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Proteus mirabilis Bloodstream Infections: Risk Factors and Treatment Outcome Related to the Expression of Extended-Spectrum β-Lactamases

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Bloodstream infection (BSI) due to *Proteus mirabilis* strains is a relatively uncommon clinical entity, and its significance has received little attention. This study was initiated to evaluate risk factors and treatment outcome of BSI episodes due to *P. mirabilis* producing extended-spectrum β-lactamases (ESBLs). Twenty-five BSI episodes caused by *P. mirabilis* occurred at our hospital (Ospedale di Circolo e Fondazione Macchi, Varese, Italy) over a 7.5-year period. Phenotypic and molecular methods were used to assess ESBL production. Clinical records of BSI patients were examined retrospectively. Demographic data, underlying diseases (according to McCabe and Jackson classification and Charlson weighted index), risk factors, and treatment outcome were investigated by comparing cases due to ESBL-positive strains to cases due to ESBL-negative strains. Eleven isolates were found to express ESBLs (TEM-52 or TEM-92). The remaining 14 isolates were ESBL negative and were uniformly susceptible to extended-spectrum cephalosporins and monobactams. Comparison of the two groups showed that previous hospitalization in a nursing home ($P = 0.04$) and use of bladder catheter ($P = 0.01$) were significant risk factors for infections due to ESBL-positive strains. In addition, cases due to ESBL-positive strains showed a significantly higher mortality attributable to BSI ($P = 0.04$). BSI cases due to ESBL-negative isolates uniformly responded to therapy, whereas 5/11 cases due to ESBL-positive isolates failed to respond ($P < 0.01$). Use of carbapenems was associated with complete response independently of ESBL production. Therapeutic failure and mortality may occur in BSI episodes caused by ESBL-positive *P. mirabilis* isolates. Thus, recognition of ESBL-positive strains appears to be critical for the clinical management of patients with systemic *P. mirabilis* infections.

Proteus mirabilis is one of the most common gram-negative pathogens encountered in clinical specimens and can cause a variety of community- or hospital-acquired illnesses, including urinary tract, wound, and bloodstream infections (BSI) (26). This organism is intrinsically resistant to nitrofurantoin and tetracycline, but it is naturally susceptible to β-lactams, aminoglycosides, fluoroquinolones, and trimethoprim-sulfamethoxazole (26). However, drug resistance has been increasingly reported for this species, and the diffusion of resistance to extended-spectrum cephalosporins due to the production of extended-spectrum β-lactamases (ESBLs) has become of great concern (37). Over the last few years, ESBL-positive *P. mirabilis* (ESBL-P-PM) isolates have been recovered worldwide, with a relatively high prevalence in some settings (8, 18, 25, 32, 36, 39). Genes encoding ESBLs are usually located in transferable plasmids and are generally mutants of the classical TEM-1/2 type β-lactamases (3, 4). Moreover, coresistance to aminoglycosides, fluoroquinolones, and trimethoprim-sulfamethoxazole has been frequently reported among ESBL-P-PM strains (7, 20, 39). Thus, treatment of severe infections due to ESBL-positive enterobacteria is often limited to carbapenems (29, 33, 37).

BSI risk factors and the impact of ESBL-related bacteremia on treatment outcome have been investigated solely in infections due to ESBL-positive isolates of *Escherichia coli* and *Klebsiella pneumoniae* (10, 17, 19, 23, 28, 40). BSI due to *P. mirabilis* is relatively uncommon (9, 12, 21, 34), and its clinical significance has received little attention (2, 16, 38). To our best knowledge, no studies on systemic infections caused by ESBL-P-PM isolates have been published.

In this work we have studied 25 cases of BSI caused by *P. mirabilis*, 14 caused by ESBL-negative *P. mirabilis* (ESBL-N-PM), and 11 by ESBL-P-PM. Clinical and microbiological data have been compared between the above two groups of BSI patients in order to evaluate risk factors and treatment outcome.

MATERIALS AND METHODS

Sample collection and clinical data. Blood cultures were processed at the Microbiology Laboratory of the Ospedale di Circolo e Fondazione Macchi (Varese, Italy), a 800-bed university hospital that provides a full range of medical and surgical services, including heart surgery, neurosurgery, a kidney transplantation unit, general intensive care unit (ICU), and neuro-ICU.

Clinical records of patients developing BSI due to *P. mirabilis* strains were examined retrospectively. The following data were recorded: age, sex, admission

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ward, primary source of infection leading to secondary BSI (when present and confirmed by culture), antimicrobial agents administered during the BSI episode, and cause of death. McCabe and Jackson groups were used to classify the severity of the underlying disease (22). Comorbidity scores were determined according to the Charlson weighted index (6), whereas the severity of septicemia was classified according to the criteria of the American College of Chest Physicians/Society of Critical Care Medicine (1).

