Abstract: P791

Citation: Clinical Microbiology and Infection Volume 8, Supplement 1, 2002

Emerging resistance among *Proteus mirabilis* isolates in Europe: report from the MYSTIC program (1997-2001)

R. Jones, P. Turner, A. Mutnick

On behalf of the MYSTIC Study Group, Europe, North Liberty, USA; Macclesfield, UK

Objective:
Resistance (R) patterns that are currently problematic in Europe (EU) can vary greatly within the same species over time, among various patient populations and among geographic regions on the same continent. The results from the MYSTIC Program which monitors meropenem (MEM; a carbapenem)-R in institutions using MEM, were used to determine R differences among *P. mirabilis* for EU from 1997 to 2001.
Methods:
MYSTIC collected MIC results from 688 *P. mirabilis* strains that were classified into patient care groups: ICU (*n* = 426), neutropenia (NP; *n* = 145), general wards (*n* = 97) and cystic fibrosis patients (pts) (CF; *n* = 20). A total of 31 centers from 10 countries participated, divided into three regions (East, North, South). All testing was by reference methods and interpreted by NCCLS criteria, including screening of ESBL phenotypes (clavulanate inhibition). Six β-lactams, ciprofloxacin (CIP), gentamicin (GM) and tobramycin (TM) were tested.
Results:
Over the monitored 5 years, the R rates varied for each agent without a clear trend toward greater R. Rank order of susceptibility was: MEM (99%) >piperacillin-tazobactam (TAZ; 96%) > cefepime (95%) > ceftazidime (CAZ; 94%) > imipenem (IPM; 92%); CIP was least active (MIC_{90}, 4 mg/L; 86% susceptible). Unexpectedly, 3.6% of *P. mirabilis* were IPM-R (MIC, ≥16 mg/L). Greater was found for strains from NP and CF, for example 40-77% susceptibility to CIP. *P. mirabilis* in East-EU sites were significantly more R to cephalosporins (ESBL rate, 24%), but CIP- and GM-R was greatest in South-EU centers. ESBL rates were 8% in North-EU, but >20% for the other geographic regions. Carbapenems (MEM > IPM) and the β-lactamase inhibitor combination (TAZ) remained most active overall.
Conclusions:
Normally susceptible species such as *P. mirabilis* have emerged as therapeutic problems in EU, following R mutations compromising CIP, CAZ and aminoglycoside use. IPM also showed decreased susceptibility of nearly 7% compared to only 4% with MEM. Continued surveillance by the MYSTIC Program appears to be a prudent practice to guide effective empiric treatment regimens.

EMERGING RESISTANCES AMONG *PROTEUS MIRABILIS* ISOLATES IN EUROPE: REPORT FROM THE MYSTIC PROGRAMME (1997-2001)

RN Jones,[1] PJ Turner,[2] AH Mutnick,[1] and the MYSTIC Study Group (Europe)

[1]The JONES Group/JMI Laboratories, North Liberty, Iowa, USA; Tufts University School of Medicine, Boston, Massachusetts, USA; and [2]AstraZeneca, Macclesfield, Cheshire, UK

MYSTIC
Meropenem Yearly Susceptibility Test Information Collection

INTRODUCTION

For a decade, TEM or SHV-derived extended-spectrum β-lactamases (ESBLs) have been described in Europe, Latin America, South Africa, and the United States (USA). The advent of ESBL-producing strains, initially among *Klebsiella* spp. and *Escherichia coli*, has represented a great threat to the use of many classes of β-lactam antimicrobials. It has been well recognised that therapeutic failure occurred when patients with serious infections due to ESBL-containing organisms were treated with the newer cephalosporins, penicillins and β-lactamase inhibitor combinations.

Proteus mirabilis is widespread in the environment and is part of the normal flora of the human gastrointestinal tract. *P. mirabilis* is commonly isolated in clinical laboratories, accounting for 1.5% of bloodstream infections and 4.9% of urinary tract infections in reported studies. *P. mirabilis* is exquisitely susceptible to a large group of antimicrobials, however, resistances mediated by ESBLs have been described. Nosocomial infections due to ESBL-producing *P. mirabilis*, especially, have been reported worldwide over the past few years.

The aim of this study was to evaluate the susceptibility patterns and potency of meropenem (MEM) and nine comparator antimicrobials against *P. mirabilis* isolates in Europe, and to assess regional variations within three defined geographically different areas of Europe using data from the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) longitudinal surveillance programme.

