Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(10) 1–5

DOI: 10.1177/0300060520962296
journals.sagepub.com/home/imr
SAGE

Clinical and drug resistance characteristics of *Providencia stuartii* infections in 76 patients

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Abstract

Objectives: To investigate the clinical and drug resistance characteristics of *Providencia stuartii* infections in the Huainan region of Anhui and provide a reference for the clinical selection of antimicrobial agents.

Methods: This single-center retrospective analysis included 76 patients with *P. stuartii* infection in Huainan during the period from October 2018 to March 2020. The hospital department in which the patients were treated and the drug susceptibility characteristics of the *P. stuartii* isolates were recorded.

Results: Among the 76 patients, the lung was the most common site of infection, and intensive care unit was the main hospital department. Extended spectrum beta-lactamase screening revealed expression by all 76 isolates of *P. stuartii*. Of the 76 isolates, 92.1% exhibited multiple drug resistance or extensive drug resistance. *P. stuartii* isolates were sensitive to cefepime and imipenem, but not to other beta-lactam antibiotics. Twenty isolates were resistant to all 21 types of antibiotics. Of the 20 patients infected with extensively drug-resistant isolates, nine (45%) died.

Conclusions: Drug resistance is increasing in *P. stuartii*. The antimicrobial agent imipenem may be effective for treatment of *P. stuartii* infections. Fluoroquinolones, aminoglycosides, and fourth-generation cephalosporins are suitable options for antibiotic therapy.

Keywords

Providencia stuartii, multiple drug resistance, extensive drug resistance, nosocomial outbreak, antibiotic therapy, imipenem, fluoroquinolone, cefepime, aminoglycoside, beta-lactamase

Date received: 15 July 2020; accepted: 8 September 2020

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Introduction

Providencia species are Gram-negative bacilli in the Enterobacteriaceae family. The genus *Providencia* includes five species: *Providencia stuartii*, *Providencia rettgeri*, *Providencia alcalifaciens*, *Providencia heimbachae*, and *Providencia rustigianii*.[1] Notably, *P. stuartii* is a rare opportunistic organism that causes healthcare-associated infections, such as acute enteric infection, urinary tract infection, and lung diseases.[2] The organism is typically isolated from human secretions, including urine, sputum, blood, stool, and wound cultures. The treatment of choice is based on antibiotic sensitivities, infection source, and comorbid conditions.[3]

Currently, the prevalence of *P. stuartii* infection is increasing because of antibiotic resistance secondary to the presence of extended spectrum beta-lactamase (ESBL) enzymes. The antibiotic resistance of *P. stuartii* is remarkable: 82% of isolates are resistant to amoxicillin-clavulanate, 40% are resistant to ampicillin-sulbactam, 80% are resistant to gentamicin, and 84% are resistant to ciprofloxacin.[3] *P. stuartii* is therefore difficult to treat; moreover, it is frequently involved in nosocomial outbreaks, particularly in nursing homes, burn wound units, and critical care units. *P. stuartii* infections are often difficult to control and have substantial impacts on patient morbidity, mortality, treatment, and management costs.[4,5] The present study was performed to investigate the clinical and drug resistance characteristics of *P. stuartii* infections in our hospital, with the aim of providing a reference for the clinical selection of antimicrobial agents.

Materials and methods

Ethics approval

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Anhui University of Science & Technology. Written informed consent was obtained from all participants.

Sources of isolates

This study included patients with *P. stuartii* infection in Huainan, China from October 2018 to March 2020. Successive non-duplicate *P. stuartii* isolates recovered during routine diagnostic activity were collected.

Bacterial identification and drug susceptibility assessment

All bacterial colonies were processed for identification and antibiotic susceptibility testing in accordance with the 2014 Clinical and Laboratory Standard Institute guidelines.[6] Isolates and drug susceptibility were analyzed using a MicroScan Walk Away 40SI automatic analyzer (Siemens, Munich, Germany). *Escherichia coli* ATCC25922 was used as a quality control strain. The probability of detection and identification were $\geq$99%.

Multiple drug resistance was defined as non-susceptibility to at least one agent in three or more antimicrobial categories. Extensive drug resistance was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories.[7]

Results

Clinical characteristics and specimen collection

There were 76 patients enrolled in this study (46 male patients and 30 female patients). Participant age ranged from 1 to 92 years (mean age, 62.1 years). The hospital departments to which the patients had been admitted were intensive care unit (32

patients), general surgery (10 patients), respiratory medicine (seven patients), and other clinical departments (23 patients). The levels of basic disease included severe cerebrovascular accident (12 patients), severe craniocerebral trauma (10 patients), chronic obstructive pulmonary disease (eight patients), malignant tumors (eight patients), pneumonia (eight patients), and biliary calculi (five patients). Twelve patients died after treatment, 13 patients abandoned treatment or were transferred to another hospital for management of recalcitrant disease, and 51 patients showed improvement and clinical cure. The average length of hospital stay was 41 days.

The time of specimen collection ranged from the day of admission to the 110th day after admission. Among the 76 isolates of *P. stuartii*, 26 had been obtained in 2018, 49 had been obtained in 2019 and one had been obtained in 2020. The specimens were from sputum (54 patients), wound secretion (eight patients), blood (five patients), pus (three patients), bile (three patients), throat swab (two patients), and urine (one patient).

