ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2006, p. 43–48 Vol. 50, No. 1
0066-4804/06/$08.00+0 doi:10.1128/AAC.50.1.43–48.2006

Multidrug-Resistant *Pseudomonas aeruginosa*: Risk Factors and Clinical Impact†

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Received 22 June 2005/Returned for modification 4 October 2005/Accepted 16 October 2005

Pseudomonas aeruginosa*, a leading nosocomial pathogen, may become multidrug resistant (MDR). Its rate of occurrence, the individual risk factors among affected patients, and the clinical impact of infection are undetermined. We conducted an epidemiologic evaluation and molecular typing using pulsed-field gel electrophoresis (PFGE) of 36 isolates for 82 patients with MDR *P. aeruginosa* and 82 controls matched by ward, length of hospital stay, and calendar time. A matched case-control study identified individual risk factors for having MDR *P. aeruginosa*, and a retrospective matched-cohort study examined clinical outcomes of such infections. The 36 isolates belonged to 12 PFGE clones. Two clones dominated, with one originating in an intensive care unit (ICU). Cases and controls had similar demographic characteristics and numbers of comorbid conditions. A multivariate model identified ICU stay, being bedridden, having high invasive devices scores, and being treated with broad-spectrum cephalosporins and with aminoglycosides as significant risk factors for isolating MDR *P. aeruginosa*. Having a malignant disease was a protective factor (odds ratio [OR] = 0.2; $P = 0.03$). MDR *P. aeruginosa* was associated with severe outcomes compared to controls, including increased mortality (OR = 4.4; $P = 0.04$), hospital stay (hazard ratio, 2; $P = 0.001$), and requirement for procedures (OR = 5.4; $P = 0.001$). The survivors functioned more poorly at discharge than the controls, and more of the survivors were discharged to rehabilitation centers or chronic care facilities. The epidemiology of MDR *P. aeruginosa* is complex. Critically ill patients that require intensive care and are treated with multiple antibiotic agents are at high risk. MDR *P. aeruginosa* infections are associated with severe adverse clinical outcomes.

Pseudomonas aeruginosa is a leading cause of nosocomial infections and is responsible for 10% of all hospital-acquired infections (17, 18). Infections caused by *P. aeruginosa* are often severe and life threatening and are difficult to treat because of the limited susceptibility to antimicrobial agents and the high frequency of an emergence of antibiotic resistance during therapy (3, 9), thus resulting in severe adverse outcomes (4).

The problem of antibiotic resistance in *P. aeruginosa* is on the increase (18). The heightened level of drug resistance is a result of the de novo emergence of resistance in a specific organism after exposure to antimicrobials (3) as well as of patient-to-patient spread of resistant organisms (8). Accumulation of resistance after exposure to various antibiotics and cross-resistance between agents may result in multidrug-resistant (MDR) *P. aeruginosa*. This condition was found primarily in patients with cystic fibrosis, where persistent infection with *P. aeruginosa* leads to the sequential emergence of resistance to multiple antibiotic agents. These MDR *P. aeruginosa* strains may be transmitted from patient to patient and sometimes lead to outbreaks among cystic fibrosis patients attending the same clinic (20). MDR *P. aeruginosa* occurs infrequently in patients without cystic fibrosis. A 4-year study in a Boston hospital revealed 22 cases of MDR *P. aeruginosa* (an incidence of 5.5 cases/10,000 patient admissions per year) that were related to de novo emergence of resistance during treatment (12).

The risk for acquiring MDR organisms may be related to temporospatial factors (extrinsic, ecological characteristics) such as the number of carriers in the same ward, the nurse-to-patient ratio, and compliance with infection control measures as well as to individual risk factors, such as patient characteristics and in-hospital events, including treatment with antibiotics (2).

A high endemic incidence rate of MDR *P. aeruginosa* was observed at our medical center. We designed this study in order to examine its occurrence, the individual risk factors in affected patients, and the clinical impact of infection with these organisms.

MATERIALS AND METHODS

Hospital setting, data collection, and microbiology. The study was performed at the Tel-Aviv Sourasky Medical Center, Israel, a 1,200-bed tertiary-care university-affiliated hospital with 70,000 patient admissions annually.

The study was designed as two separate investigations involving the same population. One was a matched case-control study to identify the individual risk factors for having MDR *P. aeruginosa*, and the other was a retrospective matched-cohort study to examine the clinical outcomes of such an infection. All case patients were those from whom MDR *P. aeruginosa* was isolated from any clinical culture during a 10-month period. A control patient was matched to each case patient for temporospatial factors as previously described (2). Briefly, controls were randomly chosen from a list of patients in the same ward during the same time period as the case patient and hospitalized for at least the same number of days at the day of culturing of MDR *P. aeruginosa*.