METHODS

Between 1997 and 2001 a total of 688 *P. mirabilis* isolates was collected by the representing MYSTIC study group. A total of 31 different medical centres in 10 countries throughout Europe (7 from the UK, 8 from Belgium, 6 from Germany, 3 from Italy, 2 from Turkey, and 1 each from the Czech Republic, Russia, Poland, Sweden, and Switzerland) participated in the study. The participating countries were further divided into three geographical regions and included: East (Czech Republic, Poland, Russia, and Turkey), North (Belgium, Germany, Sweden, and the UK), and South (Italy and Switzerland).

Isolates were categorised from four different patient care areas, and included patients from intensive care units (ICUs) (n=426), patients with neutropenia (n=145), general hospitalised patients (n=97), and cystic fibrosis patients (n=20).

Methods for reference (NCCLS agar dilution) susceptibility testing have previously been described by Turner (2000), and included the following groups of monitored antimicrobials: two carbapenems (imipenem [IPM] and MEM); three cephalosporins (cefotaxime [CTX], ceftazidime [CAZ], and cefepime [CPE]), one penicillin/β-lactamase inhibitor combination (piperacillin/tazobactam [TAZ]), one fluoroquinolone (ciprofloxacin [CIP]), and two aminoglycosides (gentamicin [GM] and tobramycin [TM]).

RESULTS

- The rank order of susceptibility for the antimicrobials tested against *P. mirabilis* over the 5-year evaluation period was: MEM (99.1%) > TAZ (96.1%) > CPE (95.1%) > CAZ (93.9%) > IPM (92.3%) > CTX (91.7%) > GM (86.4%) > CIP (85.9%) > TM (85.6%) (Table 1).

Table 1. Trends in susceptibility of *P. mirabilis* isolates from the MYSTIC Programme (688 strains; 1997-2001) listed by year of occurrence

Antimicrobial agent	MIC_{90} in mg/L (% susceptible)[a] for each year					
	1997 (n=61)	1998 (n=110)	1999 (n=210)	2000 (n=196)	2001 (n=111)	All years (n=688)
MEM	1 (100.0)	0.25 (100.0)	0.25 (99.5)	0.5 (98.5)	0.25 (98.2)	0.25 (99.1)
IPM	4 (90.2)	4 (94.6)	4 (90.5)	4 (92.4)	4 (94.6)	4 (92.3)
CTX	32 (80.3)	1 (93.3)	2 (96.6)	32 (86.1)	NT[b]	4 (91.7)
CAZ	8 (93.4)	1 (99.1)	1 (97.1)	16 (89.1)	8 (90.9)	4 (93.9)
CPE	16 (80.3)	0.5 (99.1)	1 (97.7)	4 (94.7)	NT	2 (95.1)
TAZ	8 (98.4)	4 (96.4)	4 (97.6)	16 (92.9)	8 (97.3)	8 (96.1)
CIP	8 (80.3)	1 (90.0)	2 (88.6)	8 (82.7)	4 (85.6)	4 (85.0)
GM	4 (98.4)	16 (83.6)	8 (87.6)	16 (84.3)	32 (83.0)	16 (86.4)
TM	8 (86.9)	8 (84.7)	8 (87.4)	16 (81.3)	8 (88.3)	8 (85.6)
ESBL phenotype (%)[c]	39.3	9.5	11.3	20.3	18.0	15.2

[a]Susceptibility criteria of the NCCLS (2002).
[b]NT = not tabulated, strain testing total did not achieve ≥70% of all isolates.
[c]Phenotype rate taken from the percentage of strains with MIC for CTX or CAZ of ≥2 mg/L.

Table 2. Susceptibility patterns of 688 *P. mirabilis* isolates from the MYSTIC Programme (Europe) listed by the type of patient care unit or population from which the strain was isolated

Antimicrobial agent	MIC_{90} in mg/L (% susceptible)[a] for each year			
	ICU (n=426)	Neutropenia (n=145)	General (n=97)	Cystic fibrosis (n=20)
MEM	0.25 (99.1)	1 (100.0)	0.25 (99.0)	0.25 (95.0)
IPM	8 (89.9)	4 (95.9)	4 (99.0)	8 (85.0)
CTX	2 (94.0)	32 (84.1)	NT[b]	NT
CAZ	2 (93.4)	8 (94.5)	0.5 (96.8)	16 (85.0)
CPE	1 (98.0)	16 (85.1)	NT	NT
TAZ	8 (95.1)	8 (96.6)	4 (100.0)	8 (95.0)
CIP	1 (90.1)	8 (76.6)	1 (90.7)	128 (40.0)
GM	8 (88.4)	16 (82.1)	4 990.7)	128 (60.0)
TM	NT	16 (81.7)	4 (92.7)	NT
ESBL phenotype (%)[c]	12.4	31.8	7.5	30.0

[a]Susceptibility breakpoint criteria of the NCCLS (2002).
[b]NT = not tabulated, <70% of all strains were tested.
[c]Phenotype rate taken from the percentage of strains with MIC for CTX or CAZ of ≥2 mg/L.