The following predisposing conditions (when present for at least 72 h before BSI onset) were also investigated: mechanical ventilation; intravascular and bladder catheters; thoracic, abdominal and other drainages; and upper and lower endoscopy. In addition, previous use of antibiotics, previous surgery, and use of corticosteroids or antineoplastic drugs were taken into account when they were administered for at least 2 weeks before BSI.

Definitions. Primary BSI refers to bacteremia for which no source of infection was documented. BSI was defined as secondary when laboratory evidence showed infection by the same organism at a distant site. Antibiotic treatment was defined as empirical when given before microbiological results were available; it was considered adequate when the infecting microorganism was subsequently found susceptible to the administered drugs (taking ESBL production into consideration).

Treatment outcome was classified as follows: (i) "complete response," resolution of fever, leukocytosis, and local signs and symptoms of infection; (ii) "partial response," improvement of fever, leukocytosis, and local signs and symptoms of infection without complete resolution; (iii) "relapse," recurrence of infection with the same organism at any body site within 1 month after discontinuation of therapy; (iv) "treatment failure," absence of resolution or worsening of signs and symptoms of infection; (v) "not assessable," incomplete records or death of the patient within 72 h of BSI onset. BSI patients who had complete or partial response to treatment were considered "responders," whereas those who had relapse or failure were considered "nonresponders" (40). Treatment outcome was attributed to the drug(s) that was chosen after receiving the microbiological report containing species identification (ID) and antimicrobial susceptibility tests (AST). Death was considered attributable to BSI when it occurred within 7 days of BSI diagnosis or when the patient was still under treatment. Follow-up of patients that were discharged or transferred to a different hospital within 1 month of BSI onset was performed in collaboration with the physician caring for the patient.

Microbiological methods. Blood cultures were incubated for 7 days at 35°C using the BacT/Alert system (Organon Teknika Corp., Durham, NC) during 1997, and the BACTEC 9240 instrument (Becton Dickinson Diagnostic Systems, Sparks, MD) since 1998. Results were interpreted according to guidelines published by the Centers for Diseases Control and Prevention (13). Isolates obtained from blood cultures of the same patient after at least 7 days of a previous BSI episode were considered as causing a new BSI episode (13).

ID and AST were routinely achieved by the Sceptor system (Becton Dickinson) during 1997 to 2002 or the Phoenix system (Becton Dickinson) since 2003. *P. mirabilis* isolates causing BSI were stored at −80°C in Todd-Hewitt broth supplemented with 20% glycerol for further investigation.

MICs were determined by the Etest method (AB Biodisk, Solna, Sweden). Susceptibility categories were determined according to the criteria of the Clinical Laboratory Standards Institute (CLSI), formerly the National Committee for Clinical Laboratory Standards, or NCCLS (24).

Since no criteria were commonly defined to screen for ESBL production in *P. mirabilis* isolates, we used criteria suggested by CLSI in the case of *E. coli* and *Klebsiella* spp. (24). Thus, isolates having MICs of ≥2 μg/ml for either ceftazidime, cefotaxime, ceftriaxone, or aztreonam were suspected to produce ESBLs. The double-disk synergy test (15) and two Etest strips (AB Biodisk) containing ceftazidime or cefotaxime (alone and plus clavulanate) were used as a phenotypic confirmatory test for ESBL production.

β-Lactamase characterization. *P. mirabilis* isolates were studied with isoelectric focusing using Multiphor II apparatus (Amersham Biosciences) as described previously (10). Screening for β-lactamase genes of the bla_{TEM} and bla_{SHV} type was carried out by colony blot hybridization as described previously (20). PCR amplification of bla_{TEM} alleles was performed using primers which target amplification of the entire bla_{TEM} gene and some flanking regions as described previously (31). Direct sequencing of PCR amplicons was performed on both strands as described previously (31). The deduced amino acid sequence of proteins was compared to those of known natural TEM variants (http://www.lahey.org/studies/webt.htm).

Statistical analysis. Statistical analysis was performed using the Statistica PC software (StatSoft, Tulsa, OK). Variance by logistic regression was calculated in order to compare patient groups infected by ESBL-P-PM or ESBL-N-PM. The Student unpaired *t* test was used to compare continuous variables, and the Mann-Whitney U-test was used to compare continuous variables not normally distributed. Fisher's exact test and χ^2 test were used to compare treatment outcomes between patient groups. Differences were considered statistically significant when the two-tailed *P* value was ≤0.05.

