

Epidemiology of Multidrug-resistant Bacteria Isolated from Hospitalized Patients in a Regional Central Hospital in China

Jixun Zhang

The Second Hospital, Cheeloo College of Medicine, Shandong University

Rui Li

The Second Hospital, Cheeloo college of Medicine, Shandong University

Zhenzhong Liu

The Second Hospital, Cheeloo College of Medicine, Shandong University

Chao Wang (✉ doctorwang@sdu.edu.cn)

The Second Hospital, Cheeloo College of Medicine, Shandong University <https://orcid.org/0000-0002-9908-1124>

Research

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Abstract

Objectives: Considering the dynamic changes of MDR, we did an up-to-date study and analyzed the impact of MDR on the outcome of patients.

Design: Collected MDR isolated from hospitalized patients between June 2018 and May 2020 and performed retrospective analysis.

Setting: This study was conducted in a public regional central hospital in China.

Patients: 1156 patients with MDR infections.

Results: Total 1291 MDRS were isolated, intensive care unit (ICU) accounted for 32.3% as the most. The main samples were sputum (75.1%) and 89.6% MDR were Gram-negative. The most common MDR were *Acinetobacter baumannii*, carbapenemase-producing *K. pneumoniae*, *Pseudomonas aeruginosa*, ESBL-producing *E. coli*. Methicillin-resistant *Staphylococcus aureus* (MRSA) and ESBL-producing *K. pneumoniae*. 35.6% were nosocomial infections and 64.4% were community-acquired infections. There was a statistically significant difference in mortality between patients infected with MDR and those with non-MDR (7.4% [32/432] vs 2.6% [17/655]; $P = 0.001$). The *Acinetobacter baumannii* and *Klebsiella pneumoniae* were mainly sensitive to tigecycline. The *Pseudomonas aeruginosa* was mainly sensitive to amikacin and levofloxacin. More than 80% of the *Escherichia coli* were sensitive to tigecycline and carbapenems. More than 90% of MRSA were sensitive to vancomycin, linezolid, and quinoprtin / daptotin.

Conclusions: The MDRS are mainly gram-negative bacteria. ICU contributes most MDR and pulmonary infection is the main origin of MDR. MDR infection is an independent risk factor for death. ESBL-producing Enterobacteriaceae, especially carbapenemase producing Enterobacteriaceae, should be paid more attention. This study is helpful to understand the distribution of MDR in hospital and the extent of antibiotic resistance.

Introduction

Since the application of antibiotics in humans, drug-resistant bacteria have emerged. With the wide application and upgrading of antibiotics, drug-resistant bacteria also continue to evolve and the scope of drug resistance is becoming more extensive. Multidrug-resistant bacteria (MDR) are defined as being resistant to three or more categories of antibiotics at the same time [1]. The prevalence of MDR increases mortality, length of hospitalization, and cost, which is a great global threat [2, 3]. The abuse or improper use of antibiotics accelerates the selective evolution of bacteria and is the main reason for the emergence of MDR or “super bacteria” [4]. The development of new antibiotics is far behind the mutation of MDR. In clinical practice, infections without sensitive antibiotics available frequently emerge. In particular, multidrug-resistant gram-negative bacilli such as Extended-spectrum beta-lactamase (ESBL) producing Enterobacteriaceae and carbapenemase producing Enterobacteriaceae have an increasing proportion and

often lack effective antibiotics [5, 6]. Device-associated infections should not be ignored, especially in developing countries [7]. The widespread and rapid movement of the global population can cause the transfer of MDR between different regions or countries [8]. Imported cold chain meat can also transmit multidrug-resistant bacteria [9], which is similar to the recent transmission of COVID-19 in China [10]. Horizontal gene transfer across genera among MDR can spread drug resistance [11]. Considering the dynamic changes of the types and drug resistance spectrum of MDR, we did an up-to-date study and analyzed the impact of MDR on the outcome of patients.

Materials And Methods

This study was approved by the hospital ethics committee and informed consent of all patients. We collected the data of MDR isolated from hospitalized patients with infection between June 2018 and May 2020 and performed a retrospective analysis. The main variables we collected included patient demographics, distribution of MDR, type, extent of antibiotic resistance, outcome during hospitalization, and so on. The data of patients infected with common bacteria in hospital during the same period were collected also, mainly the outcome of hospitalization. The infection caused by MDR was carefully identified as nosocomial infection or community infection. The same bacterial strain isolated from the same patient several times was regarded as only one strain, but when the resistant extent to antibiotics changes, it was a different bacterial strain. It should be noted that two or more MDR can be isolated from the same sample.

The collected data was analyzed using SPSS version 19. The $P < 0.05$ was considered statistically significant.

