Journal of Microbiology, Immunology and Infection (2014) **47**, 381–386

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

Clinical analysis of *Enterobacter* bacteremia in pediatric patients: A 10-year study

Hui-Lan Chen [a,b], Jen-Her Lu [a,b], Hsin-Hui Wang [a,b], Shu-Jen Chen [a,b], Chun-Jen Chen [a,b], Keh-Gong Wu [a,b], Ren-Bin Tang [a,b,*]

[a] *Department of Pediatrics, Taipei Veterans General Hospital, Taipei, Taiwan*
[b] *School of Medicine, National Yang-Ming University, Taipei, Taiwan*

Received 17 July 2012; received in revised form 7 February 2013; accepted 27 March 2013
Available online 15 June 2013

KEYWORDS
Bacteremia;
Enterobacter;
Neonates

Background: Enterobacter species has emerged as an important pathogen of nosocomial bacteremia. The purpose of this study is to review the clinical characteristics of bacteremia in pediatric patients.
Materials and methods: We reviewed retrospectively the medical records of patients (under the age of 18 years) having *Enterobacter* bacteremia who were treated at Taipei the Veterans General Hospital from January 2001 to June 2011.
Results: In total, 853 positive blood cultures were obtained from 620 patients during the study period. Among them, 96 episodes of *Enterobacter* bacteremia were found in 83 patients, accounting for 11.3% of all bacteremia. Eighty-two cases (98.8%) were nosocomial infections. Most of the cases were neonates (62 cases, 74.7%) and premature infants (51 cases, 61.5%). The common sources of bacteremia were the respiratory tract (53.0%), followed by intravascular catheter (10.8%), multiple sources (10.8%), and the gastrointestinal tract (8.4%). The overall case fatality rate was 18.1%, with the highest rate being reported among premature infants. The factors responsible for the deaths were leukocytosis and a higher median number of underlying diseases.
Conclusion: Based on the findings of the present study, it can be concluded that *Enterobacter* species are probably an important pathogen of nosocomial bacteremia in premature neonates. The number of underlying diseases should be considered a major factor influencing the prognosis.

* Corresponding author. Department of Pediatrics, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 11217, Taiwan.
E-mail address: rbtang@vghtpe.gov.tw (R.-B. Tang).

1684-1182/$36
http://dx.doi.org/10.1016/j.jmii.2013.03.016

Introduction

Nosocomial bloodstream infections are important causes of morbidity and mortality worldwide. *Enterobacter* species, which are the normal members of the flora of the gastrointestinal tract, are significant pathogens for a variety of infections, such as pneumonia, urinary tract infections, wound infections, and bacteremia, especially in nosocomial infections.[1–3] In healthy children, *Enterobacter* species rarely cause any disease; however, in patients with underlying diseases, especially in premature patients, they are frequent pathogens involved in bacteremia.[3–5] Several risk factors of *Enterobacter* bacteremia are known, such as gastrointestinal disease, life-threatening infections, malignancies, prematurity, use of a central venous catheter, ventriculostomy, use of a ventriculoperitoneal shunt catheter, prolonged antibiotic therapy, parenteral nutrition, and immunosuppressive therapy.[6] According to a large-scale survey conducted in the USA, *Enterobacter cloacae* accounted for 3.9% of all nosocomial bloodstream infections.[4] At the same time, a significant increase was observed in the antimicrobial resistance rates of *E. cloacae*. We conducted a retrospective study in order to review the clinical characteristics and antimicrobial susceptibility of *Enterobacter* bacteremia in pediatric patients.

Materials and methods

We reviewed retrospectively the medical records of patients under the age of 18 years, whose blood cultures yielded *Enterobacter* species, treated at the Taipei Veterans General Hospital between January 2001 and June 2011. Data were collected on age, sex, abnormal clinical findings [fever, poor activity, leukocytosis, leukopenia, and high C-reactive protein (CRP) level], underlying illness, and type of infection. The presence of the following comorbid conditions was also documented: parenteral nutrition, corticosteroid use, immunosuppressant use, and invasive procedures.