RESULTS

BSI episodes and microbiological data. During the study period (January 1997 to June 2004), 25 episodes of BSI caused by *P. mirabilis* were observed at our institution (Ospedale di Circolo e Fondazione Macchi, Varese, Italy).

The ESBL-P-PM isolates were uniformly resistant to ampicillin and piperacillin and exhibited decreased susceptibilities to expanded-spectrum cephalosporins and aztreonam compared to the ESBL-N-PM isolates. Clavulanate, sulbactam, and tazobactam decrease the MICs of amoxicillin, ampicillin, and piperacillin, respectively, below the breakpoint for susceptibility. Clavulanate was also able to significantly decrease the MICs of cefotaxime and ceftazidime. All the ESBL-P-PM isolates were resistant to gentamicin, and most of them were also resistant to fluoroquinolones. Of the ESBL-N-PM isolates, 6 (42.9%) were resistant to ampicillin, while all of them were susceptible to piperacillin, amoxicillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam, expanded-spectrum cephalosporins, and aztreonam. A minority of them were resistant to gentamicin ($n = 2$) or tobramycin ($n = 1$) or intermediate to fluoroquinolones ($n = 2$). All isolates, regardless of their ESBL phenotype, were susceptible to cefoxitin, carbapenems, and amikacin (Table 1).

As shown in Table 1, molecular analysis revealed that 6/14 ESBL-N-PM isolates produced a TEM-type enzyme that was identified as TEM-1. ESBL-P-PM isolates harbored a bla_{TEM}-type allele encoding either the TEM-52 ($n = 2$) or TEM-92 ($n = 9$) ESBL. Moreover, 3/11 ESBL-P-PM isolates showed a TEM-1 enzyme in addition to the TEM-52/92 ESBL. Notably, TEM-92 is identical to TEM-52 enzyme except for a single amino acid substitution in the leader peptide, which likely increases the efficiency of enzyme expression (31). The mature enzyme exhibits powerful activity against cefotaxime ($k_{cat}/K_m = 1.1 \times 10^7\ M^{-1} \cdot s^{-1}$) and also has good activity against both cefepime ($k_{cat}/K_m = 2.3 \times 10^5\ M^{-1} \cdot s^{-1}$) and ceftazidime ($k_{cat}/K_m = 6.0 \times 10^4\ M^{-1} \cdot s^{-1}$) (31).

Risk factors for BSI caused by ESBL-producing *P. mirabilis*. Demographic and clinical parameters of the BSI patients infected by ESBL-P-PM and ESBL-N-PM isolates are shown in Table 2. One patient had three different BSI episodes caused by ESBL-P-PM isolates; thus, only nine patients were taken into account for statistical analysis. The following parameters were found to be significantly different between the two groups: previous hospitalization in nursing homes ($P = 0.04$), use of bladder catheter ($P = 0.01$), and mortality attributable to BSI ($P = 0.04$).

Treatment and outcome of BSI. Clinical parameters, antimicrobial regimens, and treatment outcome for each BSI episode are summarized in Table 3. Patients infected by ESBL-P-PM strains were treated with different antimicrobials: expanded-spectrum cephalosporins ($n = 5$), β-lactam/β-lactamase inhibitor combination (BLBLIC) ($n = 4$), or carbapenems ($n = 2$). Three patients received a 6-day course of therapy because death occurred on day 6 for causes attributable to BSI.

TABLE 1. MICs and molecular results for all *P. mirabilis* isolates causing BSI during the study period (January 1997 to June 2004)