Data were collected from patients' records and from hospital computerized databases and applied to a preprepared electronic questionnaire. The data retrieved for each patient included age, sex, underlying disorders, cause of hospi-

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† Dedicated to the memory of Professor Shaltiel Cabili, colleague, teacher, and friend, who passed away in 2004.

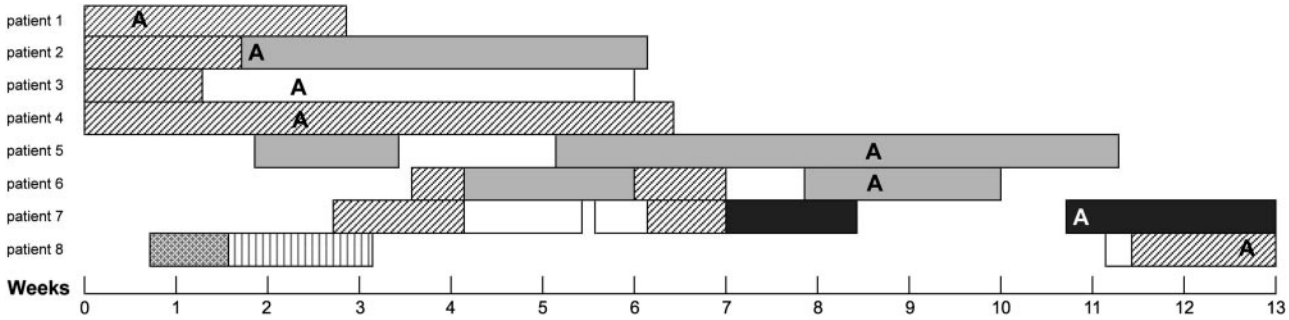

FIG. 1. Schematic representation of the spread of clone A, the major MDR *P. aeruginosa* clone, during a 13-week period. Each hospital ward is assigned a label. The day of isolation of the MDR *P. aeruginosa* is marked for each patient by the letter "A."

talization, transfer from another institution, prior hospitalization, functional capacity at the time of isolation of MDR *P. aeruginosa* and at discharge, ward of hospitalization, intensive care unit (ICU) stay, use of a Foley catheter, use of invasive devices, surgery, mechanical ventilation, severity of illness as defined by the McCabe score, dialysis, immunosuppressive therapy, and antibiotic therapy. The recorded outcomes were mortality, length of hospital stay, procedures performed after isolation of the MDR organism, and discharge to chronic care facilities.

The presence of *P. aeruginosa* was identified in the microbiology laboratory from clinical specimens by means of a gram-negative identification panel (Microscan; Dade Behring Inc., Sacramento, CA). Susceptibilities were determined by automated microdilution broth testing (Neg/Urine Combo panel; Dade Behring Inc.). Resistance to imipenem and meropenem was tested by Kirby-Bauer disk diffusion. All tests were performed according to Clinical Laboratory Standards Institute guidelines (5).

Definitions. *P. aeruginosa* was defined as being MDR when the organism was resistant to all agents studied (ceftazidime, cefepime, aztreonam, ciprofloxacin, piperacillin, and gentamicin). Susceptibility to carbapenems, amikacin, and colistin was allowed. Infection was defined according to the Centers for Disease Control and Prevention guidelines that were modified to accept community-acquired infections and to exclude asymptomatic bacteriuria (9).

Standard criteria were used to define underlying disorders (13). Disease was considered to be active if signs of disease were apparent or if the patient received treatment for the disease. Severity of illness due to comorbidities was defined according to the McCabe score (15). Systemic inflammatory response syndrome (SIRS) was defined as the presence of two of the following criteria: body temperature of >38°C or <36°C, pulse of >90 beats per min, respiratory rate of >20/minute, leucocytosis of >12,000. MODS was defined as follows: respiratory failure or renal failure when creatinine was >2 mg/dl or twice the baseline creatinine in a patient with chronic renal failure, central nervous system failure when the Glasgow coma scale was <11, cardiovascular failure when inotropic drugs were required, and hepatic failure when the bilirubin level was >2 mg/dl (19, 21).

We noted the presence of susceptible *P. aeruginosa* in any culture prior to isolation of the MDR strain for each patient included in the study. The number of antibiotics that the patient received (for at least 48 h) from the beginning of the patient's hospitalization until inclusion in the study was recorded. Recent hospitalization was defined as a hospital stay within 2 months before the index hospitalization.

