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RESEARCH ARTICLE

PROTEUS INFECTION DISEASE - A CLINICO–EPIDEMIOLOGICAL STUDY IN TERTIARY CARE UNIVERSITY HOSPITAL IN THE CENTRAL REGION OF JAPAN FROM 2008 TO 2010

[1,*]Masaaki Minami, [2]Naoki Wakiyama, [2]Minoru Ohashi, [2]Yukio Wakimoto and [3]Michio Ohta

[1]Department of Bacteriology, Graduate School of Medical Sciences, Nagoya City University, Nagoya, Japan
[2]Department of Clinical Investigation, Nagoya City University Hospital, Nagoya, Japan
[3]School of Nursing, Sugiyama Jyogakuen University, Nagoya, Japan

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ABSTRACT

Proteus species infection is important cause of morbidity and mortality. This study was conducted to find out the prevalence and antimicrobial susceptibility pattern of Proteus species isolates at tertiary care university hospital in the central region of Japan from 2008 to 2010. Proteus species was identified by standard laboratory procedure. Antimicrobial susceptibility testing was performed by micro dilution assay according to CLSI recommendation. Of one hundred eighty-three Proteus species, one hundred thirty-nine *Proteus mirabilis*, and twenty-five *Proteus vulgalis* were isolated. About fifty-five Proteus species isolates were from outpatient. The major source of Proteus isolates were urine, pus, and sputum. Positive samples were received mostly from the urology and lowest from gastroenterology, ophthalmology and pediatrics. The effective antibiotics with over 95% susceptibility rates were amikacin, cefepime, and gentamicin. The numbers of extended-spectrum beta-lactamase (ESBL) producing isolates were twenty-nine and seven Proteus species isolates had ESBL-associated multidrug resistant ability. Proteus species infection spreads among community easily and inappropriate use of antibiotics contributes to their resistance. Continuous antimicrobial susceptible surveys are need for reducing the emergency of ESBL and multidrug resistance.

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INTRODUCTION

Proteus species including *Proteus mirabilis* and *Proteus vulgalis* can cause a variety of infections such as urinary tract and blood stream infections (O'Hara *et al.*, 2000). Antimicrobial resistant Proteus species has been reported increasingly (Endimiani *et al.*, 2005). Especially, the emergence of resistance to extended-spectrum cephalosporins due to the production of extended-spectrum beta-lactamases (ESBLs) has become serious problem (Wu *et al.*, 2008). Although fluoroquinolones have emerged as the agent of choice for the treatment of serious infections caused by ESBL-producing bacteria, the incidence of ciprofloxacin resistant Proteus species is increasing (Saito *et al.,* 2007). Previous report showed the close association between ciprofloxacin resistance and ESBL-production (Sohn *et al.,* 2011). However, little is known of the epidemiology of Proteus species infection compared to *Escherichia coli* and *Klebsiella pneumoniae*.

Corresponding author: Masaaki Minami,
Department of Bacteriology, Graduate School of Medical Sciences, Nagoya City University, Nagoya, Japan.

The present study was conducted to find out the recent prevalence and antimicrobial susceptible pattern of Proteus species isolates at tertiary care university hospital in the central of Japan. Our result would be useful for contributing to larger more extensive surveillance study.

MATERIALS AND METHODS

Strains and clinical data collection

A total of 183 Proteus species were obtained from various clinical specimens at Nagoya City University hospital from 2008 to 2010. Nagoya City University hospital is an808-bed tertiary care university hospital in the central region of Japan. We used medical records appended to clinical species for the analysis of clinical feature at Nagoya City University Hospital. We considered several isolates from the same region of the same patient as one isolate per one patient for the analysis in this study. All proteus isolates were identified by standard conventional biochemical methods or the VITEK2 system (bioMérieux, Durham NC, USA). Our experimental design was approved by the ethics committee at Nagoya City University.

