-Verlag 2007

Abstract Piperacillin-Tazobactam (Pip-Taz) is an evidence-based empirical treatment of febrile neutropenia in adolescents and adults. No data are available in pediatric cancer patients <25 months of age. In this retrospective, multicenter data survey, the analysis focuses on safety, tolerance, and efficacy.

A. Simon (✉) · U. Bode · G. Fleischhack
Pediatric Hematology/Oncology, Children's Hospital Medical
Centre, University of Bonn,
Bonn, Germany
e-mail: asimon@ukb.uni-bonn.de

T. Lehrnbecher · L. Tramsen
Pediatric Hematology and Oncology, University of Frankfurt,
Frankfurt, Germany

A. H. Groll
Infectious Disease Research Program,
Centre for Bone Marrow Transplantation,
University Children's Hospital,
Muenster, Germany

A. H. Groll
Department of Pediatric Hematology and Oncology,
University Children's Hospital,
Muenster, Germany

R. Wieland
Department of Hematology and Oncology,
Children's Hospital, University of Essen,
Essen, Germany

E. Molitor
Institute for Medical Microbiology,
Immunology and Parasitology, University of Bonn,
Bonn, Germany

H. J. Laws
Clinics of Pediatric Oncology, Hematology and Immunology,
University of Duesseldorf,
Duesseldorf, Germany

The daily dose administered was 240 mg/kg given in three equally divided doses. Data on 156 Pip-Taz treatment courses in 69 children <25 months from five pediatric cancer treatment centers (2001–2005) were analyzed. The median duration of treatment with Pip-Taz was 5 days (range, 1–23 days; 1–12 Pip-Taz courses per patient). Pip-Taz was started on the first day of fever in 90% of all courses, in 6% in the first 72 h, and in 4% as second- or third-line agent. Forty-five percent of all patients were neutropenic. In all patients, the outcome was favorable independent whether Pip-Taz was given as monotherapy (42 courses; 27%) or in combination. Overall, Pip-Taz was well tolerated and discontinued due to adverse events in only two patients who experienced non-life-threatening allergic reactions (skin rash and wheezing). The results of this study are preliminary due to the methodological limitations of a retrospective survey. Taking this bias into consideration, Pip-Taz appears to be a safe, and feasible alternative in pediatric cancer patients with febrile neutropenia <25 months of age suggesting that the inclusion of children of all age groups in future prospective controlled studies evaluating Pip-Taz is justified.

Introduction

Infectious complications substantially contribute to the overall morbidity and mortality in pediatric cancer patients [1]. As an accepted standard of care, antimicrobial therapy is instituted in a febrile neutropenic cancer patient without delay to avoid severe complications. This approach is particularly important in pediatric cancer patients below 25 months of age, as the early detection of clinical signs of infection may be difficult in infants and toddlers [2]. Early empirical treatment has to cover a broad spectrum of Gram-positive and Gram-negative isolates [3–5].

It has been demonstrated [6–16] that piperacillin-tazobactam (Pip-Taz), the combination of an acylureidopenicillin with a broad-spectrum beta-lactamase inhibitor [17], represents a safe and effective empirical first-line treatment of febrile neutropenia in adolescents and adults undergoing therapy for cancer [18]. Although the formulation of Pip-Taz (Tazobac®, Wyeth Pharma GmbH, Muenster, Germany) is not licensed for children under 25 months of age presenting with febrile neutropenia, Pip-Taz has been used off-label in this age group, but retrospective data are missing as are controlled prospective trials. For example, Cometta et al. [19] excluded children under the age of 2 years in the European Organization for Research and Treatment of Cancer (EORTC) trial with first line Pip-Taz, and similarly, empirical treatment with Pip-Taz was only evaluated in 19 pediatric cancer patients older than 2 years of age who developed fever during aplasia after high dose chemotherapy and autologous stem cell transplantation [20]. Interestingly, three studies reported on the safety and efficacy of Pip-Taz treatment in neonates [21–23].

Therefore, by means of a multicenter retrospective survey, we investigated the safety and efficacy of Pip-Taz in immunocompromised febrile pediatric cancer patients less than 25 months of age.