Examining epidemiological relatedness. To examine the relationships between MDR *P. aeruginosa* isolates, the available isolates were typed using pulsed-field gel electrophoresis (PFGE). DNA preparation and cleavage were carried out with 20 U of SpeI endonuclease (New England Biolabs, Beverly, MA), as previously described (7). Electrophoresis was performed in a CHEF-DR III apparatus (Bio-Rad Laboratories Ltd., Hercules, CA). The initial switch time was 0.5 s, the final switch time was 35 s, and the run time was 22 h at 6 V/cm with a temperature of 14°C. Gels were stained and photographed (GelDoc 2000; Bio-Rad), and DNA patterns were compared and interpreted according to criteria described previously by Tenover et al. (22). These data were used to draw a chart of the hospital location at each calendar day for all cases, stratified according to PFGE type. This chart enabled a visual examination of the overlap in hospital locations over time for cases of *P. aeruginosa* with a similar PFGE type.

Statistical analysis. Statistical analyses were run using Stata (College Station, TX) version 6 software. All the analyses were matched in order to correspond to the study design. Risk factors and dichotomized outcomes were examined using conditional logistic regression. The length of hospital stay was analyzed by survival methods. After examining the survivorship function, a semiparametric (Weibull) model was used. All variables were examined by univariate analysis. Variables with a P value of <0.2 in the univariate analysis were included in the multivariate model. A final model was built and included all the variables with a P value of <0.1. Variables were examined for confounding characteristics and for effect modifications, and the significance of interaction terms was tested. All the statistical tests were two tailed. A P value of <0.05 was considered significant.

RESULTS

Data were collected from 82 inpatients with MDR *P. aeruginosa* during the study period. The incidence rate of MDR *P. aeruginosa* was 14/10,000 patient admissions per year. Fifty case patients (60%) were male, and the median age of the cohort was 65 years. Case patients were identified in 20 different wards, and there was no apparent temporospatial clustering of the case patients. Isolates from 36 patients were available for PFGE typing. These isolates belonged to 12 different clones, 2 of which dominated: clone A accounted for 10 of the 36 case patients, and clone B accounted for 9. Seventeen isolates (not belonging to clone A or B) belonged to 10 different clones. When the data on typing were combined with classic epidemiological methods, it became apparent that clone A affected mostly patients who had been in the ICU before MDR *P. aeruginosa* had been isolated or who had contact with carriers who had been in the ICU (Fig. 1). Being affected by clone B was not clustered in time or location in the hospital.

The most common site of isolation of MDR *P. aeruginosa* was a wound (39%), followed by the respiratory tract (22%) and the urinary tract (18%). The primary site of isolation was blood in only 8.5% of the study patients. The average length of hospital stay before isolation of the pathogen was 17 days. MDR *P. aeruginosa* was isolated within 48 h after admission in 13 patients (16%): 4 of them had been transferred from another institution, and the other 5 had been hospitalized during the preceding 2 months. A susceptible *P. aeruginosa* isolate was isolated prior to culturing of the MDR strain in only 19 (23%) patients. At the day of first culture, 61 (74%) study patients were classified as having an infection at the site of culture.

Individual risk factors for MDR *P. aeruginosa*. The patients' characteristics and variables that were examined as possible risk factors with the corresponding matched univariate analysis are displayed in Table 1. Case patients and their matched controls had similar demographic characteristics and number of comorbid conditions. Examination of specific comorbidities

TABLE 1. Characteristics and exposures of patients with MDR *P. aeruginosa* and their matched controls[e]

