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Multidrug-Resistant *Proteus mirabilis* Bloodstream Infections: Risk Factors and Outcomes

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Our aims were to identify (i) risk factors associated with the acquisition of multidrug-resistant (MDR, to 3 or more classes of antimicrobials) *Proteus mirabilis* isolates responsible for bloodstream infections (BSIs) and (ii) the impact on mortality of such infections. Risk factors for acquiring MDR *P. mirabilis* BSIs were investigated in a case-case-control study; those associated with mortality were assessed by comparing survivors and nonsurvivors in a cohort study. The population consisted of 99 adult inpatients with *P. mirabilis* BSIs identified by our laboratory over an 11-year period (1999 to 2009), 36 (33.3%) of which were caused by MDR strains, and the overall 21-day mortality rate was 30.3%. Acquisition of an MDR strain was independently associated with admission from a long-term care facility (odds ratio [OR], 9.78; 95% confidence interval [CI], 1.94 to 49.16), previous therapy with fluoroquinolones (OR, 5.52; 95% CI, 1.30 to 23.43) or oxyimino-cephalosporins (OR, 4.72; 95% CI, 1.31 to 16.99), urinary catheterization (OR, 3.89; 95% CI, 1.50 to 10.09), and previous hospitalization (OR, 2.68; 95% CI, 10.4 to 6.89). Patients with MDR *P. mirabilis* BSIs received inadequate initial antimicrobial therapy (IIAT, i.e., treatment with drugs to which the isolate displayed *in vitro* resistance) more frequently than those with non-MDR infections; they also had increased mortality and (for survivors) longer post-BSI-onset hospital stays. In multivariate regression analysis, 21-day mortality was associated with septic shock at BSI onset (OR, 12.97; 95% CI, 32.2 to 52.23), *P. mirabilis* isolates that were MDR (OR, 6.62; 95% CI, 16.4 to 26.68), and IIAT (OR, 9.85; 95% CI, 26.7 to 36.25), the only modifiable risk factor of the 3. These findings can potentially improve clinicians' ability to identify *P. mirabilis* BSIs likely to be MDR, thereby reducing the risk of IIAT—a major risk factor for mortality in these cases—and facilitating the prompt implementation of appropriate infection control measures.

The Gram-negative enteric bacterium *Proteus mirabilis* is an important cause of community- and health care-associated infections, including those involving the urinary tract, the abdominal cavity, and the bloodstream itself (13, 19, 50). Like many other members of the family *Enterobacteriaceae*, *P. mirabilis* can harbor numerous plasmid- and integron-mediated determinants of antimicrobial resistance (18). Multidrug-resistant (MDR) strains of *P. mirabilis* generally produce extended-spectrum β-lactamases (ESBLs) or the AmpC-type cephalosporinase and rarely carbapenemases, and their prevalence in some settings is relatively high (8, 10, 12, 13, 25, 31, 39, 41).

Over the past decade, the proportion of BSIs caused by Gram-negative bacteria has risen sharply (11, 26, 38, 51). Although 1 to 3% of all BSIs are caused by *P. mirabilis* (11, 26, 38, 51), the incidence of MDR in the strains responsible for these infections is a cause for concern. In general, MDR infections are known to have a significant impact on the prognosis and survival of hospitalized patients (9, 14, 24, 42, 43, 46), but it is unclear whether MDR strains are associated with worse clinical outcomes in *P. mirabilis* BSIs. Endimiani et al. (13) found that treatment failure and death are likely to occur in ESBL-producing *P. mirabilis* BSIs. Unfortunately, this study was small, including 23 patients and only 9 patients with ESBL BSIs. However, we can reasonably assume that empirical therapy is even more likely to be inadequate when infections are caused by MDR strains, and this can negatively affect clinical outcomes, particularly in vulnerable, critically ill patients (9, 20, 24, 47). Patients with *P. mirabilis* BSI are often elderly with multiple preexisting conditions, and many are being cared for in nursing homes (11, 47), characteristics which might reduce their ability to tolerate substantial delays in the administration of effective therapy. Better understanding of the factors that favor these infections might help clinicians identify patients who require more attention during the empirical prescription of antimicrobial therapy, and it would also be useful for developing effective strategies to prevent their spread.

We investigated a cohort of patients with *P. mirabilis* BSIs to identify the factors that might predict multidrug resistance and the impact of this resistance on mortality.

MATERIALS AND METHODS

Study design and patients. This was a retrospective case-case-control study (21, 42) of *P. mirabilis* BSIs in adults hospitalized in Rome's Catholic University Hospital (1,500 beds, approximately 50,000 admissions/year) over an 11-year period. We searched the hospital's central microbiology laboratory database to identify cases with all of the following characteristics: *P. mirabilis* BSI diagnosed between 1 January 1999 and 31 December 2009, patient age of ≥18 years, absence of bloodstream isolates other than *P. mirabilis*, and no evidence of infections at other sites caused by microorganisms other than *P. mirabilis*. Only 1 *P. mirabilis* BSI per patient—the first identified in the study period—was included in our analysis.