Definitions

Enterobacter bacteremia was defined as the presence of *Enterobacter* species in one or more positive blood cultures collected during the hospitalization of these patients with corresponding clinical conditions. Only the first episode of *Enterobacter* bacteremia in each patient was considered as "one patient". Nosocomial infection was defined as an infection occurring after 72 hours of admission. Otherwise, bacteremia was considered to be community acquired. Polymicrobial bacteremia was defined as the isolation of multiple pathogens from the same culture (the same bottle of blood culture) or from different cultures (different bottles) but at the same time.

The source of infection was determined as one of the following: respiratory tract, intestinal, biliary tract, urinary tract, surgical wounds, intravascular catheter, or multiple or unknown sources, based on clinical signs and symptoms (e.g., fever, leukocytosis, leukopenia, poor activity, and high CRP level) of infection and organisms cultured from these possible sources. Bacteremia was considered to have originated from the lungs when a ventilator was used for a prolonged time or radiologic evidence of new-onset or progressing pneumonia was found with concomitant isolation of *Enterobacter* species from blood or sputum. Bacteremia of unknown origin was defined as bacteremia for which there was no documented distal source.

Empirical antibiotic treatment was considered appropriate when all isolated pathogens were susceptible to at least one of the administered agents and it was administered prior to the time of positive blood culture. However, empirical therapy was considered inappropriate when the isolate was nonsusceptible to the antimicrobial agents(s) administered or the patients were not prescribed antimicrobial agents on the day of the onset of bacteremia.[7] Recovery was defined as improvements in patients' clinical condition, such as becoming afebrile and having stable vital signs after the initiation of antibiotic therapy. Morbidity was considered when the patients had long time sequels which were directly related to bacteremia, despite appropriate antibiotic treatments. The case fatality rate was defined as the number of deaths among patients with bacteremia. Death was not considered directly because of other conditions being apparently documented as the cause of death; otherwise, the death was attributable to the bacteremia. Nonparametric data were expressed as median and range.

Microbiology

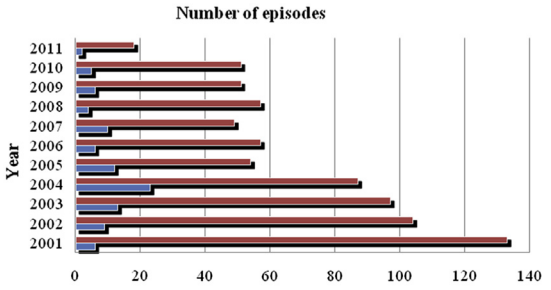
Blood samples of around 0.5—1.0 mL were collected under sterile conditions from peripheral punctures and injected directly into Baxtar blood culture bottles. These bottles were then incubated in BACTEC 9240, which is designed for the rapid detection of bacteria and fungi in clinical cultures of blood (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, USA), at 35.5°C. Antimicrobial susceptibility tests were carried out using the MicroScan AutoSCAN-4 data management system (Dade MicroScan Inc., West Sacramento, CA, USA).

Statistical analysis

Univariate analysis was performed to identify the possible risk factors associated with death attributable to *Enterobacter* bacteremia. The Mann—Whitney *U* test, independent samples *t* test, and Fisher's exact test were used as appropriate. Statistical analysis was performed using IBM SPSS version 19 (SPSS Inc., Chicago, IL, USA). A p value of <0.05 was considered statistically significant.

Results

During the 10-year retrospective study period, 853 positive blood cultures were obtained from 620 pediatric patients. The most common pathogens of bacteremia were yeast, *Staphylococcus aureus*, and *Staphylococcus epidermidis*; *Enterobacter* ranked fourth, accounting for 11.3% of all types of bacteremia. *E. cloacae* was the most common species, accounting for 78 episodes (81.3%); followed by *Enterobacter aerogenes*, for 11 episodes (11.5%); *Enterobacter sakazakii*, for four episodes (4.2%); and



	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Other pathogens	133	104	97	87	54	57	49	57	51	51	18
Enterobacter species	6	9	13	23	12	6	10	4	6	5	2

Figure 1. Yearly distribution (number of episodes) of *Enterobacter* species in all bacteremic pathogens during the 10-year study period.