- MEM had minimum inhibitory concentration (MIC_{90}) values of 0.25 mg/L and appeared to be the most active of the antimicrobials tested (Table 1). In contrast, GM had MIC_{90} values of 16 mg/L (resistant) and appeared, overall, to be the least potent of the antimicrobials tested (Table 1).
- MEM demonstrated the highest susceptibility rates among the compared antimicrobials for isolates obtained from ICU (99.1%) and neutropenic (100.0%) patients. TAZ had the highest susceptibility rates for general ward (100.0%) patients (Table 2). MEM and TAZ demonstrated equally high (95.0%) susceptibility rates among cystic fibrosis patients (Table 2).
- Most agents demonstrated acceptable susceptibility rates against *P. mirabilis*. However, in neutropenic and cystic fibrosis isolates the following agents showed reduced susceptibility rates: CIP (76.6%, 40.0%, respectively), GM (82.1%, 60.0%, respectively), and TM (81.7%, not tabulated, respectively) (Table 2).
- The prevalence of the ESBL-phenotype in *P. mirabilis*, though still present, has decreased from the baseline year's incidence of 39.3% to the rate of 18.0% during 2001 (average of 15.2% over 5 years) (Table 1).
- Neutropenic and cystic fibrosis patients had the highest rates of ESBL-phenotype producing isolates (30.0-31.8%) compared with ICU (12.4%) and general ward (7.5%) patients (Table 2).
- The hospitals participating from the Northern Region demonstrated the lowest rate of ESBL-phenotype occurrence (7.7%), compared with 24.4 and 23.4% in the East and South Regions, respectively (Table 3).
- During the 5-year evaluation, MEM (MIC_{90}, 0.25-0.5 mg/L; 96.3-99.7% susceptible) and IPM (MIC_{90}, 4 mg/L; 90.7-94.9% susceptible) demonstrated the most consistent potency and susceptibility rates throughout the three geographical regions. However, IPM has consistently displayed elevated resistance rates (7.7%) among ESBL-producing *P. mirabilis* (Table 3).

Table 3. Variations in the susceptibility of 688 *P. mirabilis* isolates from Europe based on geographical regions[a]

Antimicrobial agent	MIC_{90} in mg/L (% susceptible)[b] by region:		
	East (n=108)	North (n=366)	South (n=214)
MEM	0.5(96.3)	0.25 (99.7)	0.5 (99.5)
IPM	4 (90.7)	4 (91.3)	4 (94.9)
CTX	>128 (82.1)	0.12 (97.9)	NT[c]
CAZ	32 (84.3)	1 (97.0)	8 (93.5)
CPE	8 (92.4)	0.25 (100.0)	NT
TAZ	16 (92.6)	4 (97.3)	8 (95.8)
CIP	4 (85.2)	0.5 (93.2)	8 (73.8)
GM	NT	2 (94.3)	32 (79.4)
TM	16 (77.2)	NT	NT
ESBL phenotype (%)[d]	24.4	7.7	23.4

[a]Medical centre regions were: East = Czech Republic, Poland, Russia and Turkey; North = Belgium, Germany, Sweden and the UK; and South = Italy and Switzerland.
[b]Susceptibility breakpoint criteria of the NCCLS (2002).
[c]NT = not tabulated, <70% of all strains were tested.
[d]Phenotype rate taken from the percentage of strains with MIC for CTX or CAZ of ≥2 mg/L.

CONCLUSIONS

- **MEM continues to demonstrate potent activity and high susceptibility rates (only 0.9% resistance) against *P. mirabilis*, regardless of the presence of an ESBL-phenotype. This was superior to IPM (7.7% resistance).**
- **Among the agents tested, GM (86.4% susceptible), TM (85.6%), and CIP (85.9%) continue to demonstrate lower but acceptable levels of susceptibility against *P. mirabilis*.**
- **MEM demonstrates potent activity (MIC_{90}, 0.25 mg/L) against *P. mirabilis* isolates that are resistant to β-lactamase inhibitor combinations, as well as to fluoroquinolones and aminoglycosides.**
- **Continued use of longitudinal resistance surveillance projects, such as the MYSTIC Programme, will provide the proactive data necessary to track changing susceptibility patterns, and suggest optimal therapeutic regimens.**