Materials and methods

Eligible patients and data management

Febrile pediatric patients younger than 25 months of age undergoing therapy for cancer were eligible for this retrospective survey if they received at least one dose of Pip-Taz. The participating centers used their internal documentation databases for fever and neutropenia to identify eligible patients. Data were collected retrospectively from the patients' files. A standardized questionnaire was utilized for data entry, including basic patient data and information on the type, clinical course, and outcome of the infection. Study design and data handling were approved by the institutional ethics committee of the Primary Investigator. The standard dose of Pip-Taz was 240 mg kg⁻¹ day⁻¹ administered in three divided doses [7]. The participating centers particularly requested on this issue did not report other treatment schedules in the eligible patients.

Definitions

Neutropenia was defined as an absolute number (ANC) of granulocytes $<0.5 \times 10^9/l$ (or leukocytes $<1 \times 10^9/l$ if no differential count was available). Fever referred to a body temperature $>38^\circ\text{C}$ for 4 h or $>38.5^\circ\text{C}$ measured once.

Blood cultures and other diagnostic specimens were collected appropriately and processed in the microbiological laboratory of the participating institution. Microbiological testing was performed according to standard procedures [24].

The definitions for the different types of infection were taken from the German Onkoped NI study [25], which adapted the definitions of US Centers for Disease Control and Prevention definitions.

Toxicity data were extracted from case notes and from the patients' laboratory files during and up to 4 weeks after Pip-Taz treatment. In case of any report of toxicity, it was evaluated whether the adverse event led to the cessation of Pip-Taz treatment or not. All fatal outcomes in the subsequent 4 weeks after cessation of antibiotic treatment were documented (to calculate mortality) and thoroughly investigated for their relationship to the infection (to calculate mortality attributable to infection). Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria¹. A reporting bias considering the documentation of low grade toxicities could not be excluded due to the high rate of comorbidities and adverse effects of chemotherapy in pediatric cancer patients. Eventually, only more severe and early toxicities were detected. We did not compare monotherapy vs combination therapy groups because this was a retrospective survey and the participating centers did not use the same schedules of antimicrobial treatment in febrile neutropenia.

Results

Number of eligible patients, basic patient data

Five pediatric cancer centers affiliated to tertiary care university hospitals participated in this retrospective survey covering the period from April 2001 to April 2005. In the participating institutions, complete data sets for analysis were available in more than 95% of all Pip-Taz treatment courses in patients less than 25 months of age. The number of treatment cycles per center was 70 (44.9% of all administered courses), 48 (30.8%), 19 (12.2%), 14 (8.9%), and 5 (3.2%). In total, 156 Pip-Taz treatment courses were administered to 69 patients. The clinical characteristics of the patients are shown in Table 1.

Thirty-seven out of the 69 patients (53.5%) suffered from hematologic malignancies. The median age of the patients at the time of Pip-Taz administration was 14 months; 60 treatment courses (38.5%) were administered to children ≤ 12 months of age.

¹ <http://ctep.cancer.gov/forms/CTCAEv3.pdf>

Table 1 Patient characteristics in 156 treatment courses with piperacillin-tazobactam (69 infants and children <25 months)

	Number of cases	Percent
Underlying disease in 69 pediatric oncology patients <25 months of age		
Acute lymphoblastic leukemia	17	24.6
Acute myeloblastic leukemia	13	18.8
CNS tumor (all high grade malignancies)	7	10.1
Severe aplastic anemia	7	10.1
Neuroblastoma (stage 4)	6	8.7
Retinoblastoma	3	4.3
Langerhans cell histiocytosis	3	4.3
Rhabdomyosarcoma	3	4.3
Juvenile myelomonoblastic leukaemia (JMML)	2	2.9
Others ^a	8	11.2
Patients age ^b at initiation of Pip-Taz treatment in 156 treatment courses		
≤1 month	4	2.6
2–6 months	10	6.4
7–12 months	46	29.5
13–24 months	96	61.5

^a Hepatoblastoma, lymphohistiocytosis, myeloproloferative syndrome, mucopolysaccharidosis and stem cell transplantation, non Hodgkin lymphoma, Wiscott Aldrich syndrome, Wilms tumor

^b Median age (Q25; Q75) 14.1 months (9.2; 19.2 months).