The cases identified were divided into 2 subgroups depending on whether or not the *P. mirabilis* isolate had displayed multidrug resistance

Received 20 October 2011 Returned for modification 4 February 2012
Accepted 18 March 2012
Published ahead of print 26 March 2012
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doi:10.1128/AAC.05966-11

TABLE 1 *In vitro* antimicrobial susceptibility of MDR and non-MDR *P. mirabilis* isolates causing bloodstream infections[b]

Antimicrobial agent	Non-MDR *P. mirabilis* ($n = 63$)			MDR *P. mirabilis* ($n = 36$)		
	MIC (μg/ml)[a]			MIC (μg/ml)		
	50%	90%	No. (%) susceptible	50%	90%	No. (%) susceptible
Amikacin	1	2	63 (100)	4	4	36 (100)
Amoxicillin-clavulanic acid	<0.38	0.5	63 (100)	4	8	36 (100)
Ampicillin	0.5	>256	32 (50.8)	>256	>256	0 (0)
Aztreonam	<0.016	<0.016	63 (100)	0.25	1	36 (100)
Cefepime	<0.016	0.064	63 (100)	4	32	25 (69.4)
Cefotaxime	<0.016	<0.016	63 (100)	8	32	0 (0)
Cefoxitin	1	2	63 (100)	4	8	36 (100)
Ceftazidime	<0.016	<0.016	63 (100)	2	4	33 (91.7)
Ceftriaxone	<0.016	<0.016	63 (100)	8	16	0 (0)
Ciprofloxacin	0.016	>32	50 (79.4)	>32	>32	3 (8.3)
Gentamicin	0.5	2	51 (80.9)	>32	>32	0 (0)
Levofloxacin	0.032	>32	50 (79.4)	>32	>32	3 (8.3)
Meropenem	0.023	0.03	63 (100)	0.03	0.12	36 (100)
Piperacillin-tazobactam	0.125	0.75	63 (100)	0.5	1	36 (100)
Trimethoprim-sulfamethoxazole	0.125	>4	42 (66.7)	0.125	>4	25 (69.4)

[a] MICs that inhibit 50% and 90% of isolates, respectively.
[b] MDR, multidrug resistant.

(as defined below). Each subgroup was then compared with a control group representing uninfected members of the population at risk. It consisted of inpatients randomly chosen (with a computerized method) from the laboratory database with the following characteristics: patient age of ≥18 years and one or more blood cultures performed between 1 January 1999 and 31 December 2009, all of which were negative for any type of bacterial or fungal growth. The multivariate risk models that emerged from these two comparisons were then contrasted to identify risk factors specifically associated with BSIs caused by an MDR strain of *P. mirabilis*. The 2 case groups were also compared to identify the impact of MDR on case outcome (treatment failure at 72 h, 21-day mortality, and length of hospitalization after BSI onset).

Data collection and variables analyzed. Data were retrospectively collected from the patients' hospital charts and from the laboratory database, which contains complete profiles of all patients with positive blood cultures since 1999. For each case and control, we recorded patient demographics, source of the index hospital admission (home versus another health care facility, including acute-care and long-term care facilities [LTCFs] and nursing homes), and underlying diseases and comorbidities present on admission. Medical histories were reviewed to identify previous hospitalizations (inpatient stay in an acute-care facility lasting ≥48 h during the 12 months preceding index admission), previous surgery or other invasive procedures (those performed ≤30 days before index admission), previous immunosuppressive and/or corticosteroid therapy (≤3 months before index admission), and previous antimicrobial therapy (lasting >48 h during the 3 months preceding admission). The Charlson comorbidity index (4) was calculated for each patient and classified as high (≥3) or low (≤2).

For cases, we also recorded the BSI source (established on the basis of clinical and microbiological criteria) and calculated the Acute Physiology and Chronic Health Evaluation III (APACHE III) score using chart data relative to the first 24 h after index blood culture collection (22). The clinical outcomes considered were the 21-day mortality rate (proportion of cases ending in death ≤21 days after BSI onset) and initial treatment responses (assessed 72 h after BSI onset). The latter was classified as treatment failure if the patient had died or if signs of the infection were unchanged or had worsened.

Definitions. The following terms were defined prior to data analysis: *P. mirabilis* BSIs were documented by at least 1 blood culture growing *P. mirabilis* and clinical findings compatible with the systemic inflammatory response syndrome (37); BSI onset, i.e., the date of collection of the first blood culture yielding the study isolate (index culture); and septic shock, i.e., sepsis associated with organ dysfunction and persistent hypotension after volume replacement (37).

BSIs were classified as health care associated (HCA) if onset occurred 48 h or more after the index admission (CDC, http://ecdc.europa.eu/en/activities/surveillance/HAI/Documents/2008_HAI_%20special_chapter.pdf). Earlier-onset infections were also classified as HCA if there was a history of home or day-hospital care (consisting of intravenous therapy, wound care, specialized nursing care, endoscopy, or other invasive procedures) ≤30 days before infection onset, hospital or hemodialysis clinic care, acute inpatient care (≥2 days), or residence in a nursing home or LTCF ≤90 days before BSI onset. Other BSIs detected <48 h after admission were defined as community acquired (CA).