Enterobacter agglomerans, for three episodes (3.1%). Thirteen patients (15.7%) had two distinct episodes of bacteremia. The rates of *Enterobacter* bacteremia in all bacteremia during 2001—2010 were 4.3% (2001), 8% (2002), 11.8% (2003), 20.9% (2004), 18.2% (2005), 9.5% (2006), 16.9% (2007), 6.6% (2008), 9.1% (2009), and 7.6% (2010). We found a peak incidence of *Enterobacter* bacteremia in 2004, with 19 cases (23 episodes); the yearly distribution of *Enterobacter* species in all bacteremic pathogens during the 10-years study period is shown in Fig. 1. The clinical characteristics of patients with bacteremia are given in Table 1. There were 48 male and 35 female patients; the majority of patients were neonates (74.7%). Nosocomial infection was reported in 82 cases (98.8%), and one case (1.2%) was community acquired. Polymicrobial bacteremia (2 or 3 microorganisms) occurred in two cases (2.4%): *Enterococcus faecalis* (1), *Escherichia coli* (1), and *E. aerogenes* (1). Nearly all the patients (98.8%) received appropriate antibiotic treatment. All patients had major underlying conditions, with most of them having more than one condition (Table 2). The most prominent underlying condition in patients with *Enterobacter* bacteremia was prematurity (51 cases, 61.4%), and the most prominent predisposing factors were central venous catheter use (75 cases, 90.4%) and prolonged antibiotic therapy (77 cases, 92.8%).

Table 1 Clinical characteristics of patients with *Enterobacter* bacteremia

Parameters		*n* = 83 (%)
Age	0—1 mo	62 (74.7)
	>1—6 mo	2 (2.4)
	>6 mo—1 y	3 (3.6)
	>1—6 y	8 (9.6)
	>6—12 y	5 (6.0)
	>12—18 y	3 (3.6)
Sex	Male	48 (57.8)
	Female	35 (42.2)
Length of stay (d)[a]	NICU/PICU	55.5 (3—301)
	Hospital	63 (4—304)
Onset of bacteremia, days after admission		17 (1—164)[a]
Abnormal clinical findings	Fever (>39°C)	41 (49.4)
	Poor activity	21 (23.5)
	Leukocytosis (>11,000 cells/mm^3)	58 (69.9)
	Leukopenia (<4000 cells/mm^3)	19 (22.9)
	High CRP (>10.0 mg/dL)	26 (31.3)
Comorbid conditions	Intravenous nutrition	52 (62.7)
	Invasive procedure[b]	61 (73.5)
	Corticosteroid or cytotoxic therapy	12 (14.5)
Admission diagnosis	Prematurity	51 (61.5)
	CHD	10 (12.1)
	Sepsis	12 (14.5)
	Miscellaneous	10 (12.1)
Infection type	Nosocomial infection	82 (98.8)
	Community acquired	1 (1.2)
Empirical antibiotic treatment	Appropriate	82 (98.8)
	Inappropriate	1 (1.2)
Outcome of bacteremia	Recovery	65 (78.3)
	Morbidity[c]	3 (3.6)
	Case fatality	15 (18.1)

[a] Median (range).
[b] Central venous catheter, chest tube, cystostomy, drainage tube, endotracheal intubation, pericardial tube, rectal tube, and umbilical vein/arterial line (1 patient had 1 or more procedures).
[c] Neurological sequel (1 patient), endocarditis (1 patient), and respiratory failure (1 patient).
CHD = congenital heart disease; CRP = C-reactive protein; NICU = neonatal intensive care unit; PICU = pediatric intensive care unit.

Table 2 Major underlying conditions (patients may have more than one underlying condition)

Condition		Number of patients (%)
Underlying illness	Prematurity	51 (61.4)
	Gastrointestinal disease	40 (48.2)
	Malignancy [a]	12 (14.5)
	Other life-threatening infection [b]	21 (25.3)
	Others [c]	42 (50.6)
Predisposing factor	Central venous catheter	75 (90.4)
	Prolonged antibiotic therapy	77 (92.8)
	Prolonged parenteral nutrition	53 (63.9)
	Immunosuppressive therapy	13 (15.7)
	Ventriculostomy or ventriculoperitoneal shunt catheter	4 (4.82)

[a] Malignant brain tumor (2 patients), hematological malignancy (7 patients), and bone tumor (3 patients).
[b] Postoperative infection (17 patients) and central nervous system infection (4 patients).
[c] Congenital heart disease (10 patients), congenital anomalies (12 patients), pneumonia (8 patients), premature rupture of membrane (7 patients), respiratory failure (3 patients), asphyxia (1 patient), and herpetic gingivostomatitis (1 patient).