Isolate	MIC of antimicrobial agent (μg/ml)[a]																			Type of enzymes produced
	AMP	SAM	AMC	FOX	PIP	TZP	CRO	CTX	CTL	CAZ	TZL	FEP	IPM	MEM	ATM	CIP	LVX	AMK	GEN	TOB	
43/97	>256	2	4	3	>256	0.75	3	8	0.032	2	0.064	4	1.5	0.125	0.125	4	4	4	96	16	TEM-52, TEM-1
1/98	>256	4	6	3	>256	0.5	4	8	0.032	2	0.064	4	3	0.064	0.094	>32	8	3	>256	6	TEM-52
405/01	>256	8	6	4	>256	0.5	3	8	0.032	4	0.250	3	0.5	0.094	0.38	>32	>32	4	>256	24	TEM-92
130/02	>256	2	6	2	>256	0.38	8	32	0.094	1	0.032	3	2	0.047	0.064	>32	16	3	>256	8	TEM-92, TEM-1
629/02	>256	8	12	4	>256	0.75	4	4	0.032	2	0.064	8	1	0.094	0.094	>32	>32	4	>256	24	TEM-92
139/03[b]	>256	4	8	4	>256	0.5	4	8	0.032	2	0.064	32	1	0.064	0.125	>32	>32	4	>256	24	TEM-92
309/03[b]	>256	4	8	4	>256	0.5	4	8	0.032	2	0.064	32	1	0.064	0.125	>32	>32	4	>256	24	TEM-92
463/03[b]	>256	4	8	4	>256	0.5	4	8	0.032	2	0.064	32	1	0.064	0.125	>32	>32	4	>256	24	TEM-92
601/03	>256	2	4	4	>256	1	2	8	0.032	2	0.064	3	2	0.094	0.19	>32	>32	1.5	64	4	TEM-92, TEM-1
A19/03	>256	8	2	1.5	>256	0.75	2	4	0.032	2	0.064	2	2	0.047	0.047	0.75	2	3	96	8	TEM-92
A68/03	>256	4	4	6	>256	1	1.5	6	0.094	4	0.125	4	0.25	0.032	0.125	16	>32	1	64	4	TEM-92
65/99	>256	4	0.5	1	0.125	0.125	<0.016	<0.016	<0.016	<0.016	<0.016	0.064	0.5	0.023	<0.016	0.016	0.032	1.5	0.5	0.75	TEM-1
1289/01	>256	4	3	1.5	0.5	0.19	<0.016	<0.016	<0.016	<0.016	<0.016	0.047	0.75	0.032	<0.016	1	4	1.5	12	2	TEM-1
2501/01	0.5	0.5	0.38	2	0.125	0.125	<0.016	<0.016	<0.016	<0.016	<0.016	<0.016	1	0.032	<0.016	0.016	0.032	1	0.5	0.75	None
2512/01	0.5	0.5	0.38	1	0.125	0.125	<0.016	<0.016	<0.016	<0.016	<0.016	<0.016	0.5	0.032	<0.016	0.016	0.032	1	0.5	0.75	None
108/02	>256	8	1.5	1.5	0.5	0.19	<0.016	<0.016	<0.016	<0.016	<0.016	0.032	1	0.023	<0.016	0.016	0.032	2	1	0.5	TEM-1
461/02	0.5	0.5	0.38	1	0.125	0.125	<0.016	<0.016	<0.016	<0.016	<0.016	<0.016	0.75	0.032	<0.016	0.032	0.047	1.5	0.5	0.5	None
683/02	0.75	0.5	0.38	1	0.125	0.125	<0.016	<0.016	<0.016	<0.016	<0.016	0.094	1	0.032	<0.016	0.016	0.032	2	0.5	0.75	None
794/02	>256	2	0.5	1	0.125	0.125	<0.016	<0.016	<0.016	<0.016	<0.016	0.064	0.5	0.023	<0.016	0.016	0.032	6	128	32	TEM-1
85/03	1	1	0.38	1	0.125	0.125	<0.016	<0.016	<0.016	<0.016	<0.016	0.032	1	0.032	<0.016	0.016	0.032	1.5	4	8	None
654/03	>256	2	0.5	2	0.38	0.19	<0.016	<0.016	<0.016	<0.016	<0.016	0.032	0.75	0.032	<0.016	0.016	0.032	0.5	1	0.5	TEM-1
753/03	0.5	0.5	0.38	1	0.125	0.125	<0.016	<0.016	<0.016	<0.016	<0.016	<0.016	1	0.032	<0.016	0.016	0.032	2	0.5	0.75	None
A48/03	1	0.75	0.38	1	0.75	0.75	<0.016	<0.016	<0.016	<0.016	<0.016	<0.016	0.5	0.016	<0.016	0.016	0.032	1.5	2	1	None
134/04	>256	4	0.38	1	0.125	0.094	<0.016	<0.016	<0.016	<0.016	<0.016	0.047	1	0.032	<0.016	0.032	0.064	2	128	4	TEM-1
634/04	1	1	0.38	1	0.25	0.125	<0.016	<0.016	<0.016	<0.016	<0.016	0.023	1	0.032	<0.016	2	4	0.5	2	0.75	None