The term "initial antimicrobial therapy" refers to the drugs administered empirically before *in vitro* susceptibility data were available. Its classification (adequate versus inadequate) was based exclusively on *in vitro* data for agents with potential activity against *P. mirabilis* (i.e., glycopeptides, anti-anaerobic-organism agents, and antifungals were excluded from this analysis). The initial treatment was classified as inadequate if any of the following was true: (i) no antibiotics with potential activity against *P. mirabilis* were prescribed during the first 24 h after BSI onset, (ii) the infecting pathogen was nonsusceptible *in vitro* (as defined below) to the drug(s) being administered, and/or (iii) the regimen used was not consistent with the current recommendations in *The Sanford Guide to Antimicrobial Therapy* (15). The time to antibiogram report was calculated as the number of hours between index blood culture collection and report of the *in vitro* susceptibility profiles to the ward requesting the culture (both recorded in the laboratory database).

Microbiological methods. The Vitek 2 (bioMérieux, Inc., Hazelwood, MO) and/or Phoenix (Becton Dickinson Microbiology Systems, Sparks, MD) automated systems had originally been used to identify *P. mirabilis* isolates and assess their *in vitro* antimicrobial susceptibilities (40). Isolates were then stored at −80°C. At time of the study, isolates were restored, and their *in vitro* antimicrobial susceptibility was reassessed with the Etest (bioMérieux) (in accordance with the manufacturer's recommendations). MICs were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) breakpoints and guidelines (7). Multidrug resistance was defined as nonsusceptibility to at least 1 agent in 3 or more of the following antimicrobial classes: oxyimino-cephalosporins, β-lactam–β-lactam inhibitor combinations, fluoroquinolones, trimethoprim-sulfamethoxazole, or aminoglycosides (27). Restored isolates also underwent

TABLE 2 Clinical characteristics of patients with bloodstream infection caused by MDR and non-MDR *P. mirabilis* strains[b]

Characteristic	No (%) of patients		*P* value
	MDR *P. mirabilis* group ($n = 36$)	Non-MDR *P. mirabilis* group ($n = 63$)	
Demographics			
Male sex	25 (69.4)	37 (58.7)	0.28
Age >65 years	14 (38.8)	40 (63.5)	0.01
Comorbidities			
Solid tumor	14 (38.9)	17 (26.9)	0.21
Hematological malignancy	4 (11.1)	6 (9.5)	0.80
Liver disease	6 (16.7)	8 (12.7)	0.58
Chronic renal failure	15 (41.7)	10 (15.9)	0.004
Diabetes	10 (27.8)	14 (22.2)	0.53
Charlson index ≥3	17 (47.2)	32 (50.8)	0.73
Immunosuppressive therapy	8 (22.2)	22 (34.9)	0.18
Epidemiological category			
HCA BSI detected ≥48 h postadmission	29 (80.5)	53 (84.1)	0.65
HCA BSI detected <48 h postadmission	5 (13.9)	6 (9.5)	0.50
Community-acquired BSI	2 (5.5)	4 (6.3)	0.87
Clinical presentation			
Source of infection			
Central venous catheter	0	4 (6.3)	0.12
Abdominal cavity	3 (8.3)	2 (3.2)	0.26
Lower respiratory tract	1 (2.8)	2 (3.2)	0.91
Surgical wound	4 (11.1)	1 (1.6)	0.03
Urinary tract	19 (52.8)	28 (44.4)	0.42
Unknown	12 (33.3)	28 (44.4)	0.27
Shock	8 (22.2)	22 (34.9)	0.18
APACHE III score (median [range])[a]	38 (10–71)	45 (3–118)	0.07
Inadequate initial antimicrobial therapy	14 (38.8)	7 (11.1)	0.001
Outcomes			
Treatment failure after the first 72 h	20 (55.5)	23 (36.5)	0.06
21-day mortality	18 (50)	12 (19.1)	0.001
Median (range) post-BSI hospital stay (days) for patients discharged alive	34 (8–129)	14 (2–105)	0.001

[a] Calculated on the basis of chart data relative to the 24 h following BSI onset. When data were missing for one variable, that variable was assigned a value of 0 indicating that it was within normal limits. If more than one variable was missing, the case was excluded from the study.
[b] Data are expressed as number (%) unless otherwise stated. Abbreviations: BSI, bloodstream infection; HCA, health care associated (as defined in Materials and Methods); MDR, multidrug resistant.

PCR amplification of bla_{TEM}, bla_{SHV}, bla_{CTX-M}, bla_{CMY}, bla_{VIM}, bla_{KPC}, bla_{PER}, and bla_{OXA} genes and sequencing of both strands of the PCR products, as previously described (10, 17, 41, 43).

Statistical analysis. Continuous variables were compared with the Student *t* test (normally distributed variables) or the Mann-Whitney U test (nonnormally distributed variables). Categorical variables were evaluated using the chi-square or two-tailed Fisher exact test. Values are expressed as means ± standard deviation (SD) or median (range) (continuous variables) or as percentages of the group they were derived from (categorical variables). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for all associations. Variables emerging from this analysis with a *P* value of <0.2 were included at model entry, and a backward stepwise approach was used to identify independent risk factors. The Kaplan-Meier method was used for survival analysis. Two-tailed tests were used to determine statistical significance; a *P* value of <0.05 was considered significant. All statistical analyses were performed with the Intercooled Stata program, version 11, for Windows (Stata Corporation, College Station, TX).