ACKNOWLEDGMENTS

The authors acknowledge the support of an educational/research grant from AstraZeneca. The participating MYSTIC Study Group (Europe) investigators were: UK - Dr Masterton (Edinburgh), Dr Bint (Newcastle), Dr Hood (Glasgow), Dr Chadwick (Salford), Dr Gaya (London), Dr Holliman (London), Dr Riley (London); Belgium - Professor Goossens (Antwerp), Professor Verschraegen (Ghent), Professor Lauwers (Brussels), Professor Verhaegen (Leuven), Professor Struelens (Brussels), Professor Delmee (Louvain), Dr Glupczynski (Godinne), Professor De Mol (Liege); Germany - Dr Pritzbuer (Bremen), Professor Bauernfeind (Munich), Professor Thomssen (Göttingen), Professor Rodloff (Leipzig), Professor Heesemann (Munich), Professor Hahn (Berlin); Italy - Dr Giacobone (Pavia), Professor Fontana (Verona), Professor Fraschini (Milan); Turkey - Professor Kurt (Ankara), Professor Eraksoy (Istanbul); Czech Republic - Dr Chmelarova (Ostrava); Russia - Dr Resvan (Moscow); Poland - Professor Dzierzanowska (Warsaw); Sweden - Dr Larsson (Gothenburg); and Switzerland - Professor Bille (Lausanne).

SELECTED REFERENCES

Chanal C, Bonnet R, De Champs C, Sirot D, Labia R, Sirot J. Prevalence of beta-lactamases among 1,072 clinical strains of *Proteus mirabilis*: A 2-year survey in a French hospital. Antimicrob Agents Chemother 2000; 44: 1930-1935.

De Champs C, Bonnet R, Sirot D, Chanal C, Sirot J. Clinical relevance of *Proteus mirabilis* in hospital patients: A two year survey. J Antimicrob Chemother 2000; 45: 537.

Gales AC, Jones R, Gordon K, Sader H, Wilke W, Beach M, Pfaller M, Doern G. Activity and spectrum of 22 antimicrobial agents tested against urinary tract infection pathogens in hospitalized patients in Latin America: Report from the second year of the SENTRY Antimicrobial Surveillance Program (1998). J Antimicrob Chem 2000; 45: 295-303.

Goossens H. for the MYSTIC Study Group (European centres only). MYSTIC (Meropenem Yearly Susceptibility Test Information Collection) results from Europe: Comparison of antibiotic susceptibilities between countries and centre types. J Antimicrob Chemother 2000; 46: 39-52.

Luzzaro F, Perilli M, Amicosante GL, Belloni R, Zollo A, Bianchi C, Toniolo A. Properties of multidrug-resistant, ESBL-producing *Proteus mirabilis* isolates and possible role of beta-lactam/beta-lactamase inhibitor combinations. Int J Antimicrob Agents 2001; 17: 131-135.

Mariotte S, Nordmann P, Nicolas MH. Extended-spectrum β-lactamase in *Proteus mirabilis*. J Antimicrob Chemother 1994; 33: 925-935.

National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial tests for bacteria that grows aerobically. Fifth edition: Approved standard document M7-A5. NCCLS, Wayne, PA, 2000.

National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial susceptibility testing. Approved standard document M100-S12. NCCLS, Wayne, PA, 2002.

Paterson DL, Ko WC, Von Gottberg A, Casellas JM, Mulazimoglu L, Klugman KP, Bonomo RA, Rice LB, McCormack JG, Yu V. Outcome of cephalosporin treatment for serious infections due to apparently susceptible organisms producing extended-spectrum β-lactamases: Implications for the clinical microbiology laboratory. J Antimicrob Chemother 2001; 39: 2206-2212.

Pfaller MA, Jones RN. A review of the in vitro activity of meropenem and comparative antimicrobial agents tested against 30,254 aerobic and anaerobic pathogens isolated worldwide. Diagn Microbiol Infect Dis 1997; 28: 157-163.

Pitout JDD, Thomson KS, Hanson ND, Ehrhardt AF, Moland ES, Sanders CC. Beta-lactamases responsible for resistance to expanded-spectrum cephalosporins in *Klebsiella pneumoniae*, *Escherichia coli*, and *Proteus mirabilis* isolates recovered in South Africa. Antimicrob Agents Chemother 1998; 42: 1350-1354.

Turner PJ. MYSTIC (Meropenem Yearly Susceptibility Test Information Collection): A global overview. J Antimicrob Chemother 2000; 46: 9-23.