Results

A total of 1291 MDRS were isolated from 1156 patients during the two years. Some patients were infected with two kinds of MDR at the same time, or the same genus with different drug resistance at different times. Among these patients, 671 (58.0%) were male and 485 (42.0%) were female, with an average age of 61.3 years (from 1 day to 93 years). The multidrug resistant strains isolated from the intensive care unit (ICU) were 417 (32.3%), followed by 268 (20.8%) in the geriatric department, 112 (8.7%) in the respiratory department, 88 (6.8%) in cardiology and macrovascular surgery, and 47 (3.6%) in neurology (Table 1). Considering the different number of beds in different departments, we adjusted the number of MDR in each department by using the number of beds, showing a large difference in the proportion of distribution (Table 2). The distribution of samples was as follows: 969 (75.1%) cases were sputum, 135 (10.5%) were urine, 70 (5.4%) were secretions, 35 (2.7%) were drainage fluid, 29 (2.7%) were puncture fluid, 26 (2.0%) were blood, 13 (1.0%) were alveolar lavage fluid (Table 3).

Table 1

The top ten departments with the number of MDR isolated.

| Department | Percentage (%) |
|--|----------------|
| ICU | 417 (32.3) |
| Geriatrics | 268 (20.8) |
| Respiratory department | 112 (8.7) |
| Cardiology and Macrovascular surgery | 88 (6.8) |
| Neurology | 47 (3.6) |
| Rehabilitation department | 45 (3.5) |
| Pediatrics | 34 (2.6) |
| Neurosurgery | 32 (2.5) |
| Urology Surgery | 25 (1.9) |
| General surgery | 25 (1.9) |
| MDR = multidrug-resistant bacteria, ICU = intensive care unit. | |

Table 2

The top ten departments after adjusting with the number of beds.

| Department | Percentage (%) |
|--------------------------------------|----------------|
| ICU | 27.5 |
| Geriatrics | 16.7 |
| Cardiology and macrovascular surgery | 7.5 |
| Respiratory department | 6.5 |
| Rehabilitation department | 5.2 |
| Dermatology | 3.5 |
| Emergency department | 3.1 |
| Pediatric surgery | 2.9 |
| Neurosurgery | 2.7 |
| Burns department | 2.4 |
| ICU = intensive care unit. | |

Table 3
The specimen sources for the isolation
of MDR.

| Specimen | Number (%) |
|-------------------------------------|------------|
| Sputum | 969 (75.1) |
| Urine | 135 (10.5) |
| Secretions | 70 (5.4) |
| Drainage fluid | 35 (2.7) |
| Puncture fluid | 29 (2.2) |
| Blood | 26 (2.0) |
| Alveolar lavage fluid | 13 (1.0) |
| Bile | 6 (0.5) |
| Endotracheal tube | 5 (0.4) |
| Catheter tip | 3 (0.2) |
| MDR = multidrug-resistant bacteria. | |

Of the 1291 MDR strains, 1157 (89.6%) were Gram-negative and 134 (10.4%) were Gram-positive. The detailed distribution of MDR was as follows: *Acinetobacter baumannii* 546 (42.3%), carbapenemase-producing *K. pneumoniae* 191 (14.8%), *Pseudomonas aeruginosa* 163 (12.6%), ESBL-producing *E. coli* 130 (10.1%), Methicillin-resistant *Staphylococcus aureus* (MRSA) 127 (9.8%) and ESBL-producing *K. pneumoniae* 52 (4%) (Table 4). According to the location of infection, 460 (35.6%) strains isolated from 432 patients were hospital-acquired infections, of which 32 patients died during hospitalization, and 831 (64.4%) strains from 724 patients were community-acquired infections. During the same period, there were 663 nosocomial infections (655 patients) caused by non-multidrug-resistant bacteria (non-MDR), and 17 patients died during hospitalization. There was a statistically significant difference in mortality between patients infected with MDR and those with non-MDR (7.4% [32/432] vs 2.6% [17/655]; $P=0.001$) (Table 5). The sensitivity test results of the five most common MDR (*Baumannii*, *K. pneumoniae*, *P. aeruginosa*, *E. coli*, and MRSA) to commonly used antibiotics were counted (Table 6). The sensitivity rates of *Acinetobacter baumannii* to tigecycline, cefoperazone sulbactam were 90.7%, 13.0%, respectively, and below 10% to others. 90.1% of *Klebsiella pneumoniae* were sensitive to tigecycline, 39.1% sensitive to amikacin, 29.6% sensitive to imipenem, and 25.5% sensitive to ceftazidime. The top five antibiotics that *Pseudomonas aeruginosa* was sensitive to were amikacin (76.1%), levofloxacin (44.8%), ciprofloxacin (39.3%), piperacillin tazobactam (36.8%), meropenem (35.6%). Of the *Escherichia coli* isolates, 94.2% were sensitive to tigecycline, 92.8% sensitive to amikacin, 91.4% sensitive to ertapenem, 88.5% sensitive to meropenem, 88.5% sensitive to imipenem, 73.4% sensitive to piperacillin tazobactam, and 50.3% sensitive to ceftazidime. Of the MRSA isolates, 98.4% were sensitive to vancomycin, 98.4% sensitive to

linezolid, 92.1% sensitive to quinoprtin / daptopin, 74.8% sensitive to moxifloxacin, 73.2% sensitive to levofloxacin, and 64.6% sensitive to ciprofloxacin.