Drug susceptibility results

All 76 isolates of *P. stuartii* had positive ESBL screening results. There were 50 (65.8%) multiple drug-resistant isolates and 20 (26.3%) extensively drug-resistant isolates. Of the 20 patients infected with extensively drug-resistant isolates, nine died (45%); this patient fatality rate was considerably greater than in patients infected with non-extensively drug-resistant isolates (5.8%).

The drug susceptibility results are shown in Table 1. *P. stuartii* was most sensitive to

Table 1. Drug susceptibility results for 76 isolates of *Providencia stuartii*.

	Sensitive		Intermediate		Resistance	
Antimicrobial agent	n	%	n	%	n	%
Ampicillin/sulbactam sodium	0	0	14	18.4	62	81.6
Ampicillin	0	0	8	10.5	68	89.5
Amoxicillin/clavulanic acid potassium	0	0	13	17.1	63	82.9
Ticarcillin/clavulanic acid potassium	0	0	42	55.3	34	44.7
Piperacillin	0	0	41	53.9	35	46.1
Piperacillin/tazobactam	0	0	50	65.8	26	34.2
Aztreonam	0	0	35	46.1	41	53.9
Cefazolin	0	0	3	3.9	73	96.1
Cefoxitin	0	0	5	6.6	71	93.7
Cefotaxime	0	0	34	44.7	42	55.3
Ceftriaxone	0	0	27	35.5	49	64.5
Ceftazidime	0	0	46	40.5	30	39.5
Cefepime	42	55.3	6	7.9	28	36.8
Imipenem	48	63.2	3	3.9	25	32.9
Gentamicin	39	51.3	3	3.9	34	44.7
Tobramycin	39	51.3	3	3.9	34	44.7
Amikacin	43	56.6	4	5.3	29	38.2
Ciprofloxacin	43	56.6	4	5.3	29	38.2
Levofloxacin	45	59.2	3	3.9	28	36.8
Gatifloxacin	47	61.8	4	5.3	25	32.9
Sulfamethoxazole/trimethoprim	15	19.7	0	0	61	80.3

imipenem, followed by gatifloxacin, levofloxacin, amikacin, ciprofloxacin, and cefepime. Although *P. stuartii* isolates were sensitive to cefepime and imipenem, they were not sensitive to other beta- lactam antibiotics. Twenty isolates were resistant to all 21 types of antibiotics.

Discussion

P. stuartii is a rare enterobacteriaceae opportunistic pathogen. *P. stuartii* was first isolated in 1904 by Rettger, and was named in 1951 by Kauffmann.[8] *P. stuartii* occurs naturally in soil, water, and sewage; it often affects humans and animals, which can lead to outbreaks of hospital infection.[9] Notably, *P. stuartii* inherently produces AmpC beta-lactamase, which causes it to be naturally resistant to penicillin and the first- and second-generation cephalosporins.[10] There has been increasing attention to *P. stuartii* in recent years, as ESBL-expressing and carbapenem-resistant isolates have become more common.[11–13]

ESBLs are Ambler class A plasmid-borne beta-lactamases. These enzymes confer bacteria with the ability to hydrolyze the most commonly used beta-lactam antibiotics, including penicillins and oxyimino-beta-lactams (e.g., cefotaxime, ceftazidime, and aztreonam).[14] In the present study, all isolates of *P. stuartii* expressed ESBLs; 92.1% of the isolates were multiple drug-resistant or extensively drug-resistant. Drug sensitivity tests showed that the 76 isolates of *P. stuartii* were sensitive to cefepime and imipenem, but not to other beta-lactam antibiotics. Twenty isolates were resistant to all 21 types of antibiotics tested.

Extensively drug-resistant *P. stuartii* has become a particularly important problem in North Africa and the southern Mediterranean.[13] In the present study, of the 20 patients with extensively drug-resistant *P. stuartii* infections, 18 were treated in intensive care unit and two were treated in respiratory medicine; nine of the 20 subsequently died. In four patients, extensively drug-resistant *P. stuartii* was isolated from sputum specimens on the day of admission. Because extensively drug-resistant *P. stuartii* infections rarely occur outside hospital settings, these bacteria are presumed to cause rapid nosocomial respiratory tract infection.[9]

In recent years, *P. stuartii* has been shown to exhibit intrinsic resistance to antibiotics that are considered last-resort treatments, such as colistin and tigecycline. Moreover, carbapenemase-expressing isolates have been described, which could become an important clinical concern.[11–13] The present study revealed that imipenem was the most effective antimicrobial for treatment of *P. stuartii* infections. Fluoroquinolones, aminoglycosides, and fourth-generation cephalosporins were also effective treatment options. Penicillins; first-, second-, and third-generation cephalosporins; and compound preparations of beta-lactamase inhibitors should be avoided.

Because of the limited scope of the study, we did not investigate the mechanisms of drug resistance in *P. stuartii*. However, the production of ESBL enzymes by *P. stuartii* is presumably the main mechanism underlying resistance.[15] *P. stuartii* may also develop outer membrane pump gene mutations, which alter outer membrane permeability.

In conclusion, drug resistance is increasing in *P. stuartii*. *P. stuartii* appears to be sensitive to the antimicrobial agent imipenem. Fluoroquinolones, aminoglycosides, and fourth-generation cephalosporins are also likely to provide useful options for antibiotic therapy. Future studies should include larger numbers of patients to investigate the mechanism of resistance antibiotic resistance in *P. stuartii* by means of genetic and molecular biology assays.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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