Characteristic	Cases (n = 82)	Controls (n = 82)	OR (95% CI)	P value
Demographics				
Age (yr)[a] (mean ± SD)	65 ± 17	63 ± 20	1.0 (0.9–1.02)	0.5
Male gender [no. (%)]	50 (60)	41 (50)	1.5 (0.8–2.9)	0.16
No. of comorbidities [mean (SD)]	1.2 (0.9)	1.3 (0.8)	0.8 (0.6–1.2)	0.5
Exposures prior to MDR *P. aeruginosa* isolation[b]				
Transfer from institution [no. (%)]	11 (13)	1 (1)	11.1 (1.4–85)	0.02
Home antibiotic Rx [no. (%)]	13 (15)	5 (6)	2.6 (0.9–7.2)	0.06
ICU stay [no. (%)]	32 (39)	16 (19)	17 (2.3–127)	0.006
Surgery [no. (%)]	43 (52)	37 (45)	1.5 (0.7–3.2)	0.2
Immunosuppressive therapy [no. (%)][c]	7 (8)	11 (13)	0.5 (0.1–1.6)	0.2
Foley catheter [no. (%)]	63 (76)	41 (50)	6.5 (2.2–18.6)	<0.001
Central venous line [no. (%)]	39 (47)	26 (31)	3.8 (1.4–10.1)	0.008
Dialysis [no. (%)]	4 (4)	5 (6)	0.7 (0.1–3.3)	0.7
Mechanical ventilation [no. (%)]	42 (51)	17 (20)	27 (3.6–198.6)	0.001
Severity of illness[d]				
Vasopressor treatment [no. (%)]	23 (28)	11 (13)	4.0 (1.3–11.9)	0.01
Bedridden [no. (%)]	56 (68)	38 (46)	3.4 (1.4–7.9)	0.004
McCabe score,[a] Nonfatal [no. (%)]	50 (61)	45 (54)	1.1 (0.6–1.9)	0.6
Antibiotic treatment				
No. of patients treated[c] (%)	64 (78)	53 (64)	3.2 (1.3–7.9)	0.014
No. of antibiotics (mean ± SD)	2.3 ± 1.6	1.7 ± 1.5	1.4 (1.1–1.9)	0.006
Agent [no. (%)][a]				
Penicillin	63 (76)	50 (60)	3.1 (1.2–7.9)	0.01
Cephalosporin (narrow spectrum)	3 (3)	2 (2)	1.5 (0.2–8.9)	0.6
Cephalosporin (extended spectrum)	15 (18)	14 (17)	1.0 (0.4–2.4)	0.8
Cephalosporin (broad spectrum)	26 (31)	15 (18)	2.1 (0.9–4.4)	0.05
Cephalosporin ("fourth generation")[f]	3 (3)	3 (3)	1.8 (0.2–4.9)	1.0
Quinolones	11 (13)	6 (7)	1.8 (0.6–4.9)	0.2
Antipseudomonal drugs	48 (58)	31 (37)	5.2 (1.8–15.2)	0.002
Carbapenems	6 (7)	6 (7)	1.0 (0.2–3.9)	1.0
Aminoglycosides	30 (36)	18 (21)	2.7 (1.1–6.4)	0.02
Vancomycin	6 (7)	7 (8)	0.8 (0.2–2.7)	0.7
Macrolides	6 (7)	4 (4)	1.5 (0.4–5.3)	0.5
Chloramphenicol	5 (6)	3 (3)	1.6 (0.3–6.9)	0.4
Metronidazole	6 (7)	9 (10)	0.5 (0.1–1.9)	0.3
Sulfamides	2 (2)	0		1.0

[a] Continuous variable.
[b] Exposures that occurred between hospital admission and inclusion in the study.
[c] Immunosuppressive therapy referred to chemotherapy within 3 weeks of study entry or treatment with at least 20 mg of prednisone daily for at least 2 weeks before study entry (16).
[d] Severity of illness 48 hours before inclusion in the study.
[e] Matched univariate analysis. CI, confidence interval; Rx, prescription.
[f] Fourth generation refers to cefepime.

revealed that the frequency of cardiovascular, renal, and lung diseases and diabetes mellitus did not differ between the groups and that fewer case patients had a malignant disease than matched controls (odds ratio [OR] = 0.3; P = 0.02). Admission from a chronic care facility was associated with an increased risk for isolation of MDR *P. aeruginosa* (OR = 11.1; P = 0.02) but not hospitalization within the previous 2 months (OR 1.0; P = 0.8). ICU stay was a significant risk factor for infection with MDR *P. aeruginosa* (OR = 17; P = 0.006) as was the use of invasive devices, especially Foley catheters (OR = 6.5; $P < 0.001$), mechanical ventilation (OR = 27; P = 0.001), and the use of a central line (OR = 3.8; P = 0.008). At 48 h before inclusion in the study, the study group included more severely ill patients than the control group, as expressed by a higher rate of bedridden patients (68% versus 46%; P = 0.004) and a higher incidence of MODS and SIRS (35% versus 18% [P = 0.006] and 56% versus 25% [$P < 0.001$], respectively).