Preceding or concomitant chemotherapy, neutropenia

One hundred thirty-two of the 156 Pip-Taz courses were given shortly after a chemotherapy cycle with a median latency of 10 days (range, 1–144 days; Q75 16.3 days). Pip-Taz was administered simultaneously with chemotherapy in 20 courses (12.8%), and in 4 courses (2.6%) between 2 and 6 days before stem cell transplantation. In 71 courses (45.5%) of Pip-Taz treatment, neutropenia was present at the initiation of antibiotic therapy; the median duration of neutropenia was 4.5 days (range, 1–31, Q75 7 days).

Duration of Pip-Taz treatment, number of cycles

The median duration of treatment with Pip-Taz was 5 days (range, 1–23, and Q75 7 days). Thirty-one patients (45%) received more than one Pip-Taz treatment course (2–12 courses).

Pip-Taz as monotherapy

Pip-Taz was used as monotherapy in 27% of all documented courses (Table 2). The cumulative treatment days of the monotherapy cycles ($n=192$) account for 19% of all Pip-Taz treatment days in the study. The median duration of Pip-Taz monotherapy treatment was 4 days (range, 1–10 days; Q75 5 days).

Pip-Taz combination therapy

The most commonly used antibiotics in the Pip-Taz combination therapy group were aminoglycosides (gentamicin or tobramycin), glycopeptides (teicoplanin or vancomycin), and meropenem. Overall, there were 1,558 cumulative antibiotic treatment days (median 7 days; range, 1–58 days; Q75 7 days), and Pip-Taz treatment accounted for 64.3% of all days with antibiotics in this population.

Type of infection, median length of stay

In 22% of the Pip-Taz courses, a pathogen could be isolated from the blood stream, whereas in 58%, the fever could not be attributed to a microbiologically or clinically defined source (Table 3). In patients treated with Pip-Taz given as monotherapy, infectious episodes were categorized as follows: microbiologically documented infections [$(n=7$; 16.6%); in three patients, a pathogen could be isolated from the bloodstream (two methicillin-sensitive coagulase-negative staphylococci, one *viridans* streptococcus)], four patients suffered from a viral infection (in three children, respiratory syncytial virus and in one child norovirus was isolated), soft tissue infections without identified pathogen (clinically documented infection; $n=2$; 4.8%), and fever of unknown origin (FUO; $n=33$; 78.6%). Median length of stay in hospital related to the infection was 7 days (range 1–59; Q75 13 days).

Table 2 Characterization of 156 Pip-Taz treatment courses in pediatric cancer patients <25 months of age

	Number of cases	Percent
Risk factors at the beginning of Pip-Taz treatment (indicate a higher risk for a complicated course)		
Severe neutropenia	71	45.5
Inpatient before the onset of fever [median, 5 days (1–136, Q75 13 days)]	84	54.5
Parenteral nutrition	32	20.5
Mucositis (WHO grade III or IV)	9	5.8
Systemic steroids for >1 week	6	3.8
Type of chemotherapy associated with fever		
Conventional chemotherapy	143	91.7
High dose, autologous SCT	4	2.6
High dose, allogenic SCT	9	5.8
Venous access for Pip-Taz administration		
Non-tunneled CVC	25	16.0
Broviac/Hickman	97	62.2
Port	23	14.7
Peripheral venous line	11	7.1
Monotherapy with Pip-Taz	42	26.9
Combination therapy with Pip-Taz	114	73.1

SCT Stem cell transplantation; CVC central venous catheter

Table 3 Number and distribution (%) of final clinical diagnoses attributed to the Infectious complications (treated with Pip-Taz) by the attending physicians

Diagnosis	Number of cases	Percent
Bloodstream infection (BSI)	34	21.8
Febrile neutropenia with concomitant relevant pathogen ^a	12	7.7
Soft tissue infection, including surgical wound infections (STI)	8	5.1
Urinary tract infection	6	3.8
Pneumonia ^b	4	2.6
Enterocolitis, <i>C. difficile</i> toxin positive ^c	1	0.6
Fever of unknown origin	91	58.3

^a For example, five patients had concomitant respiratory syncytial virus infection, two were noro- or rotavirus positive, in one, CMV was detected in blood by polymerase chain reaction (PCR).