[a] Abbreviations for antimicrobial agents follow (NCCLS 2004 breakpoints for susceptibility [S] and resistance [R] [in micrograms per milliliter] are given in parentheses): AMP, ampicillin (S ≤ 8, R ≥ 32); SAM, ampicillin plus sulbactam (S ≤ 8/4, R ≥ 32/16); AMC, amoxicillin plus clavulanate (S ≤ 8/4, R ≥ 32/16); FOX, cefoxitin (S ≤ 8, R ≥ 32); PIP, piperacillin (S ≤ 16, R ≥ 128); TZP, piperacillin plus tazobactam (S ≤ 16/4, R ≥ 128/4); CRO, ceftriaxone (S ≤ 8, R ≥ 64); CTX, cefotaxime (S ≤ 8, R ≥ 64); CTL, cefotaxime plus clavulanate; CAZ, ceftazidime (S ≤ 8, R ≥ 32); TZL, ceftazidime plus clavulanate; FEP, cefepime (S ≤ 8, R ≥ 32); IPM, imipenem (S ≤ 4, R ≥ 16); MEM, meropenem (S ≤ 4, R ≥ 16); ATM, aztreonam (S ≤ 8, R ≥ 32); CIP, eiprofloxacin (S ≤ 1, R ≥ 4); LVX, levofloxacin (S ≤ 2, R ≥ 8); AMK, amikacin (S ≤ 16, R ≥ 32); GEN, gentamicin (S ≤ 4, R ≥ 8); TOB, tobramycin (S ≤ 4, R ≥ 8).

[b] These strains caused three different BSI in the same patient.

TABLE 2. Demographic and clinical parameters of patients with BSI due to *Proteus mirabilis* strains and differences between ESBL-P-PM and ESBL-N-PM isolates

Demographic and clinical parameters	No. (%) of patients[a]		*P* value[b]
	ESBL-P-PM	ESBL-N-PM	
No. of BSI patients	9[c]	14	ND
No. of BSI episodes	11[c]	14	ND
Age (yr) (mean ± SD)	70.9 ± 17.5	67.3 ± 18.2	NS
Sex (male/female)	7/2	7/7	ND
McCabe and Jackson groups[d]			
Nonfatal	5 (55.6)	8 (57.1)	NS
Ultimately fatal	3 (33.3)	4 (28.6)	NS
Rapidly fatal	1 (11.1)	2 (14.3)	NS
Charlson weighted index (mean ± SD)[e]	4.0 ± 2.5	4.1 ± 2.6	NS
Severity of septicemia			
Sepsis	6 (66.7)	11 (78.6)	NS
Severe sepsis	2 (22.2)	2 (14.3)	NS
Septic shock	1 (11.1)	1 (7.1)	NS
Previous hospitalizations (during the last 12 months)	6 (66.7)	8 (57.1)	NS
Previous hospitalization in nursing home	5 (55.6)	3 (21.4)	0.04
Hospital-acquired BSI	3 (33.3)	6 (42.9)	NS
Hospital stay before BSI diagnosis (days) (mean ± SD)	16.8 ± 30.3	6.0 ± 6.9	0.10
Length of hospital stay (days) (mean ± SD)	86.2 ± 193.4	19.4 ± 8.0	0.10
Empirical treatment			
Provided	9 (100.0)	12 (85.7)	NS
Adequate	5 (55.6)	12 (85.7)	0.04
Adequate treatment after ID/AST results	4 (44.4)	12 (85.7)	0.04
Predisposing factors			
Bladder catheter	9 (100.0)	8 (57.1)	0.01
Previous use of antibiotics	4 (44.4)	3 (21.4)	0.09
Intravascular catheter	4 (44.4)	3 (21.4)	0.09
Corticosteroids or antineoplastic therapy	2 (22.2)	4 (28.6)	NS
Previous surgery	0 (0.0)	3 (21.4)	NS
Drainages	0 (0.0)	3 (21.4)	NS
Intubation	1 (11.1)	1 (7.1)	NS
Secondary BSI			
All patients	4 (44.4)	3 (21.4)	0.09
Urinary tract	4 (44.4)[f]	3 (21.4)[g]	0.09
Other	0 (0.0)	0 (0.0)	NS
Overall mortality	3 (33.3)	2 (14.3)	NS
Mortality attributable to BSI	3 (33.3)	0 (0.0)	0.04

[a] Data are number (%) of patients, unless otherwise indicated.
[b] NS, not significant; ND, not determined.
[c] One patient had three different BSI; therefore, statistical analysis was performed considering only 9 BSI patients.
[d] McCabe and Jackson groups used to classify the severity of the underlying disease (22).
[e] Comorbidity scores determined according to the Charlson weighted index (6).
[f] Three from bladder catheter.
[g] One from bladder catheter.

In the remaining 8 cases, the duration of therapy was at least 8 days. Overall, the average treatment duration was 10.5 days (range, 6 to 21 days). Patients infected by ESBL-N-PM strains were also treated with different antimicrobials: expanded-spectrum cephalosporins ($n = 4$), BLBLIC ($n = 5$), or carbapenems ($n = 3$). Patients were treated for at least 7 days. The average duration of treatment was 10.9 days (range, 7 to 19 days). Two BSI patients were excluded from statistical analysis of treatment outcome: case number 1289/01 (who had been treated with ciprofloxacin), and case number 134/04 (who died on day 1 for causes not attributable to BSI).