The respiratory tract (53.0%), intravascular catheter (10.8%), multiple sources (10.8%), gastrointestinal tract (8.4%), and genitourinary tract (8.4%) were the major sources of bacteremia. Other sources included surgical wounds (2.4%) and the biliary tract (1.2%). During the study period, most of the patients had two to three episodes of bacteremia caused by other microorganisms.

In this study, the overall case fatality rate was 18.1% (15/83). Death was attributed to *E. cloacae* bacteremia in 14 cases (93.3%) and *E. aerogenes* bacteremia in one case (6.7%). The prognostic factors, including clinical and laboratory factors, potentially related to deaths due to bacteremia in patients with *Enterobacter* species infection are shown in Table 3. Factors that correlated significantly with a poor prognosis in the univariate analysis were leukocytosis >11,000 cells/mm^3 ($p = 0.030$) and a higher median number of underlying diseases ($p < 0.001$).

Antimicrobial susceptibility to *Enterobacter* species isolated from blood culture is summarized in Table 4. During the study period, *E. cloacae* was found to be resistant to ampicillin/sulbactam (100%), ampicillin (96.7%), cefazolin (96.5%), ceftriaxone (94.2%), cefuroxime (84.3%), piperacillin (73.0%), and ceftazidime (57.4%). No isolate was resistant to cefepime, ciprofloxacin, and meropenem. From 2001 to 2005, three of 44 (6.8%) isolates were resistant to amikacin, 15 of 41 (36.6%) to trimethoprim/sulfamethoxazole, 14 of 30 (46.7%) to piperacillin, 25 of 42 (59.5%) to tobramycin, and 35 of 43 (81.4%) to cefuroxime. However, from 2006 to 2011, rates of resistance to cefuroxime increased to 88.9% ($p = 0.857$), piperacillin to 84.2% ($p = 0.247$), trimethoprim/sulfamethoxazole to 77.8% ($p = 0.097$), tobramycin to 66.7% ($p = 0.843$), and amakin to 11.1% ($p = 0.672$) (Fig. 2).

Discussion

The incidence of nosocomial *Enterobacter* bacteremia is gradually increasing[7] and was reported to account for 10.9% of nosocomial infections in a study from Taiwan conducted in 1999.[8] Bonadio et al[9] reported that *E. cloacae* bacteremia was a relatively rare infection in pediatric population and the rate of isolation of this organism relative to all positive blood cultures was 0.6%. Other studies reported that *Enterobacter* bacteremia accounted for 5–6% of all bacteremia[6] and 8.7% cases of neonatal sepsis.[10] In our recent study, *Enterobacter* bacteremia was found to account for 11.3% of all bacteremia; based on the findings,

Table 3 Prognostic factors associated with death in bacteremia due to *Enterobacter* species

Variable	Survival $n = 68$ (%)	Death attributed to bacteremia $n = 15$ (%)	p
Age (≤1 mo)	49 (72.1)	13 (86.7)	0.244
Sex			0.182
Male	37 (54.7)	11 (73.3)	
Female	31 (45.6)	4 (26.7)	
Length of hospital stay >1 wk	66 (97.1)	15 (100)	0.504
Median number of underlying illnesses (interquartile range)	2 (1.0)	3 (1.0)	<0.001
Sepsis (fever >39°C, poor activity)	50 (73.5)	12 (80)	0.604
Leukocytosis (>11,000 cells/mm^3)	44 (66.2)	14 (93.3)	0.030
Leukopenia (<4000 cells/mm^3)	18 (26.5)	1 (6.7)	0.100
C-reactive protein >10 mg/dL	20 (29.4)	6 (40)	0.426
Inappropriate empirical therapy	1 (1.5)	0 (0)	0.639
Polymicrobial bacteremia	1 (1.5)	1 (6.7)	0.238