Variables found to be associated with the isolation of MDR *P. aeruginosa* were examined by a multivariate model, which revealed a statistically significant interaction between the uses of different devices (mechanical ventilation, Foley catheter, and central line). Thus, we could construct a dichotomized score: patients with mechanical ventilation or with a central line and a Foley catheter were given a high device score, and patients with either a Foley catheter or a central line were given a low device score. Multivariate analysis identified the following variables as significant independent risk factors for MDR *P. aeruginosa*: ICU stay (OR = 10.1; P = 0.04), being bedridden (OR = 3.5; P = 0.04), high invasive devices score (OR = 13.9; P = 0.02),

and number of antibiotic classes with which the patient had been treated (OR = 1.8; $P = 0.01$). Having a malignant disease remained protective in the multivariate model as well (OR = 0.2; $P = 0.03$).

We studied the role of antimicrobial agents and the extent of exposure to antibiotics before inclusion in the study, and the results of the matched univariate analysis are displayed in Table 1; 78% of the case patients and 64% of the controls were treated with antimicrobials between admission and the date of matching (OR = 3.2; $P = 0.014$). The number of antibiotic agents was associated with the isolation of MDR *P. aeruginosa* (OR = 1.4; $P = 0.006$). In the univariate analysis, penicillins, aminoglycosides, and broad-spectrum cephalosporins were all associated with the isolation of MDR *P. aeruginosa*. Among the antipseudomonal agents that had been used, carbapenems were the only class for which exposure did not confer increased risk for isolation of MDR *P. aeruginosa*. After examining in the multivariate model to adjust for confounding variables, the antibiotic agents that remained significantly associated with the isolation of MDR *P. aeruginosa* were broad-spectrum cephalosporins and aminoglycosides (OR = 9.6 [$P = 0.003$] and OR = 6.1 [$P = 0.04$], respectively).

Impact of MDR *P. aeruginosa* on patients' outcomes. (i) Mortality. There were 18 (21%) cases of in-hospital mortalities among the case patients and 10 (12%) cases among the controls (OR = 2.3; $P = 0.08$). All the fatalities among the former group were related to active infection. Results of a univariate analysis for the association between cohort characteristics and mortality are shown in Table 2. In the multivariate model, the only variables significantly associated with mortality were isolation of MDR *P. aeruginosa* (OR = 4.4; $P = 0.04$) and the McCabe score (OR = 9.6; $P = 0.03$) (Table 3).

(ii) Length of hospital stay. The median length of stay after inclusion in the study was 20 days for the case patients and 10 days for the controls. The results of the univariate analysis are displayed in Table 2. Other variables associated with prolonged hospitalization were a stay in an ICU and parameters associated with severe illness and intensive care, e.g., mechanical ventilation, central line, Foley catheter, being bedridden, and signs of SIRS ($P < 0.001$ for each of these variables). After inclusion in a multivariate model to control for confounding (Table 3), the isolation of MDR *P. aeruginosa* was associated with an increased length of hospital stay (hazard ratio [HR] = 2; $P = 0.001$).

(iii) Need for surgery. Twenty-two case patients (27%) and 13 controls (16%) underwent surgery after inclusion into the study (OR = 2.5; $P = 0.05$). Multivariate analysis revealed that the isolation of MDR *P. aeruginosa* was the only variable associated with a higher incidence of surgery after inclusion in the study. The objective of surgery among the case patients was to remove the source of infection (debridement, removal of grafts and prostheses, and amputation). Mortality was higher in the subgroup of patients who did not have surgery than in their matched controls (21% versus 8.7%; OR = 9; $P = 0.037$). In contrast, mortality was similar for case patients and controls when the former underwent surgery (22.7% versus 30.8%; $P = 0.6$), indicating that surgery for removing the source of infection reduced the excess mortality associated with infection.

(iv) Other performed procedures. Thirty-one case patients (38%) and nine controls (11%) had invasive procedures after inclusion in the study (OR = 5.4; $P = 0.001$). There were essentially three types of procedures: those aimed at removing the source of infection (drainage), those that are diagnostic (e.g., bronchoscopy), and those associated with prolonged hospitalization (tracheostomy, Hickman catheter implantation, and feeding jejunostomy). Multivariate analysis indicated that only the isolation of MDR *P. aeruginosa* was associated with an increased number of performed procedures.

(v) Discharge to chronic care facilities and functional status at discharge. Patients were divided into three groups according to their destination after discharge: home, rehabilitation center, and chronic care facility. The case patients were more often discharged to a chronic care facility (OR = 6; $P = 0.01$), and only 34% of them (compared to 59% of the controls) were fully active at discharge, while 20% (compared to 8% of the controls) were bedridden (Table 3).