RESULTS

During the study period, *P. mirabilis* BSIs were diagnosed in 103 adult inpatients. Four of these cases were excluded because they had mixed BSIs and/or two or more variables used in our analyses were not available from the medical records or laboratory database. The remaining 99 patients were included in the study, along with 100 uninfected control patients.

Characteristics of *P. mirabilis* isolates. As shown in Table 1, almost all the *P. mirabilis* isolates were inhibited by meropenem, β-lactam–β-lactam inhibitor combinations, and amikacin. Thirty-six (36.3%) were classified as MDR. They carried the following ESBL genes: bla_{TEM-52} ($n = 13$; 36.1%), bla_{TEM-11} ($n = 11$; 30.5%), bla_{TEM-72} ($n = 10$; 27.8%), and in rare cases bla_{TEM-93} ($n = 1$) and $bla_{TEM-111}$ ($n = 1$). The laboratory database showed that antimicrobial susceptibility findings were reported 38 to 72 h after index blood culture collection (mean ± SD, 44.6 ± 4.94 h).

TABLE 3 Univariate analysis of risk factors for isolation of MDR and non-MDR strains of *P. mirabilis*[c]

Characteristic	No. (%) of patients			Univariate analysis			
		Cases		MDR *P. mirabilis* vs controls		Non-MDR *P. mirabilis* vs controls	
	Controls ($n = 100$)	MDR *P. mirabilis* ($n = 36$)	Non-MDR *P. mirabilis* ($n = 63$)	OR (95% CI)	*P*	OR (95% CI)	*P*
Demographics							
Male sex	52 (52)	25 (69.4)	37 (58.7)	2.09 (0.87–5.23)	0.07	1.31 (0.66–2.61)	0.40
Age >65 years	30 (30)	14 (38.9)	40 (63.5)	1.48 (0.61–3.51)	0.32	4.05 (1.97–8.37)	<0.001
Baseline clinical characteristics							
Solid tumor	32 (32)	14 (38.9)	17 (26.9)	1.35 (0.56–3.18)	0.45	0.78 (0.36–1.65)	0.49
Hematological malignancy	3 (3)	4 (11.1)	6 (9.5)	4.04 (0.63–28.71)	0.06	3.40 (0.68–21.66)	0.07
Liver disease	5 (5)	6 (16.6)	8 (12.7)	3.80 (0.88–16.75)	0.02	2.76 (0.74–11.21)	0.07
Diabetes	18 (18)	10 (27.8)	14 (22.2)	1.75 (0.63–4.59)	0.21	1.30 (0.54–3.04)	0.50
Chronic renal failure	16 (16)	15 (41.7)	10 (15.9)	3.75 (1.45–9.52)	0.001	0.99 (0.37–2.52)	0.98
Charlson index ≥3	41 (41)	17 (47.2)	32 (50.8)	1.28 (0.55–2.96)	0.51	1.48 (0.74–2.94)	0.22
History (prior to index admission)							
Admission from LTCF	3 (3)	8 (22.2)	2 (3.2)	9.23 (2.01–56.44)	<0.001	1.06 (0.08–9.52)	0.94
Previous hospitalization	45 (45)	24 (66.7)	33 (52.4)	2.44 (1.03–5.96)	0.02	1.34 (0.68–2.65)	0.35
Hospital stay (days) before BSI onset (median [range])[a]	19 (6–44)	15 (2–89)	8 (2–140)		0.26		0.001
Previous ICU stay	15 (15)	8 (22.2)	18 (28.6)	1.61 (0.53–4.58)	0.32	2.26 (0.97–5.30)	0.03
Immunosuppressive therapy	11 (11)	8 (22.2)	22 (34.9)	2.31 (0.72–7.00)	0.09	4.34 (1.80–10.80)	<0.001
Radiotherapy	3 (3)	5 (13.9)	1 (1.6)	5.21 (0.93–34.97)	0.02	0.52 (0.01–6.68)	0.57
Surgery	44 (44)	20 (55.6)	26 (41.3)	1.59 (0.68–3.69)	0.23	0.89 (0.44–1.77)	0.73
Total parenteral nutrition	22 (22)	16 (44.4)	7 (11.1)	2.83 (1.15–6.85)	0.01	0.44 (0.14–1.17)	0.07
Invasive procedures	45 (45)	30 (83.3)	43 (68.2)	6.11 (2.21–19.33)	<0.001	2.62 (1.29–5.39)	0.003
Dialysis	13 (13)	9 (25)	6 (9.5)	2.23 (0.74–6.34)	0.09	0.70 (0.20–2.13)	0.50
Central venous catheter	39 (39)	14 (38.8)	23 (36.5)	0.99 (0.41–2.32)	0.99	0.89 (0.44–1.81)	0.74
Urinary catheter	30 (30)	22 (61.1)	38 (60.3)	3.66 (1.54–8.80)	0.001	3.54 (1.73–7.25)	<0.001
Others							
Previous UTIs (≥2 episodes)	8 (8)	9 (25)	13 (20.6)	3.83 (1.17–12.51)	0.008	2.99 (1.05–8.86)	0.01
Previous antimicrobial use	29 (29)	24 (66.7)	29 (46)	4.89 (2.01–12.14)	<0.001	2.08 (1.02–4.24)	0.02
Oxyimino-cephalosporins	7 (7)	9 (25)	9 (14.3)	4.42 (1.31–5.22)	0.004	2.21 (0.68–7.39)	0.12
Fluoroquinolones	5 (5)	8 (22.2)	8 (12.7)	5.42 (1.41–22.58)	0.002	2.76 (0.74–11.21)	0.07
Aminoglycosides	2 (2)	3 (8.3)	2 (3.2)	4.45 (0.48–54.75)	0.08	1.60 (0.11–22.62)	0.63
β-Lactam–β-lactamase inhibitors	16 (16)	9 (25)	7 (11.1)	1.75 (0.60–4.77)	0.23	0.65 (0.21–1.82)	0.38
Others[b]	5 (5)	4 (11.1)	6 (9.5)	2.37 (0.44–11.70)	0.20	2.00 (0.48–8.64)	0.26