Table 4 Antimicrobial susceptibility of *Enterobacter* organisms

Antimicrobial agents	*E. cloacae*			*E. sakazakii*			*E. aerogenes*		
	No. tested	Susceptible		No. tested	Susceptible		No. tested	Susceptible	
		No.	%		No.	%		No.	%
Ampicillin	61	1	1.6	4	0	0	10	0	0
Ampicillin/sulbactam	9	0	0	4	0	0			
Piperacillin	63	17	27.0	4	0	0	10	0	0
Gentamicin	70	23	32.9	4	0	0	10	0	0
Amikacin	71	53	74.6	4	4	100	10	10	100
Cefazolin	57	1	1.8	4	0	0	10	0	0
Cefuroxime	70	7	10	4	0	0	10	0	0
Ceftazidime	68	23	33.8	4	0	0	10	0	0
Ceftriaxone	69	28	40.6	4	0	0	10	0	0
Imipenem	52	50	96.2	4	4	100	10	10	100
Meropenem	37	37	100						
Ciprofloxacin	7	7	100						
Trimethoprim/sulfamethoxazole	68	22	32.4	4	0	0	10	0	0
Tobramycin	69	24	34.8						
Cefepime	1	1	100						

our study suggests that *Enterobacter* is becoming a more frequent cause of bacteremia in pediatric patients.

Enterobacter sepsis is mostly a nosocomial infection,[11] and there is strong evidence to suggest that alterations in the gastrointestinal bacterial flora of hospitalized patients lead to the selection of virulent and frequently resistant strains of *Enterobacter* species, with a subsequent risk of infection.[12,13] Several other studies have indicated that *Enterobacter* infections are particularly severe in children younger than 18 months.[14–16] Our study involved mostly neonates (74.7%) and premature infants (61.5%). Hervas et al[10] reported that the predisposing factors for nosocomial infections in patients of a neonatal intensive care unit (NICU) were mainly prematurity (57.7%) and respiratory problems (37.7%), which are similar to our results. All the patients in our study had an underlying illness and/or predisposing factors that are known to contribute to colonization of *Enterobacter* species, and our case fatality rate was 18.1%, in comparison with 21–24% reported in other series.[6,14,17]

The US National Nosocomial Infections Surveillance System revealed that the common sources of *E. cloacae* bacteremia were (in the descending order) unknown (primary bacteremia), respiratory tract, genitourinary tract, intravascular catheter, wounds/surgery, gastrointestinal tract/abdomen, skin/soft tissue, biliary tract, and burns.[18] Another study reported that the most common portal of entry for pathogens was the gastrointestinal tract (39%),[19] but in our study, the most common source of infection was the respiratory tract (53.01%), which may be related to the invasive medical interventions and respiratory problems associated with prematurity. In our study, no significant difference in mortality was noted among patients who acquired bacteremia from different routes. We reported 82 cases (98.8%) of nosocomial *Enterobacter* bacteremia, which was higher than the rate reported in pediatric patients (57–67%)[9,14] and in adult populations (72–84%).[20–24] Many factors favor the development of nosocomial infections in neonates. Nosocomial patients are always associated with an immunocompromised status, long-term hospitalization, and invasive procedures or surgeries. A substantial percentage of the patients were premature infants who had complications, especially respiratory distress and gastrointestinal diseases; underwent an invasive procedure (e.g., intubation or central venous catheter); received parenteral nutrition and prolonged antibiotics; and had a prolonged hospital stay.

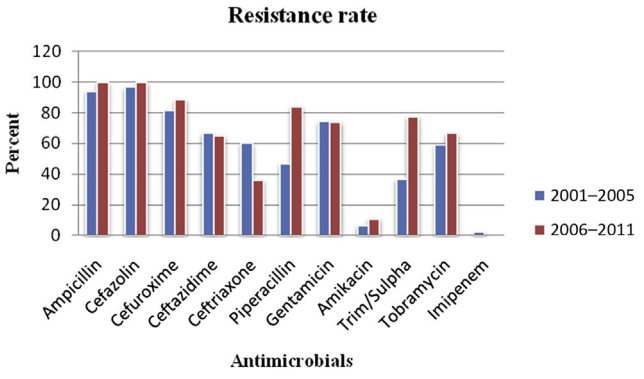


Figure 2. Resistance of *Enterobacter* isolates to selected antimicrobials in 2001–2005 and 2006–2011.