TABLE 2. Matched univariate analysis for risk factors for mortality and increased length of hospital stay[a]

Variable	Mortality		Length of hospitalization	
	OR (95% CI)	*P* value	HR (95% CI)	*P* value
Demographics				
Age	1.0 (0.9–1.09)	0.07	1	0.4
Female gender	0.4 (0.1–1.6)	0.2	0.6	0.02
Underlying conditions				
No. of comorbidities	1.8 (0.8–4.2)	0.1	1	0.3
Chronic lung disease	NA		1.01	0.06
Renal insufficiency	NA		0.99	0.04
Diabetes	NA		1	0.3
Malignancy	NA		1	0.5
Cardiovascular	NA		1	0.5
Organ transplant	NA		1.25	0.5
Exposures before MDR *P. aeruginosa* isolation				
Home antibiotic prescription	1 (0.2–4.9)	1	0.6	0.09
Transfer from institution	NA		0.8	0.4
ICU stay	1 (0.2–4.9)	1	2.1	<0.001
Surgery	0.8 (0.2–2.9)	0.7	1.6	0.01
Immunosuppressive therapy	1.5 (0.2–8.9)	0.4	1.4	0.1
Invasive devices				
Devices score	2.5 (0.4–12.8)	0.2	2.6	<0.001
Foley catheter	5 (0.5–42.7)	0.1	3.0	<0.001
Mechanical ventilation	3.5 (0.7–16.8)	0.1	3.0	<0.001
Central line	1.2 (0.3–4.6)	0.7	2.5	<0.001
Dialysis	NA		2.1	0.1
Severity of illness				
Vasopressor prescription	1.6 (0.3–6.9)	0.4	1.8	0.003
ADL, bedridden	NA		2.5	<0.001
McCabe score	5.3 (1.3–21.5)	0.01	1.2	0.07
SIRS	4 (0.8–18.3)	0.08	5	<0.001
No. of antibiotics	1.5 (0.8–2.8)	0.1	1.5	<0.001
MDR *P. aeruginosa* isolation	2.3 (0.8–6.0)	0.08	2 (3.0–1.4)	<0.001

[a] NA, not available; ADL, activities of daily living.

TABLE 3. Impact of MDR *P. aeruginosa* on study patient outcomes compared to their matched controls

Outcome	% of cases (n = 82)	% of controls (n = 82)	Univariate analysis		Multivariate analysis	
			RR[f] (95% CI)	P value	OR (95% CI)	P value
Mortality[a]	21	12	2.3 (0.8–6.0)	0.08	4.4	0.04
Length of stay[b]	20[c]	10[c]	2.0 (1.4–3.0)	<0.001	2.0	0.001
Surgery[d]	27	16	2.5 (1.0–6.4)	0.05	2.5 (1.0–6.4)	0.05
Procedures[d]	38	11	5.4 (2.0–14.0)	0.001	5.4 (2.0–14.0)	0.001
Chronic care[e]	55	24	6.0 (1.3–26.8)	0.01	6.0 (1.34–26.8)	0.02
Full activity at discharge[e]	34	59	6.7 (2.0–22.4)	0.002	4.7 (1.3–16.2)	0.015

[a] Multivariate model adjusted for McCabe score.
[b] Multivariate survival analysis model adjusted for male gender, being bedridden, and invasive device score. RR and OR denote the hazard ratio.
[c] Median length of stay after inclusion in the study.
[d] No other variable was retained in the multivariate model.
[e] Multivariate analysis for surviving patients admitted from home.
[f] RR, relative risk.

DISCUSSION

Resistance to antimicrobial agents is an increasing public health threat (18). It limits therapeutic options and leads to increased mortality and morbidity (6). Given the increasing resistance rates in *P. aeruginosa*, multidrug resistance can be expected to become more prevalent in many hospitals. We conducted this study to better understand the individual risk factors for having MDR *P. aeruginosa* and to examine the consequences of its occurrence.

Most of our MDR *P. aeruginosa* cases were hospital acquired (84%); acquisition from health institutions (chronic care facilities and previous hospitalization) was evidently responsible for the remaining cases, with the exception of three patients who had no apparent contact with the healthcare system. The latter finding was indicative of the very low likelihood of community acquisition of these organisms. Most cases were not clustered in time and hospital location at the time MDR *P. aeruginosa* was isolated. Moreover, the organisms that were typed by PFGE belonged to several clones. Among the isolates that were typed, however, two clones caused half of the cases, and one patient had been hospitalized in an ICU. MDR has usually been described as developing in a susceptible strain of *P. aeruginosa* exposed sequentially to various antibiotic agents (3). In the current study, we found that a susceptible *P. aeruginosa* isolate was isolated prior to an MDR strain only in 23% of the cases. These findings suggest that the endemicity of MDR *P. aeruginosa* in our institution is related to various mechanisms, including de novo emergence of resistance in previously susceptible isolates, clusters secondary to patient-to-patient transmission, introduction from other institutions, and some as-yet-unexplained origins.