Overall, 12/12 (100%) cases due to ESBL-N-PM isolates were responders, whereas 5/11 (45.5%) cases due to ESBL-P-PM isolates failed to respond ($P < 0.01$). Concerning treatment outcome, with expanded-spectrum cephalosporins, 4/4 BSI cases due to ESBL-N-PM strains showed a complete response, while 3/5 cases due to ESBL-P-PM strains failed to respond ($P = 0.07$). Notably, the two responders in the latter group (cases number 43/97 and A68/03) received aminoglycosides in addition to cephalosporins. With BLBLIC, 5/5 BSI cases due to ESBL-N-PM strains but only 1/4 of cases due to ESBL-P-PM were classified as responders ($P = 0.02$). Finally, all BSI patients treated with carbapenems showed a complete response, regardless of ESBL production. One patient who developed three subsequent BSI episodes due to TEM-92-positive *P. mirabilis* deserves specific mention. The patient was initially treated with ceftriaxone without microbiological eradication (case 139/03). The second BSI episode was treated with ampicillin plus sulbactam showing a partial response (case 309/03). The third episode was initially treated with cefepime alone without resolution of infection (case 463/03). Complete response was finally obtained with the addition of amikacin (two 500-mg doses).

Empirical treatment was provided in all cases of BSI caused

TABLE 3. Clinical parameters, antimicrobial regimens, and treatment outcome of patients with BSI due to ESBL-N-PM and ESBL-P-PM strains

Isolate	Age (yr)	Sex[a]	McCabe and Jackson group[b]	Charlson weighted index[c]	Severity of septicemia	Empirical antimicrobial treatment[d]	
						Agent (daily dose)	Adequate
43/97 ESBL	83	F	Nonfatal	2	Sepsis	CRO (1,000 mg × 2)	No
1/98 ESBL	91	M	Nonfatal	3	Sepsis	CRO (1,000 mg)	No
405/01 ESBL	43	M	Nonfatal	0	Sepsis	AMC (1,000 mg × 3)	Yes
130/02 ESBL	77	M	Nonfatal	5	Sepsis	SAM (1,500 mg × 3)	Yes
629/02 ESBL	65	M	Rapidly	7	Sepsis	SAM (3,000 mg × 3) AMK (500 mg × 3)	Yes
139/03 ESBL[e]	45	M	Nonfatal	0	Sepsis	CRO (2,000 mg)	No
309/03 ESBL[e]	45	M	Nonfatal	0	Sepsis	CRO (1,000 mg × 2)	No
463/03 ESBL[e]	45	M	Nonfatal	0	Sepsis	FEP (1,000 mg × 3)	No
601/03 ESBL	81	M	Ultimately	4	Septic shock	TZP (2,250 mg × 3)	Yes
A19/03 ESBL	84	F	Ultimately	6	Severe sepsis	CAZ (2,000 mg × 3) CIP (400 mg × 3)	Yes
A68/03 ESBL	71	M	Ultimately	7	Severe sepsis	CAZ (1,000 mg × 3)	No
65/99	77	F	Nonfatal	2	Sepsis	CRO (2,000 mg)	Yes
1289/01	61	F	Rapidly	9	Sepsis	CRO (2,000 mg)	Yes
2501/01	92	F	Ultimately	7	Severe sepsis	SAM (1,500 mg × 3) AMK (500 mg)	Yes
2512/01	52	M	Rapidly	5	Sepsis	SAM (3,000 mg × 3)	Yes
108/02	62	M	Nonfatal	2	Septic shock	IPM (1,000 mg × 4) AMK (1,000 mg)	Yes
461/02	63	F	Ultimately	6	Severe sepsis	CRO (2,000 mg) LVX (500 mg × 3)	Yes
683/02	16	M	Nonfatal	0	Sepsis	CRO (1,000 mg × 2)	Yes
794/02	69	M	Nonfatal	5	Sepsis	None	No
85/03	73	M	Nonfatal	2	Sepsis	TZP (2,250 mg × 3)	Yes
654/03	61	F	Ultimately	8	Sepsis	TZP (2,250 mg × 3)	Yes
753/03	77	M	Nonfatal	3	Sepsis	TZP (2,250 mg × 3)	Yes
A48/03	78	F	Nonfatal	2	Sepsis	CRO (2,000 mg)	Yes
134/04	77	M	Ultimately	4	Sepsis	None	No
634/04	84	F	Nonfatal	3	Sepsis	TZP (2,250 mg × 3)	Yes