In the present study, the most common underlying disease associated with *Enterobacter* bacteremia was prematurity, followed by gastrointestinal disease. Although no single underlying disease was associated with mortality, a higher median number of underlying diseases was correlated significantly with poor prognosis in bacteremic patients. The number of underlying diseases should be considered as a major factor influencing the prognosis.

During the years 1992–1998, an increase in the resistance rate of *Enterobacter* to third-generation cephalosporins (from 22.2% to 59.2%) was observed in one study, which was related to the use of cefotaxime for empirical treatment of nosocomial infections in the NICU.[25] *E. cloacae* isolates in

this study had high rates of resistance to cefuroxime (84.3%) and ceftriaxone (94.2%), which was similar to other study results.[26] *Enterobacter* readily develops resistance to second- and third-generation cephalosporins, and this is associated with the previous use of extended-spectrum cephalosporins.[20,25] We observed a relatively high resistance rate of *Enterobacter* to second- and third-generation cephalosporins and to extended-spectrum penicillins; however, the lack of statistical significance may be attributed to the small number of cases. Widespread antimicrobial resistance now exists among *Enterobacter* strains, which has been reported to affect the clinical outcome of affected patients in some studies.[20,25,27] In the past decade, many studies have reported outbreaks caused by *Enterobacter* in neonatal settings, especially by multiple drug-resistant strains.[10,19,28] However, there are also studies suggesting that the emergence of resistant organisms and the use of corresponding antibiotics may be coincidental.[29]

In conclusion, *Enterobacter* species are emerging nosocomial pathogens with increasing antimicrobial resistance. Our study includes a review of clinical characteristics of bacteremia in pediatric patients. Leukocytosis and a high median number of underlying diseases are significantly associated with death attributable to bacteremia. Inappropriate use of antibiotics and polymicrobials are not associated with mortality. The limitations of our study are its retrospective nature and small sample size. Therefore, additional studies are needed to explain further the characteristics of *Enterobacter* bacteremia.