MDR *P. aeruginosa* was isolated from various sites and often from more than one site in the same patient. A total of 74% of the patients were identified as being infected at the time of the first isolation, and almost all the others developed an active infection with MDR *P. aeruginosa* later during their hospitalization. The individual risk factors identified in this study included a stay at an ICU, being bedridden, and the use of invasive devices. These factors portray a severely ill patient who requires intensive contact with caregivers and for whom the disease, treatment, and invasive devices compromise protective barriers. ICU stay had been found in previous studies to be an important risk factor for acquisition of resistant organisms, and the SCENIC study reported that half of the patients hospitalized in ICUs acquired a nosocomial infection (11). We also documented transmission of a dominant clone in the ICU in the current study. The intensive nursing care given to these patients and the placement of several invasive devices introduce multiple opportunities for failure of infection control measures. Moreover, the intensity of selection pressure by broad-spectrum antibiotics is high in the ICU (1). The care of bedridden patients also requires intensive contact with healthcare providers who serve as the vector for transmission of these MDR bacteria. Treatment with multiple antibiotic agents, as described previously for other resistant organisms (10, 14), and treatment with broad-spectrum cephalosporins and aminoglycosides specifically also emerged as being important risk factors. We relate this effect to the eradication of competitive flora and to the selective advantage of MDR strains. Imipenem exposure was not associated with MDR *P. aeruginosa*; this likely relates to our definition of MDR, which allowed imipenem susceptibility. Interestingly, we noticed a protective effect of malignant disease. This effect may be related to better hygienic measures and stricter adherence to contact precautions practiced with these patients as well as the high likelihood of the patients being assigned to private rooms.

The second aim of our study was to measure the direct clinical impact of MDR *P. aeruginosa*. We studied patients with active infection as well as patients with colonization (26%) at the time of first isolation, because almost all patients with colonization develop an active infection afterwards. This decision might have influenced our results towards underestimating the adverse impact of infection. We found that MDR *P. aeruginosa* was associated with severe outcomes, compared to matched controls, in terms of increased mortality (OR = 4.4; P = 0.04), increased length of hospital stay (HR = 2; P = 0.001), and the need for more procedures (OR = 5.4; P = 0.001). Moreover, the functional capacity of the surviving study patients at discharge was poorer than that of the controls, and more of the former group were discharged to a rehabilitation center or to chronic care facilities.

The limited means of effectively treating MDR *P. aeruginosa* infections led to performing more surgery and other procedures (debridement, amputation, and removal of prostheses) among the study patients in order to eradicate the source of infection. Indeed, in the subgroup of patients for whom the

nidus of infection could be removed by these procedures, morbidity and mortality were not increased, in contrast to their counterparts, for whom curative surgery was not an option. Thus, our findings confirm the results of a previous study (12) that reported that MDR *P. aeruginosa* was associated with adverse outcomes and that these outcomes are even worse when the nidus of infection cannot be removed surgically.

In conclusion, this analytic study highlights the complex epidemiology of MDR *P. aeruginosa* in hospitals. These infections are likely to affect critically ill patients who require intensive care and treatment with multiple antibiotic agents. Infection with MDR *P. aeruginosa* is associated with adverse clinical outcome, and strict isolation of patients infected with MDR microorganisms and judicial use of antibiotics should be emphasized in order to prevent the spread of MDR *P. aeruginosa*.

ACKNOWLEDGMENTS

This work was supported by a grant from Teva Pharmaceutical Industries Ltd., Israel, and by a grant from the Center for the Study of Emerging Diseases, Jerusalem, Israel.