^b Invasive pulmonary aspergillosis was probable in one patient.

^c In addition, stool specimens contained rotavirus.

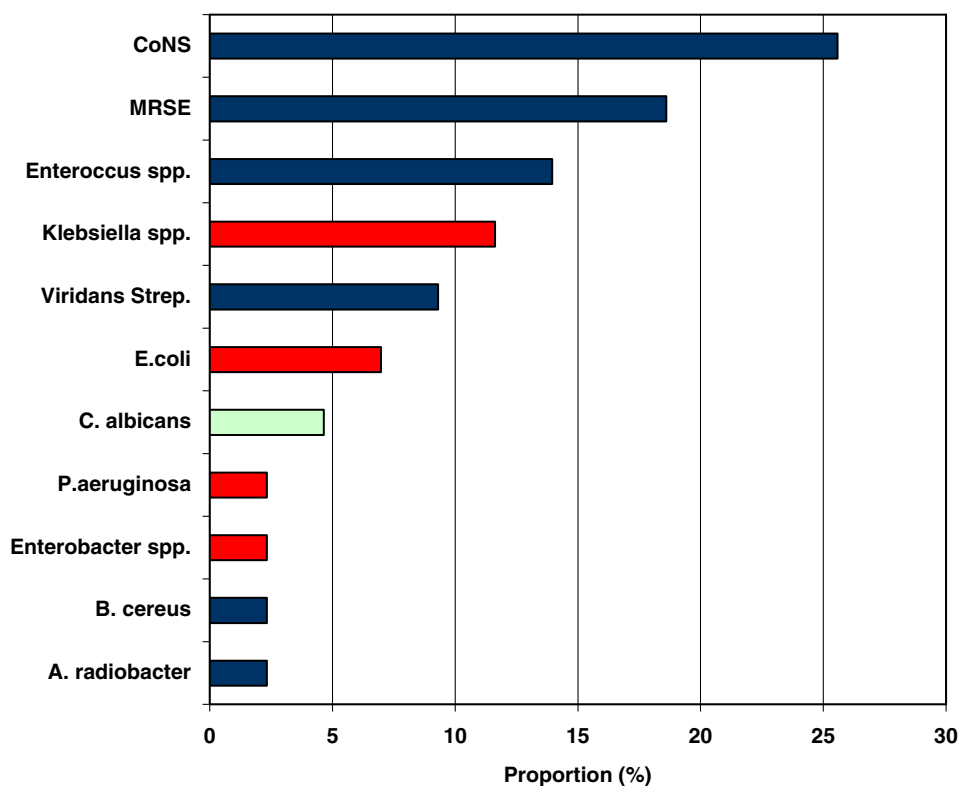
Safety and tolerance

Taking into consideration the methodological limitations of a retrospective survey, treatment with Pip-Taz was well tolerated and had to be discontinued in only two patients (2.9%) due to an acute event of hypersensitivity (irritability,

erythema and itching of the skin, and wheezing), which occurred immediately after the start of Pip-Taz therapy in patients, who had been exposed to beta-lactam antibiotics before. Both events were managed successfully with intravenous antihistamines and steroids without intensive care admission. One patient in the monotherapy group with a history of febrile convulsion experienced a febrile seizure 4 h after the first dose of Pip-Taz. Despite of the continuation of treatment with Pip-Taz, no additional seizure occurred. In one patient of the monotherapy group and in two patients of the combination therapy group (Pip-Taz plus teicoplanin), a transient rise in ALT and AST (less than five times above the level of normal), but these findings normalized during treatment with Pip-Taz.

Outcome and mortality

In one patient, the Broviac catheter had to be removed after unsuccessful treatment of a MRSE-infection with Pip-Taz, vancomycin, and linezolid. All children receiving Pip-Taz monotherapy survived became afebrile and were discharged without relapse of fever. No fatal outcome due to infection occurred in the 69 patients analyzed (attributable mortality 0%), but two patients died due to their underlying malignancy (mortality 2.9%).