[a] In cases, the number of days from admission to BSI onset. This variable was evaluated only for BSI detected after ≥48 h hospital admission. In controls, who never developed BSI, the values reflect the length of the entire hospital stay.

[b] Other antimicrobials included macrolides, glycopeptides, and aminopenicillins.

[c] Data are expressed as numbers (%) unless otherwise stated. Abbreviations: ICU, intensive care unit; LTCF, long-term care facility; BSI, bloodstream infection; UTI, urinary tract infection; MDR, multidrug resistant.

Patient characteristics. Table 2 shows the baseline characteristics of the study cohort. In most cases (82/99 [82.8%]) *P. mirabilis* BSI onset occurred >48 h after admission, and the median (range) pre-BSI-onset hospital stay was 12 (2 to 140) days. At this time 54.9% (45/82) of the patients were in medical wards, 23.2% (19/82) were in ICUs, and 21.9% (18/82) were in surgical wards. In the remaining 17 cases (17.2%), the BSI was detected at hospital admission, but 11 of these (11.1% of the total cohort) were also classified as HCA infections. Only 6 (6.1% of the total cohort) had BSIs that could be classified as CA.

Risk factors for MDR and non-MDR *P. mirabilis* BSIs. Table 3 shows risk factors associated with the acquisition of BSIs caused by MDR and non-MDR strains of *P. mirabilis* in univariate analysis. In multivariate analysis, MDR *P. mirabilis* BSIs were independently associated with admission from an LTCF (OR, 9.78), previous therapy with fluoroquinolones (OR, 5.52) or oxyimino-cephalosporins (OR, 4.72), and previous hospitalization (OR, 2.68). Previous immunosuppressive therapy (OR, 4.78) and age of >65 years (OR, 3.87) were independent predictors of infection with a non-MDR *P. mirabilis* strain, and urinary catheterization was significantly associated with both types of infection (MDR OR, 3.89; non-MDR OR, 2.84) (Table 4).

Outcomes. Shortly after index blood culture collection, all patients were started on empirical antimicrobial therapy, and in all but 1 case the drugs administered were potentially active against *P. mirabilis*. These consisted of meropenem in 26 cases, piperacillin-

TABLE 4 Logistic regression analysis of risk factors for BSIs caused by MDR and non-MDR strains of *P. mirabilis*[a]

Variable	*P* value	OR (95% CI)
BSI caused by an MDR strain of *P. mirabilis*		
Admission from a long-term care facility	0.006	9.78 (1.94–49.16)
Previous fluoroquinolone therapy	0.02	5.52 (1.30–23.43)
Previous oxyimino-cephalosporin therapy	0.01	4.72 (1.31–16.99)
Urinary catheterization	0.005	3.89 (1.50–10.09)
Previous hospitalization	0.04	2.68 (1.04–6.89)
BSI caused by a non-MDR strain of *P. mirabilis*		
Immunosuppressive therapy	0.001	4.78 (1.96–11.67)
Age >65 years	<0.001	3.87 (1.86–8.06)
Urinary catheterization	0.005	2.84 (1.38–5.86)

[a] Abbreviations: BSI, bloodstream infection; MDR, multidrug resistant.