[a] F, female; M, male.
[b] McCabe and Jackson groups used to classify the severity of the underlying disease (22).
[c] Comorbidity scores determined according to the Charlson weighted index (6).
[d] Antimicrobial agent abbreviations: CRO, ceftriaxone; GEN, gentamicin; AMC, amoxicillin plus clavulanate; SAM, ampicillin plus sulbactam; MEM, meropenem; AMK, amikacin; FEP, cefepime; TZP, piperacillin plus tazobactam; CAZ, ceftazidime; CIP, ciprofloxacin; IPM, imipenem; LVX, levofloxacin. 1,000 mg × 2, two 1,000-mg doses. N.c., not changed.
[e] These cases occurred in the same patient.
[f] UTI, urinary tract infection.

by ESBL-P-PM isolates and in most cases (12 [85.7%]) of BSI caused by ESBL-N-PM isolates. It was found to be adequate in 55.6% of BSI caused by ESBL-P-PM isolates and in the 12 cases of BSI caused by ESBL-N-PM ($P = 0.04$). Treatment after ID/AST results was found to be adequate in around half of cases of BSI caused by ESBL-P-PM isolates (4 cases [44.4%]) and in all cases of BSI caused by ESBL-N-PM isolates ($P = 0.04$).

DISCUSSION

Initially more prevalent in *K. pneumoniae* and *E. coli*, ESBLs are now also emerging resistance determinants in other enterobacterial species, including *P. mirabilis* (37). In fact, ESBL production has been reported among *P. mirabilis* in several epidemiological settings, with a prevalence that can exceed 20% in some areas (39). This trend is a matter of major concern, since *P. mirabilis* is a common cause of human infections and accounts for approximately 3% of nosocomial infections (5), while ESBL-producing *P. mirabilis* strains are usually resistant to several antimicrobial agents and can result in difficult-to-treat infections (7, 20).

Concerning BSI, several studies have analyzed risk factors, clinical outcome, and treatment outcome of BSI caused by ESBL-positive isolates of *E. coli* and *K. pneumoniae* (10, 17, 19, 23, 28, 40), while analogous aspects have not been investigated for BSI caused by ESBL-P-PM isolates. Although *P. mirabilis* is a less common cause of BSI (1 to 2% of total cases, ranking fourth among gram-negative bacilli following *E. coli*, *K. pneumoniae*, and *Enterobacter* spp.) (9, 12, 21, 34), the increasing diffusion of ESBL in strains of this species is now making this issue more interesting.

Our retrospective study addressed this aspect, by evaluating a total of 25 BSI episodes caused by either ESBL-N-PM or

TABLE 3—*Continued*

Antimicrobial therapy administered after ID and AST results[d]				Treatment outcome	Patient outcome and comments
Agent	Timing from BSI onset	Duration (days)	Daily dose		
CRO	4 days before	8	1,000 mg × 2	Partial response	Transferred on day 8 to nursing home
GEN	First day	5	2,000 mg		
N.c.	First day	6	N.c.	Failure	Death on day 6 for causes attributable to BSI
N.c.	First day	9	N.c.	Relapse	Transferred on day 12 to clinic for rehabilitation
MEM	3 days after	21	1,000 mg × 3	Complete response	Discharged on day 46
AMK	3 days after	21	500 mg		
N.c.	2 day before	6	N.c.	Failure	Death on day 4 for causes attributable to BSI
N.c.	First day	12	N.c.	Relapse	New BSI on day 12
SAM	3 days after	12	1,500 mg × 4	Partial response	Recurrent UTI[f]; new BSI on day 42
N.c.	First day	10	N.c.	Failure	Complete response when AMK (500 mg × 2) added on day 53 for 6 days
N.c.	2 days before	6	N.c.	Failure	Death on day 4 for causes attributable to BSI
IPM	4 days after	12	1,000 mg × 3	Complete response	Transferred on day 21 to nursing home
CAZ	1 day before	13	2,000 mg × 2	Complete response	Discharged on day 13
AMK	2 days after	10	500 mg × 2		
N.c.	1 day before	10	N.c.	Complete response	Transferred on day 11 to nursing home
CIP	5 days after	9	400 mg × 3	Partial response	Complete response after IMP (1,000 mg × 3) use; death on day 24
N.c.	First day	9	N.c.	Complete response	Discharged on day 10
N.c.	1 day before	8	N.c.	Complete response	Discharged on day 10
N.c.	10 days before	19	N.c.	Complete response	Discharged on day 90
IPM	5 days after	8	1,000 mg × 2	Complete response	Discharged on day 26
N.c.	First day	6	N.c.	Complete response	Discharged on day 6
IPM	1 day after	7	500 mg × 2	Complete response	Patient submitted to day hospital for dialysis
CAZ	2 days after	16	2,000 mg × 3	Complete response	Discharged on day 20
N.c.	1 day before	15	N.c.	Complete response	Discharged on day 25
N.c.	1 day after	12	N.c.	Complete response	Discharged on day 8
N.c.	First day	7	N.c.	Complete response	Transferred on day 15 to clinic for rehabilitation
None	None	None	None	Not assessable	Death on day 1
N.c.	1 day before	9	N.c.	Complete response	Discharged on day 10