REFERENCES

1. **Bergmans, D.** 1998. Cross-colonisation with *Pseudomonas aeruginosa* of patients in an intensive care unit. Thorax **53:**1053–1058.
2. **Carmeli, Y., G. M. Eliopoulos, and M. H. Samore.** 2002. Antecedent treatment with different antibiotic agents as a risk factor for vancomycin-resistant *Enterococcus*. Emerg. Infect. Dis. **8:**802–807.
3. **Carmeli, Y., N. Troillet, G. Eliopoulos, and M. H. Samore.** 1999. Emergence of antibiotic-resistant *Pseudomonas aeruginosa*: comparison of risks associated with different antipseudomonal agents. Antimicrob. Agents Chemother. **43:**1379–1382.
4. **Carmeli, Y., N. Troillet, A. W. Karchmer, and M. H. Samore.** 1999. Health and economic outcomes of antibiotic resistant *Pseudomonas aeruginosa*. Arch. Intern. Med. **159:**1127–1132.
5. **Clinical and Laboratory Standards Institute.** 2005. Performance standards for antimicrobial susceptibility testing. Fifteenth informational supplement M100-S15. Clinical and Laboratory Standards Institute, Wayne, Pa.
6. **Cosgrove, S. E., and Y. Carmeli.** 2003. The impact of antimicrobial resistance on health and economic outcomes. Clin. Infect. Dis. **36:**1433–1437.
7. **D'Agata, E., L. Venkataraman, P. DeGirolami, and M. Samore.** 1997. Molecular epidemiology of ceftazidime-resistant gram-negative bacilli in a non-outbreak setting. J. Clin. Microbiol. **35:**2602–2605.
8. **Fridkin, S. K., and R. Gaynes.** 1999. Antimicrobial resistance in intensive care units. Clin. Chest Med. **20**:303–316.
9. **Garner, J. S., W. R. Jarvis, T. G. Emori, T. C. Horan, and J. M. Hughes.** 1988. CDC definitions for nosocomial infections. Am. J. Infect. Control **16:**128–140.
10. **Gould, I. M.** 1994. Risk factors for acquisition of multi-drug resistant Gram-negative bacteria. Eur. J. Clin. Microbiol. Infect. Dis. Suppl. **1:**30–38.
11. **Haley, R. W., and R. H. Schachtman.** 1980. The emergence of infection surveillance and control programs in US hospitals: an assessment, 1976. Am. J. Epidemiol. **111:**574–579.
12. **Harris, A. D., C. Toress-Vierra, L. Ventakataraman, P. C. DeGirolami, M. H. Samore, and Y. Carmeli.** 1999. Epidemiology and clinical outcomes of infections with multi-resistant *Pseudomonas aeruginosa*. Clin. Infect. Dis. **28:**1128–1133.
13. **Isselbacher, K. J., E. Braunwald, J. D. Wilson, J. B. Martin, A. S. Fauci, and D. L. Kasper (ed.).** 1998. Harrisson's principles of internal medicine, 14th ed. McGraw-Hill International Book Co., New York, N.Y.
14. **Jarvis, W. R.** 1992. Predominant pathogens in hospital infections. J. Antimicrob. Chemother. **29**(Suppl. A)**:**19–24.
15. **McCabe, W. R., and G. G. Jackson.** 1962. Gram-negative bacteremia I. Etiology and ecology. Arch. Intern. Med. **110**:847–885.
16. **Melby, J. D.** 1974. Systemic corticosteroid therapy: pharmacologic and endocrinologic considerations. Ann. Intern. Med. **81:**505–512.
17. **Morrison, A. J., Jr., and R. P. Wenzel.** 1984. Epidemiology of infection due to *Pseudomonas aeruginosa*. Rev. Infect. Dis. **6**(Suppl. 3)**:**627–642.
18. **National Nosocomial Infection Surveillance System.** National Nosocomial Infection Surveillance (NNIS) System report, data summary from January 1992 through June 2004, issued October 2004. Am. J. Infect. Control **32:**470–485.
19. **Rangel-Frausto, S. M.** 1995. The natural history of the systemic inflammatory response syndrome (SIRS). JAMA **273:**117–123.
20. **Saiman, L., F. Mehar, W. W. Niu, H. C. Neu, K. J. Shaw, G. Miller, and A. Prince.** 1996. Antibiotic susceptibility of multiply resistant *Pseudomonas aeruginosa* isolated from patients with cystic fibrosis, including candidates for transplantation. Clin. Infect. Dis. **23:**532–537.
21. **Sauaia, A.** 1996. Early predictors of post-injury multiple organ failure. World J. Surg. **20:**392–400.
22. **Tenover, F. C., R. D. Arbeit, R. V. Goering, P. A. Mickelsen, B. E. Murray, D. H. Persing, and B. Swaminathan.** 1995. Interpreting chromosomal DNA restriction patterns produced by pulsed-field gel electrophoresis: criteria for bacterial strain typing. J. Clin. Microbiol. **33:**2233–2239.