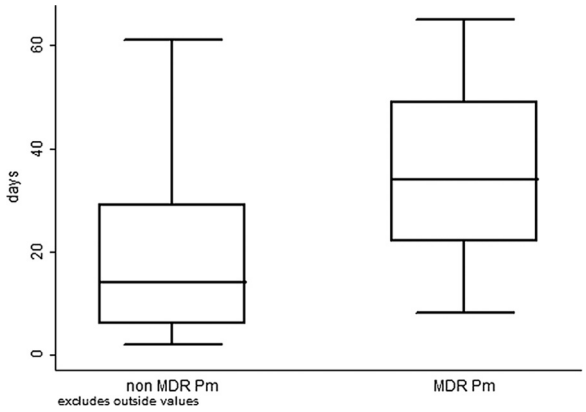

FIG 2 Hospital length of stay (LOS) following BSI onset in survivor patients infected by an MDR or a non-MDR isolate of *Proteus mirabilis* (Pm).

tazobactam or amoxicillin-clavulanate ($n = 22$), ciprofloxacin or levofloxacin ($n = 20$), cefotaxime or ceftriaxone ($n = 15$), amikacin or gentamicin ($n = 10$), and trimethoprim-sulfamethoxazole ($n = 1$). Four patients received an oxyimino-β-lactam plus an aminoglycoside. The remaining patient was initially treated with a regimen that provided no coverage whatsoever for Gram-negative bacteria.

In 20 cases, the drugs prescribed were potentially effective, but the *P. mirabilis* strain responsible for the infection was resistant to them (a fluoroquinolone in 8 cases, an oxyimino-cephalosporin in 7, gentamicin in 2, trimethoprim-sulfamethoxazole in 1, and in 2 cases gentamicin plus an oxyimino-cephalosporin). The overall rate of inadequate initial antimicrobial therapy (IIAT) was thus 21.2% (21/99). IIAT was more common in patients harboring an MDR strain (38.8% versus 11.1% of those with a non-MDR strain [OR, 5.9; 95% CI, 16.3 to 16.75; $P = 0.001$]).

Treatment failure rates at 72 h were about 1.5 times higher among patients with MDR BSIs (55.5% versus 36.5% in the non-MDR BSI group [OR, 2.17; 95% CI, 01.7 to 5.44; $P = 0.06$]). Twenty-one days after BSI onset, death had claimed 30 (30.3%) of the 99 patients (50% of the MDR BSI group versus 19.1% of those with non-MDR infections; OR, 4.25; 95% CI, 1.56 to 11.65; $P = 0.001$). Survival curve analysis confirmed the higher risks of mortality associated with MDR infections ($P < 0.001$) (Fig. 1). For the 69 patients who were alive at discharge, the median (range) hospital stay after BSI onset was 20 (2 to 129) days. It was significantly longer in patients with MDR *P. mirabilis* BSIs (34 [8 to 129] days versus 14 [2 to 105] days for those with non-MDR BSI; $P = 0.006$) (Fig. 2).

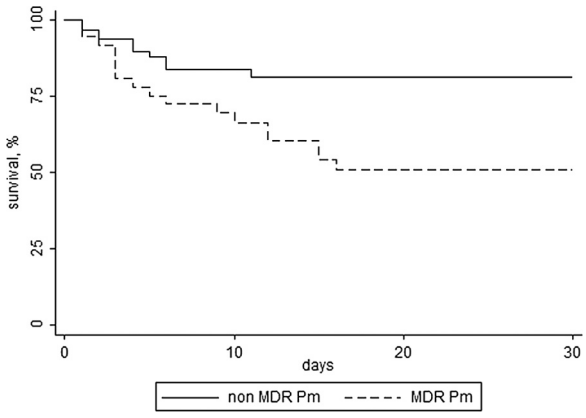

FIG 1 Kaplan-Meier survival estimates among patients with BSI caused by *Proteus mirabilis* (Pm; MDR or non-MDR isolate).

Risk factors for mortality in patients with *P. mirabilis* BSI. As shown in Table 5, septic shock at presentation (OR, 12.97), IIAT (OR, 9.85), and infection by an MDR strain (OR, 6.62) were independent risk factors for mortality.

DISCUSSION

Our 11-year surveillance data confirm that multidrug resistance is likely to be encountered in *P. mirabilis* strains responsible for BSIs in our hospital and highlight the high mortality associated with such infections. These findings corroborate previous reports on infections caused by antibiotic-resistant Gram-negative bacteria (7, 13, 16, 43–46). Almost all of the MDR BSIs in our cohort developed after hospitalization or as a result of recent contact with the health care system. Only 6 patients had what appeared to be CA infections. Unrecognized diffusion of MDR bacteria in hospital settings can increase the risk of IIAT, with obvious adverse effects on individual case outcomes. However, patients with these infections also require special monitoring and infection control measures, and for these reasons, it would be useful to know what types of patients are most likely to contract *P. mirabilis* infections caused by MDR strains.

We used a case-case-control model to answer this question. The most striking difference between the 2 case groups was related to previous contact with the health care system and previous use of fluoroquinolones or oxyimino-cephalosporins, both of which were associated exclusively with MDR *P. mirabilis* BSIs. Recent hospitalization and preadmission care in an LTCF are well-documented predictors of colonization and/or infection by antibiotic-resistant strains of bacteria (regardless of species) (2, 47). LTCFs have frequently been singled out as important reservoirs of antibiotic-resistant *Enterobacteriaceae* (30, 48), and this is particularly true for *P. mirabilis* in Italy (25, 29, 31, 34). Movement of patients and staff between long-term care and acute-care facilities would be expected to promote the spread of resistant bacteria. It is unclear whether *de novo* acquisitions are more likely to occur in LTCFs or during occasional stays in acute-care hospitals. However, it seems unlikely that the latter facilities are the main source: hospital geriatric units have recently been reported to have largely