Antimicrobial susceptibility analysis

Proteus species isolates were examined for 10 antibiotic susceptibilities as follow CAZ; ceftazidime, CTX; cefotaxime, CFPM; cefepime, IPM;imipenem, AZT; aztreonam, GM; gentamicin, AMK; amikacin, MINO; minocycline, CPFX; ciprofloxacin, ST; Trimethoprim-sulfamethoxazole. Minimal inhibitory concentration (MICs) were determined using broth micro dilution methodology with the VITEK2 system. Evaluation of antimicrobial resistance was based on Clinical Laboratory Standard Institute (CLSI) break point (M100-S20). For the purposes of this study, isolates showing *in vitro* resistance to CAZ or CTX were classified as ESBL-producing organism (Sohn *et al.,* 2011). Multidrug resistance (MDR) was defined as non-susceptibility to more than any three antimicrobial agents (Magiorakos *et al.,* 2012).

Statistical analysis of the data

We conducted the statistical analysis with the chi-squared test or Fisher's exact test when appropriate. Differences were considered significant when p was <0.05.

RESULTS

One hundred eighty-three Proteus species were isolated in this study.Of them, one hundred thirty-nine *Proteus mirabilis*, 25 *Proteus vulgalis*, and 2 *Proteus penneri* were isolated (Table 1). One hundred isolates (54.6%) were from outpatient and 83 (45.4%) were from inpatient (Figure 1).

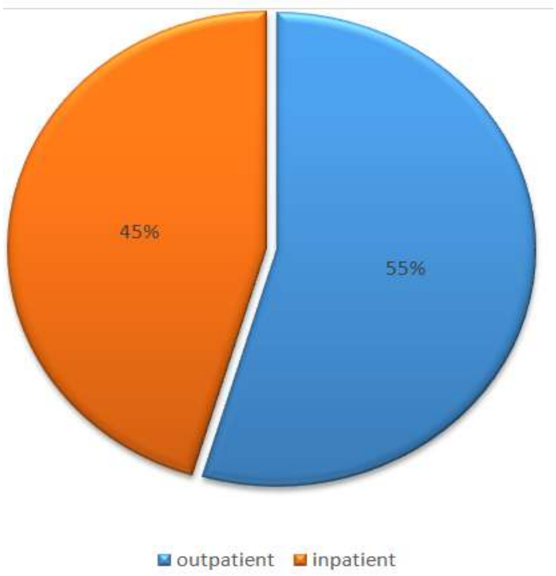

Figure 1. Demographic pattern of hospitalization of Proteus species infection

Urine 115 (62.8%), pus 19 (10.4%), sputum 10(5.5%), pharyngeal mucus 5(2.7%), and blood 5 (2.7%) were the source of Proteus isolates ($p < 0.05$) (Table 2). Most of the Proteus species isolates were from the urology (93/50.8%) followed by dermatology (20/10.9%), surgery (13/7.1%) and lowest from gastroenterology (1/0.5%), ophthalmology (1/0.5%), and pediatrics (1/0.5%) ($p< 0.05$) (Table 3).

Table 1. Species wise distribution of Proteus species infection

Species	Number	%
Proteus mirabilis	139	76.0
Proteus vulgalis	25	13.7
Proteus penneri	2	1.1
Other Proteus sp	17	9.3

Table 2. Clinical department wise distribution of Proteus species infection

Clinical department	Number	%
Urology	93	50.8
Dermatology	20	10.9
Surgery	13	7.1
General medicine	8	4.4
Intensive care unit	7	3.8
Neurosurgery	7	3.8
Neurology	6	3.3
Otolaryngology	6	3.3
Orthopedics	5	2.7
Emergency medicine	4	2.2
Respiratory medicine	3	1.6
Cardiology	2	1.1
Dental surgery	2	1.1
Nephrology	2	1.1
Obstetrics & Gynecology	2	1.1
Gastroenterology	1	0.5
Ophthalmology	1	0.5
Pediatrics	1	0.5

Table 3. Biological source wise distribution of Proteus species infection

Biological source	Number	%
Urine	115	62.8
Pus	19	10.4
Sputum	10	5.5
Pharyngeal mucus	5	2.7
Blood	5	2.7
Secretion	5	2.7
Ear discharge	4	2.2
Skin	4	2.2
Decubitus	4	2.2
Catheter	3	1.6
Punctured fluid	3	1.6
Ascites	3	1.6
Eye discharge	1	0.5
Pleural effusion	1	0.5
Digestive tract discharge	1	0.5