ESBL-P-PM isolates that occurred at the Varese University hospital over a 7.5-year period. The relatively high number of episodes caused by ESBL-P-PM isolates (44.0%) observed during this period likely reflects the notable diffusion of ESBL-P-PM isolates in the northern Italian setting (20, 36). The absolute prevalence of the TEM-52/92 enzymes encountered in this study is fully consistent with the high prevalence of these ESBLs observed in *P. mirabilis* from this epidemiological setting (30, 31).

In agreement with previous studies on BSI episodes due to ESBL-positive *E. coli* and *K. pneumoniae* (17, 23) isolates, our results confirm that risk factors, including previous hospitalization in a nursing home and use of bladder catheters, are significantly associated with BSI episodes due to ESBL-P-PM isolates. For other known risk factors, such as prolonged hospitalization before BSI, previous use of antibiotics, use of intravascular catheter, and previous urinary tract infection, statistical significance was not attained, but this was likely due to the low number of studied cases. Concerning mortality attributable to BSI, our findings showed that it was significantly higher in BSI episodes caused by ESBL-P-PM isolates than in those caused by ESBL-N-PM isolates. This finding is in agreement with previous studies reporting a higher BSI-attributable mortality in episodes caused by ESBL-positive *E. coli* and *K. pneumoniae* isolates than in episodes caused by ESBL-negative isolates (11, 19), although other studies failed to confirm this result (17, 23). Statistical analysis also revealed higher rates of adequate empirical and rational therapeutic regimens in cases of BSI caused by ESBL-N-PM isolates and an overall better treatment outcome for BSI caused by ESBL-N-PM isolates ($P < 0.01$).

Although all the ESBL-P-PM isolates were susceptible to BLBLIC in vitro and most of them were also susceptible to expanded-spectrum cephalosporins, BLBLIC and expanded-spectrum cephalosporins were consistently effective only against ESBL-N-PM isolates, whereas carbapenems showed a good clinical efficacy against both ESBL-negative and ESBL-positive strains. The only two patients infected by ESBL-P-PM isolates who showed clinical response following treatment with expanded-spectrum cephalosporins were also treated with an aminoglycoside. In interpreting the above data, it is important to note the following. (i) Differences between the investigated groups of BSI patients cannot be ascribed to differences in drug dosage, since all patients received adequate dosages (14). (ii) Treatment was started in all cases within 4 days of BSI onset, as recommended (35) (only case 461/02 was started on

day five, but a positive treatment outcome was obtained). (iii) The average time of treatment was approximately 10 days, as currently recommended (41). Present results, therefore, indicate that expanded-spectrum cephalosporins and BLBLIC are not reliable options for BSI episodes due to ESBL-P-PM isolates. These findings are consistent with previous reports on BSI caused by other species of ESBL-positive enterobacteria (17, 19, 27, 28, 40) and strongly underscore the need to extend the revision of the CLSI interpretive criteria for ESBL producers also to *P. mirabilis*. The significantly higher rates of inadequate empirical and rational therapeutic regimens in BSI episodes caused by ESBL-P-PM isolates (see above) are clearly related to this issue and to an overall low awareness of the problem. Special tests capable of detecting ESBL-P-PM isolates would be useful for the therapeutic management of infections. In our study ESBL-P-PM strains were detected equally well by the double-disk method and the Etest synergy strips (20), as in the case of *E. coli* and *Klebsiella* spp. (24).

In conclusion, although large multicenter studies may be required for defining diagnostic and therapeutic guidelines for infections due to different species of ESBL-positive enterobacteria, our results indicate that—as suggested for other species (29, 33, 37)—carbapenems are preferable to other β-lactams for BSI caused by ESBL-P-PM isolates. This conclusion reinforces our previous observation that the treatment outcome of BSI episodes due to TEM-52-positive enterobacteria was satisfactory in patients treated with carbapenems (10).

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