TABLE 5 Risk factors associated with 21-day mortality in patients with *P. mirabilis* bloodstream infections[b]

Variable	No. of patients		*P*	OR (95% CI)
	Nonsurvivors ($n = 30$)	Survivors ($n = 69$)		
Univariate analysis				
Demographics				
Male sex	19 (63.3)	43 (62.3)	0.92	1.04 (0.39–2.83)
Mean age (yr ± SD)	63 ± 21	61 ± 18	0.68	
Source of infection				
Urinary tract	21 (70)	42 (60.8)	0.38	1.50 (0.55–4.28)
Lower respiratory tract	2 (6.7)	2 (2.9)	0.38	2.39 (0.16–34.19)
Surgical wound	4 (13.3)	1 (1.4)	0.01	10.46 (0.95–522.45)
Central venous catheter	0	5 (7.2)	0.13	
Biliary tract	2 (6.7)	3 (4.3)	0.62	1.57 (0.12–14.44)
Unknown	8 (26.6)	16 (23.1)	0.71	1.20 (0.38–3.52)
Comorbidities				
Liver disease	5 (16.7)	9 (13.1)	0.63	1.33 (0.31–4.96)
Chronic renal insufficiency	9 (30)	16 (23.2)	0.47	1.41 (0.47–4.05)
Diabetes mellitus	7 (23.3)	17 (24.6)	0.88	0.93 (0.28–2.77)
Hematological malignancy	7 (23.3)	3 (4.3)	0.04	6.69 (1.35–42.37)
Solid tumor	16 (53.3)	15 (21.7)	0.01	4.11 (1.48–11.36)
Charlson index (median [range])	3 (1–7)	2 (0–11)	0.24	
History				
Previous surgery	13 (43.3)	33 (47.8)	0.68	0.83 (0.31–2.15)
Previous antibiotic therapy	14 (46.6)	39 (56.5)	0.36	0.67 (0.25–1.73)
Prior hospitalization	19 (63.3)	38 (55.1)	0.44	1.40 (0.53–3.79)
Corticosteroid therapy	10 (33.3)	20 (28.9)	0.66	1.25 (0.43–3.34)
Epidemiological category				
HCA BSI detected ≥48 h postadmission	25 (83.3)	57 (82.6)	0.93	1.05 (0.30–4.22)
HCA BSI detected <48 h postadmission	4 (13.3)	7 (10.1)	0.64	1.36 (0.26–5.89)
Community-acquired BSI	1 (3.3)	5 (7.2)	0.45	0.44 (0.01–4.22)
Ward at BSI onset				
Medicine	19 (63.3)	36 (52.2)	0.30	1.58 (0.60–4.25)
Surgery	3 (10)	19 (27.5)	0.05	0.29 (0.05–1.13)
Intensive care unit	8 (26.7)	14 (20.3)	0.48	1.42 (0.45–4.26)
Clinical presentation				
Mean APACHE III score (median [range])[a]	49 (10–88)	35 (3–118)	0.02	
Septic shock	17 (56.6)	13 (18.8)	<0.001	5.63 (1.98–16.04)
Microorganism related				
Multidrug resistance	18 (60)	18 (26.1)	0.001	4.25 (1.56–11.65)
Treatment-related IIAT	16 (53.3)	5 (7.2)	<0.001	14.62 (4.10–57.81)
Multivariate analysis				
Presentation with septic shock			<0.001	12.97 (3.22–52.23)
IIAT			0.001	9.85 (2.67–36.25)
MDR-resistant *P. mirabilis* isolate			0.008	6.62 (1.64–26.68)

[a] Calculated on the basis of chart data relative to the 24 h following BSI onset. When data were missing for one variable, that variable was assigned a value of 0, indicating that it was within normal limits. If more than one variable was missing, the case was excluded from the study.

[b] Abbreviations: BSI, bloodstream infection; HCA, health care associated (as defined in Materials and Methods); IIAT, inadequate initial antimicrobial therapy; MDR, multidrug resistant.

lower ESBL-producing enterobacterial colonization rates than LTCFs (9% versus 64%) (28).

Our multivariate analysis confirmed the historical association between antimicrobial use and the emergence and dissemination of antibiotic-resistant bacteria of the family *Enterobacteriaceae* (1, 33, 43, 44, 47). Exposure to piperacillin-tazobactam and empirical cephalosporin use have recently been identified as independent risk factors for MDR *P. mirabilis* UTIs (8). MDR Gram-negative bacteria—and *P. mirabilis* in particular—are known for their ability to persistently colonize the gastrointestinal tracts of patients treated with antibiotics (5), which eradicate susceptible rival strains and modify the host's resistance. An organism resistant to multiple drugs may also be more subject to selection by the use of any one of those drugs. Its negative effects on the normal flora can also increase the host's vulnerability to assaults by new strains, elevating the risk of colonization by resistant organisms encountered during or shortly after antibiotic treatment. If the colonizing organism is an MDR strain of *P. mirabilis*, there is a good chance that the subsequent infection will be treated inadequately in the empirical phase.