References

1. Kang CI, Chung DR, Ko KS, Peck KR, Song JH. Clinical predictors of *Enterobacter* bacteremia among patients admitted to the ED. *Am J Emerg Med* 2012;**30**:165—9.
2. Chang EP, Chiang DH, Lin ML, Chen TL, Wang FD, Liu CY. Clinical characteristics and predictors of mortality in patients with *Enterobacter aerogenes* bacteremia. *J Microbiol Immunol Infect* 2009;**42**:329—35.
3. Sanders Jr WE, Sanders CC. *Enterobacter* spp.: pathogens poised to flourish at the turn of the century. *Clin Microbiol Rev* 1997;**10**:220—41.
4. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis* 2004;**39**:309—17.
5. Bodey GP, Elting LS, Rodriguez S. Bacteremia caused by *Enterobacter*: 15 years of experience in a cancer hospital. *Rev Infect Dis* 1991;**13**:550—8.
6. Andresen J, Asmar BI, Dajani AS. Increasing *Enterobacter* bacteremia in pediatric patients. *Pediatr Infect Dis J* 1994;**13**: 787—92.
7. Fung CP, Wang LS, Juang YC, Liu CY, Cheng DL. *Enterobacter cloacae* bacteremia: clinical analysis of 41 cases. *J Chin Med Assoc* 1988;**42**:297—304.
8. Jan TN, Kuo BI, Shen SH, Fung CP, Lee SH, Yang TL, et al. Nosocomial Gram-negative bacteremia in critically ill patients: epidemiologic characteristics and prognostic factors in 147 episodes. *J Formos Med Assoc* 1999;**98**:465—73.
9. Bonadio WA, Margolis D, Tovar M. *Enterobacter cloacae* bacteremia in children: a review of 30 cases in 12 years. *Clin Pediatr* 1991;**30**:310—3.
10. Hervas JA, Ballesteros F, Alomar A, Gil J, Benedi VJ, Alberti S. Increase of *Enterobacter* in neonatal sepsis: a twenty-two-year study. *Pediatr Infect Dis J* 2001;**20**:134—40.
11. John Jr JF, Sharbaugh RJ, Bannister ER. *Enterobacter cloacae* bacteremia, epidemiology, and antibiotic resistance. *Rev Infect Dis* 1982;**4**:13—28.
12. Falkiner FR. *Enterobacter* in hospital. *J Hosp Infect* 1992;**20**: 137—40.
13. Kuhn I, Ayling-Smith B, Tullus K, Burman LG. The use of colonization rate and epidemic index as tools to illustrate the epidemiology of focal Enterobacteriaceae strains in Swedish neonatal wards. *J Hosp Infect* 1993;**23**:287—97.
14. Gallagher PG. *Enterobacter* bacteremia in pediatric patients. *Rev Infect Dis* 1990;**12**:808—12.
15. Reddy CM, Willoughby LF, Hara S, Crump EP. Neonatal meningitis due to *Enterobacter cloacae*. *J Natl Med Assoc* 1978;**70**:347—8.
16. Gaston MA. Enterobacter: an emerging nosocomial pathogen. *J Hosp Infect* 1988;**11**:197—208.
17. Bhutta ZA. *Enterobacter* sepsis in the newborn—a growing problem in Karachi. *J Hosp Infect* 1996;**34**:211—6.
18. National Nosocomial Infections Surveillance System. National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1990—May 1999, issued June 1999. *Am J Infect Control* 1999;**27**:520—32.
19. Modi N, Damjanovic V, Cooke RWI. Outbreak of cephalosporin-resistant *Enterobacter cloacae* infection in a neonatal intensive care unit. *Arch Dis Child* 1987;**62**:148—51.
20. Chow JW, Fine MJ, Shlaes DM, Quinn JP, Hooper DC, Johnson MP, et al. *Enterobacter* bacteremia: clinical features and emergence of antibiotic resistance during therapy. *Ann Intern Med* 1991;**115**:585—90.
21. Haddy RI, Cecil ML, Norris LL, Market RJ. *Enterobacter* bacteremia in the community hospital. *J Fam Pract* 1991;**32**:601—6.
22. Weischer M, Kolmos HJ. Retrospective 6-year study of *Enterobacter* bacteremia in a Danish university hospital. *J Hosp Infect* 1992;**20**:15—24.
23. Bouza E, Garcia de la Torre M, Erice A, Loza E, María Diaz-Borrego J, Buzón L. *Enterobacter* bacteremia: an analysis of 50 episodes. *Arch Intern Med* 1985;**145**:1024—7.
24. Watanakunakorn C, Weber J. *Enterobacter* bacteremia: a review of 58 episodes. *Scand J Infect Dis* 1989;**21**:1—8.
25. Shales DM. The clinical relevance of *Enterobacter* infections. *Clin Ther* 1993;**15**(Suppl. A):21—8.
26. Lin YC, Chen TL, Ju HL, Chen HS, Wang FD, Yu KW, et al. Clinical characteristics and risk factors for attributable mortality in *Enterobacter cloacae* bacteremia. *J Microbiol Immunol Infect* 2006;**39**:67—72.
27. Liu CP, Wang NY, Lee CM, Weng LC, Tseng HK, Liu CW, et al. Nosocomial and community-acquired *Enterobacter cloacae* bloodstream infection: risk factors for and prevalence of SHV-12 in multiresistant isolates in a medical center. *J Hosp Infect* 2004;**58**:63—77.
28. Acolet D, Ahmet Z, Houang E, Hurley R, Kaufmann ME. *Enterobacter cloacae* in a neonatal intensive care unit: account of an outbreak and its relationship to use of third generation cephalosporins. *J Hosp Infect* 1994;**28**:273—86.
29. Dalben M, Varkulja G, Basso M, Krebs VL, Gibelli MA, van der Heijden I, et al. Investigation of an outbreak of *Enterobacter cloacae* in a neonatal unit and review of the literature. *J Hosp Infect* 2008;**70**:7—14.