Fig. 1 Distribution (%) of 43 pathogens (100%) detected in 34 positive blood cultures [72% Gram-positive (dark bars); CoNS+MRSE ($n=11$ 8) 44% Gram-negative (23%); *Candida* spp. $n=2$ (5%); Polymicrobial: ≤ 3 bacterial isolates: $n=4$ (12%)]

CoNS = Coagulase-negative staphylococci (Methicillin-sensitive)

MRSE = Methicillin-resistant CoNS

Blood culture isolates

The distribution of the 43 isolates derived from 34 positive blood cultures shows a strong preponderance of Gram-positive isolates (72%; Fig. 1). The most prevalent Gram-negative isolate was *Klebsiella* spp. *Candida albicans* was found in the blood culture of two patients who were subsequently treated with fluconazole. Four of the five *Klebsiella* isolates were tested for sensitivity to Pip-Taz and showed intermediate susceptibility (1) or resistance (3) to piperacillin, but all were susceptible to Pip-Taz.

Discussion

The results of this multicenter retrospective survey have to be discussed as preliminary due to methodological limitations of a retrospective survey including only a limited number of patients receiving Pip-Taz monotherapy. Taking this into consideration, piperacillin-tazobactam (Pip-Taz) appears as a safe and feasible alternative for empirical treatment in febrile pediatric cancer patients below 25 month of age with or without neutropenia.

These findings argue for the inclusion of children of this age group in future prospective clinical trials with Pip-Taz treatment in febrile neutropenia. Positive results from other studies using Pip-Taz in neonates, children with intra-abdominal infections, and febrile neutropenic cancer patients older than 2 years are corroborated [4–7, 20, 26].

In all episodes where Pip-Taz was used as monotherapy or in combination with other antibiotics, treatment outcome was favorable. The frequency of severe drug-related adverse events or clinically significant laboratory abnormalities after Pip-Taz use was low in our patient group of very young children. In only 2 of the 69 analyzed patients (2.9%), the drug was discontinued due to an adverse event. One additional patient experienced a febrile convulsion, but any relation to Pip-Taz is unclear. High piperacillin peak concentrations may lower the threshold for convulsions. Therefore, the dosage of Pip-Taz has also to be adjusted in patients with severe renal insufficiency [27].

Pip-Taz should be included into the panel of routine in vitro sensitivity testing. Importantly, the production of extended-spectrum-beta-lactamases (ESBL) in Gram-negative isolates resistant to extended spectrum cephalosporines (ceftazidime, ceftriaxone) has to be identified. Pip-Taz is not recommended for treatment of pathogens capable of ESBL production because the concentration of the beta-lactamase-inhibitor at the site of the infection may not be sufficient to overcome this mechanism of resistance.

In addition, some of these pathogens may produce beta-lactamases, which are not inhibited by tazobactam [28].

Although Pip-Taz is not first choice in the treatment of BSI with detection of CoNS in the blood culture, there is probably no need to treat all those patients in the first line with more effective antibiotics like vancomycin as also suggested by the IDSA [3]. Infection due to *viridians* streptococci, which represent 10% of all blood culture isolates in this population [1], can be successfully managed with Pip-Taz in most cases. In a few patients, treatment with a glycopeptide remains necessary [3].

A potentially favorable feature of first-line use of Pip-Taz for the empirical treatment in immunocompromized patients is a lower selective pressure on *Clostridium difficile* [29], vancomycin-resistant enterococci [30] and Gram-negative isolates producing extended spectrum beta-lactamases, but this has to be confirmed in future prospective trials.

Acknowledgement The contribution of the study nurses Gertrud Wiszniewsky (Bonn) and Brigitte Remus (Essen) to the data collection is thankfully acknowledged. This study was supported by Wyeth Pharma GmbH, Muenster, Germany. Wyeth Pharma GmbH has no influence on data analysis or submission of this article.