In previous studies, bladder catheterization has been independently linked with antibiotic-resistant strains of *Enterobactericeae*

in patients with BSIs, including those that are community acquired (2, 47), and Endimiani et al. (13) found it to be a significant risk factor for BSI caused by ESBL-positive *P. mirabilis* strains. In our study, bladder catheterization was independently associated with *P. mirabilis* BSIs in general, not just those caused by non-MDR strains. Our data confirm that bladder catheterization is an independent risk factor for developing *P. mirabilis* BSI, but it is important to recall that the presence of a bladder catheter may also be an indirect indicator of relatively poor functional status or significant comorbidities (23).

In addition to the infecting pathogen, the severity and source of the infection, underlying diseases, age, and IIAT have all been associated with mortality in patients with BSIs (3, 20, 43). Our multivariate analysis pinpointed 3 independent predictors of death 21 days after BSI onset: presentation with septic shock, infection with a *P. mirabilis* strain that was MDR, and IIAT, the only one that can be modified to reduce mortality. In our cohort, the 21-day mortality rate among patients who received IIAT (53.3%) was 7 times higher than that observed in patients who initially received active antibiotics (7.2%), and IIAT is a distinct risk in patients with MDR infections. Indeed, in our series the presence of multidrug resistance increased the probability of IIAT more than 5-fold (OR, 5.53). All of our MDR isolates produced TEM-derived ESBLs and showed very similar resistance profiles characterized by low aztreonam MICs (0.5 to 4 mg/liter) and moderately high or elevated MICs (≥2) for the oxyimino-cephalosporins, which is consistent with previous reports (13, 25, 43, 49).

In 2010, the CLSI (6) lowered the susceptibility breakpoints for certain cephalosporins and for aztreonam relative to *Enterobacteriaceae* and eliminated its recommendation for ESBL screening and confirmatory tests. When the new breakpoints were applied, all our MDR ESBL-producing strains emerged as resistant to cefotaxime and ceftriaxone, but most were classified as susceptible to ceftazidime (91.6%), cefepime (69.4%), and aztreonam (100%). Therefore, in these cases therapy with these drugs would be defined as adequate. If we had used the clinical breakpoints furnished by the European Committee on Antimicrobial Susceptibility Testing (EUCAST; http://www.eucast.org), all of the strains would have be categorized as nonsusceptible to both cefepime and ceftazidime, and therapy with these drugs would have been classified as inadequate. Some investigators (49) have questioned the true efficacy of ceftazidime, cefepime, and aztreonam against ESBL-producing strains of *Enterobacteriaceae* strains that appear to be susceptible to these drugs on the basis of CLSI breakpoints, and others have reported poor outcomes when severe infections caused by ESBL producers are treated with oxyimino-cephalosporins, even when the MICs fall within the susceptible range (32, 35). As Wang et al. (49) have pointed out, larger multicenter studies (including tertiary as well as primary care centers and LTCFs) are needed to better define the efficacy of these antibiotics and optimal MIC cutoff points for their use in the treatment of severe infections caused by apparently susceptible ESBL-producing *Enterobacteriaceae* strains.

As far as empirical therapy is concerned, our experience indicates that meropenem and β-lactam–β-lactam inhibitor combinations may be good choices for treatment of sepsis in a patient at high risk for MDR *P. mirabilis* infections. Similar findings have recently been reported by Rodríguez-Baño and colleagues (36). However, Luzzaro et al. (25) found that piperacillin-tazobactam was sometimes ineffective against *P. mirabilis* strains producing AmpC-type β-lactamases (CBLs), which are being isolated with increasing frequency in some European hospitals (10, 12). In any case, any decision on empirical therapy should be based on sound knowledge of the local epidemiology and the patient's clinical condition.

It is important to stress that our analysis was retrospective with sample numbers that were relatively small, and it was performed at a single health care center, so the results are not necessarily applicable to other settings. However, the relationship between inadequate treatment of serious bacterial infections and poor outcome has been consistently demonstrated in other studies (16, 43–45).

In summary, multidrug resistance has a significant impact on mortality rates in patients with *P. mirabilis* BSI. Delays in the initiation of effective antimicrobial therapy have deleterious effects on clinical outcomes, and efforts should be made to ensure that appropriate therapy is initiated promptly. Faster identification of infecting microorganisms and treatment options is clearly a first-rank priority for clinical microbiology laboratories, but clinicians can and should take steps of their own to improve the outcome of these cases. Our findings indicate, for example, that when patients with *P. mirabilis* BSIs have recent histories of contact with the health care system and/or therapy with fluoroquinolones or oxyimino-cephalosporins, the possibility that the isolate will prove to be MDR should be seriously considered. This information can be exploited to improve the efficacy of the empirical prescriptions but also to ensure that early, effective measures are taken to prevent further diffusion of these dangerous bacterial strains within the hospital.

ACKNOWLEDGMENTS

We thank Marian Kent for her assistance in editing the manuscript.

We report no potential conflicts of interest. Financial support was from Università Cattolica del Sacro Cuore (Fondi Ateneo, Linea D1-2010).

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