Table 4. Antibiotic resistant wise distribution of Proteus species

Antibiotics resistant	Number	%
MINO	139	76.0
IPM	36	19.7
CAZ or CTX	29	15.8
ST	22	12.0
CPFX	16	8.7
AZT	9	4.9
GM	7	3.8
CFPM	3	1.6
AMK	1	0.5

The results of antimicrobial susceptibility of Proteus species isolates to various antibiotics tested in this study are shown in Table 4. The best antibiotics with over 95% susceptibility rates were amikacin (99.5%), cefepime (98.4%), and gentamicin (96.2%). Significant resistant were observed in minocycline (139/76%). The numbers of ESBL isolates were 29 (15.8%). Furthermore, our study revealed that 7 Proteus species isolates had ESBL-associated multidrug resistant ability (3.8%) (Table 6). The most common patterns of MDR including ESBLwas resistant to minocycline, and ciprofloxasin (5/ 2.7%), followed by resistant to minocycline, and gentamicin (2/ 1.1%).

DISCUSSION

In this study, we described the characteristics of Proteus species isolates from 2008 to 2010 at tertiary care university hospital in the central region of Japan. With respect to hospitalized group, Proteus species were isolated more from outpatient than inpatient. Our study showed the outpatient to inpatient ratio was about 1.2 time and there was no significant differences among hospitalization. In the analysis of biological sources, we found that biological sources where most patients with Proteus species were detected were urine. Furthermore, in the analysis of clinical departments, we found that department where most patients with Proteus species were detected was urology. Proteus species infection, especially urinary tract disease was usually popular as urological diseases (Armbruster *et al.,* 2012).

The disease burden of Proteus species infections has increased due to widespread emergence of antimicrobial resistance in many countries from the late of1980s (Richard *et al.,* 2001). Antimicrobial susceptible analysis of Proteus species in our study revealed that minocycline was no longer effective against these bacteria because minocycline resistant rates of Proteus species were about 80%. Our result showed that the prevalence of imipenem non-susceptibility was not low (about 20%). Another report demonstrated that about 2 % of Proteus species had imipenem-resistance (Sohn *et al.,* 2011). The overall rates of resistance to fluoroquinolone in Proteus species remained low (8.7%) in our study. Other reports showed that about 25% of Proteus species had ciprofloxacin resistance (Saito *et al.,* 2007; Sohn *et al.,* 2011). Previous studies documented that about a half of Proteus species had beta-lactam resistance in Europe (Champs *et al*., 2000).SENTRY surveillance program in 2001, in which, overall, ESBL phenotypes among global Proteus isolates were 6.4% (Winokur *et al.,* 2001). However, ESBL Proteus species was very prevalent in Asian countries (23.7%) followed by eastern and southern Europe (21.3 % and 20.5%, respectively), and contrasting with the 3.9% and 5.9% in North America and northern Europe, respectively (Turner *et al.,* 2005). Our result is almost consistent with previous Asian result of ESBL producing Proteus species.

From our result, multi drug resistance rate of Proteus species was about 4% in Japan. Italian report showed that 36% of Proteus species had multidrug resistant activity (Tumbarello *et al.,* 2012). Previous report that the rate of ESBL with ciprofloxacin-resistant was about 15% in Asia (Sohn *et al.,* 2011; Saito *et al.,* 2007). Furthermore, the emergence of MDR Proteus species including New Delhi metallo-β-lactamase also reported in India (Bhattacharya *et al.,* 2013). Henceforth we need to focus on the antimicrobial susceptible pattern in Proteus species.

Conclusion

Incidence of Proteus species infection is increasing. The indiscriminate and inadvertent use of antibiotics has led to the emergence of multidrug resistance among commonly used antibiotics. Our investigation aims to guide clinicians on appropriate use of antibiotics. This aim is not only to reduce the morbidity and mortality in the patients but also to control the emergence and spread of resistance among Proteus species. Continuous surveillance of the use of antibiotics helps in preserving the effectiveness of antibiotics. The results from our study strongly emphasize the need for continuous epidemiological monitoring of antibiotic resistant.

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