References

1. Gaur AH, Flynn PM, Shenep JL (2004) Optimum management of pediatric patients with fever and neutropenia. *Indian J Pediatr* 71:825–835
2. Fleischhack G, Hartmann C, Simon A, Wulff B, Havers W, Marklein G, Hasan C, Bode U (2001) Meropenem versus ceftazidime as empirical monotherapy in febrile neutropenia of paediatric patients with cancer. *J Antimicrob Chemother* 47:841–853
3. Simon A, Groger N, Wilkesmann A, Hasan C, Wiszniewsky G, Engelhart S, Kramer MH, Bode U, Ammann RA, Fleischhack G (2006) Restricted use of glycopeptides in paediatric cancer patients with fever and neutropenia. *Int J Antimicrob Agents* 28:417–422
4. Adam D, Linglöff T, Floret D, Kirsch T (2001) Piperacillin/Tazobactam versus Cefotaxime plus metronidazole for the treatment of severe intraabdominal infection in hospitalized pediatric patients. *Current Therapeutic Research* 62:488–502
5. Maltezou HC, Nikolaidis P, Lebesii E, Dimitriou L, Androulakakis E, Kafetzis DA (2001) Piperacillin/Tazobactam versus cefotaxime plus metronidazole for treatment of children with intra-abdominal infections requiring surgery. *Eur J Clin Microbiol Infect Dis* 20:643–646
6. Le Guyader N, Auvrignon A, Vu-Thien H, Portier E, Tabone MD, Leverger G (2004) Piperacillin-tazobactam and netilmicin as a safe and efficacious empirical treatment of febrile neutropenic children. *Support Care Cancer* 12:720–724
7. Fleischhack G, Schmidt-Niemann M, Wulff B, Havers W, Marklein G, Hasan C, Bode U (2001) Piperacillin, beta-lactam inhibitor plus gentamicin as empirical therapy of a sequential regimen in febrile neutropenia of pediatric cancer patients. *Support Care Cancer* 9:372–379
8. Bohme A, Shah PM, Stille W, Hoelzer D (1998) Piperacillin/tazobactam versus cefepime as initial empirical antimicrobial therapy in febrile neutropenic patients: a prospective randomized pilot study. *Eur J Med Res* 3:324–330

9. Gorschluter M, Hahn C, Fixson A, Mey U, Ziske C, Molitor E, Horre R, Sauerbruch T, Marklein G et al (2003) Piperacillin-tazobactam is more effective than ceftriaxone plus gentamicin in febrile neutropenic patients with hematological malignancies: a randomized comparison. *Support Care Cancer* 11:362–370
10. Hess U, Bohme C, Rey K, Senn HJ (1998) Monotherapy with piperacillin/tazobactam versus combination therapy with ceftazidime plus amikacin as an empiric therapy for fever in neutropenic cancer patients. *Support Care Cancer* 6:402–409
11. Kelsey SM, Weinhardt B, Pocock CE, Shaw E, Newland AC (1992) Piperacillin/tazobactam plus gentamicin as empirical therapy for febrile neutropenic patients with haematological malignancy. *J Chemother* 4:281–285
12. Micozzi A, Nucci M, Venditti M, Gentile G, Girmenia C, Meloni G, Martino P (1993) Piperacillin/tazobactam/amikacin versus piperacillin/amikacin/teicoplanin in the empirical treatment of neutropenic patients. *Eur J Clin Microbiol Infect Dis* 12:1–8
13. Reich G, Cornely OA, Sandherr M, Kubin T, Krause S, Einsele H, Thiel E, Bellaire T, Dorken B, Maschmeyer G (2005) Empirical antimicrobial monotherapy in patients after high-dose chemotherapy and autologous stem cell transplantation: a randomised, multicentre trial. *Br J Haematol* 130:265–270
14. Rossini F, Terruzzi E, Verga L, Larocca A, Marinoni S, Miccolis I, Giltri G, Isella M, Parma M, Pogliani EM (2005) A randomized clinical trial of ceftriaxone and amikacin versus piperacillin tazobactam and amikacin in febrile patients with hematological neoplasia and severe neutropenia. *Support Care Cancer* 13:387–392
15. Cornely OA, Wicke T, Seifert H, Bethe U, Schwonzen M, Reichert D, Ullmann AJ, Karthaus M, Breuer K et al (2004) Once-daily oral levofloxacin monotherapy versus piperacillin/tazobactam three times a day: a randomized controlled multicenter trial in patients with febrile neutropenia. *Int J Hematol* 79:74–78
16. Bow EJ, Rotstein C, Noskin GA, Laverdiere M, Schwarzer AP, Segal BH, Seymour JF, Szer J, Sanche S (2006) A randomized, open-label, multicenter comparative study of the efficacy and safety of piperacillin-tazobactam and cefepime for the empirical treatment of febrile neutropenic episodes in patients with hematologic malignancies. *Clin Infect Dis* 43:447–459
17. Perry CM, Markham A (1999) Piperacillin/tazobactam: an updated review of its use in the treatment of bacterial infections. *Drugs* 57:805–843
18. Glasmacher A, von Lilienfeld-Toal M, Schulte S, Hahn C, Schmidt-Wolf IG, Prentice A (2005) An evidence-based evaluation of important aspects of empirical antibiotic therapy in febrile neutropenic patients. *Clin Microbiol Infect* 11:17–23
19. Cometta A, Zinner S, de Bock R, Calandra T, Gaya H, Klastersky J, Langenaeken J, Paesmans M, Viscoli C, Glauser MP (1995) Piperacillin-tazobactam plus amikacin versus ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. *Antimicrob Agents Chemother* 39:445–452
20. Numberger W, Bonig H, Burdach S, Gobel U (1998) Tolerability of piperacillin/tazobactam in children and adolescents after high dose radio-/chemotherapy and autologous stem cell transplantation. *Infection* 26:65–67
21. Berger A, Kretzer V, Apfalter P, Rohrmeister K, Zaknun D, Pollak A (2004) Safety evaluation of piperacillin/tazobactam in very low birth weight infants. *J Chemother* 16:166–171
22. Flidel-Rimon O, Friedman S, Gradstein S, Bardenstein R, Shinwell ES (2003) Reduction in multiresistant nosocomial infections in neonates following substitution of ceftazidime with piperacillin/tazobactam in empiric antibiotic therapy. *Acta Paediatr* 92:1205–1207
23. Pillay T, Pillay DG, Adhikari M, Sturm AW (1998) Piperacillin/tazobactam in the treatment of Klebsiella pneumoniae infections in neonates. *Am J Perinatol* 15:47–51
24. Isenberg H (2004) Clinical microbiology procedures handbook, 2nd edn. ASM Press, Cleveland
25. Simon A, Fleischhack G, Hasan C, Bode U, Engelhart S, Kramer MH (2000) Surveillance for nosocomial and central line-related infections among pediatric hematology-oncology patients. *Infect Control Hosp Epidemiol* 21:592–596
26. Aksoylar S, Cetingul N, Kantar M, Karapinar D, Kavakli K, Kansoy S (2004) Meropenem plus amikacin versus piperacillin-tazobactam plus netilmicin as empiric therapy for high-risk febrile neutropenia in children. *Pediatr Hematol Oncol* 21:115–123
27. Malanga CJ, Kokontis L, Mauzy S (1997) Piperacillin-induced seizures. *Clin Pediatr (Phila)* 36:475–478
28. Paterson DL, Bonomo RA (2005) Extended-spectrum beta-lactamases: a clinical update. *Clin Microbiol Rev* 18:657–686
29. Wilcox MH, Freeman J, Fawley W, MacKinlay S, Brown A, Donaldson K, Corrado O (2004) Long-term surveillance of cefotaxime and piperacillin-tazobactam prescribing and incidence of *Clostridium difficile* diarrhoea. *J Antimicrob Chemother* 54:168–172
30. Winston LG, Charlebois ED, Pang S, Bangsberg DR, Perdreau-Remington F, Chambers HF (2004) Impact of a formulary switch from ticarcillin-clavulanate to piperacillin-tazobactam on colonization with vancomycin-resistant enterococci. *Am J Infect Control* 32:462–469