Table 4
Distribution of MDR.

| MDR | Number (%) |
|---|--------------------|
| Gram negative bacteria | 1157 (89.6) |
| <i>Acinetobacter baumannii</i> | 546 (42.3) |
| carbapenemase-producing <i>K. pneumoniae</i> | 191 (14.8) |
| <i>Pseudomonas aeruginosa</i> | 163 (12.6) |
| ESBL-producing <i>E.coli</i> | 130 (10.1) |
| ESBL-producing <i>K.pneumoniae</i> | 52 (4.0) |
| Carbapenemase-producing <i>Enterobacter aerogenes</i> | 24 (1.9) |
| ESBL-producing <i>Proteus mirabilis</i> | 19 (1.5) |
| Carbapenemase-producing <i>Serratia marcescens</i> | 11 (0.9) |
| Carbapenemase-producing <i>E.coli</i> | 9 (0.7) |
| Carbapenemase-producing <i>Enterobacter cloacae</i> | 7 (0.5) |
| ESBL-producing <i>Klebsiella acidogenes</i> | 3 (0.2) |
| Carbapenemase-producing <i>Klebsiella acidogenes</i> | 1 (0.1) |
| <i>Proteus pennis</i> | 1 (0.1) |
| Gram positive bacteria | 134 (10.4) |
| MRSA | 127 (9.8) |
| Vancomycin resistant <i>Enterococcus faecium</i> | 4 (0.3) |
| Vancomycin resistant <i>Enterococcus faecalis</i> | 3 (0.2) |
| Total | 1291 |
| MDR = multidrug-resistant bacteria, ESBL = Extended-spectrum beta-lactamases, MRSA = Methicillin-resistant <i>Staphylococcus aureus</i> . | |

Table 5

Mortality comparison between nosocomial infection patients with MDR and with non- MDR during hospitalization.

| Patients | Number | Number of deaths (%) | <i>P</i>-Value |
|---|---------------|-----------------------------|-----------------------|
| Patients with MDR | 432 | 32(7.4) | 0.001 |
| Patients with non-MDR | 655 | 17(2.6) | |
| MDR = multidrug-resistant bacteria, non-MDR = non-multidrug-resistant bacteria. | | | |

Table 6
Sensitivity of main MDR to commonly used antibiotics.

| Antibiotics | Sensitive N(%) | | | | |
|-------------------------|------------------|---------------------|--------------------|---------------|------------|
| | <i>Baumannii</i> | <i>K.pneumoniae</i> | <i>Paeruginosa</i> | <i>E.coli</i> | MRSA |
| Cefazolin | 0 | 0 | * | 4 (2.9) | 0 |
| Cefuroxime | 0 | 0 | * | 0 | 0 |
| Ceftriaxone | 12 (2.2) | 0 | * | 0 | 0 |
| Cefotaxime | 4 (0.7) | 0 | * | 0 | 0 |
| Ceftazidime | 16 (2.9) | 0 | 43 (26.4) | 8 (5.7) | 0 |
| Cefepime | 8 (1.5) | 0 | 26 (16.0) | 6 (4.3) | 0 |
| Cefoxitin | 19 (3.5) | 62 (25.5) | * | 70 (50.3) | 0 |
| Piperacillin-tazobactam | 16 (2.9) | 48 (19.8) | 60 (36.8) | 102 (73.4) | 0 |
| Cefoperazone sulbactam | 71 (13.0) | 10 (4.1) | * | 37 (26.6) | 0 |
| Levofloxacin | 8 (1.5) | 28 (11.5) | 73 (44.8) | 39 (28.1) | 93 (73.2) |
| Ciprofloxacin | 0 | 24 (9.9) | 64 (39.3) | 33 (23.7) | 82 (64.6) |
| Moxifloxacin | 0 | 25 (10.3) | 66 (40.5) | 35 (25.2) | 95 (74.8) |
| Amikacin | 44 (8.1) | 95 (39.1) | 124 (76.1) | 129 (92.8) | * |
| Meropenem | 4 (0.7) | 52 (21.4) | 58 (35.6) | 123 (88.5) | * |
| Imipenem | * | 72 (29.6) | 26 (16.0) | 123 (88.5) | * |
| Ertapenem | * | 52 (21.4) | 5 (3.1) | 127 (91.4) | * |
| Tigecycline | 495 (90.7) | 219 (90.1) | * | 128 (94.2) | * |
| Linezolid | * | * | * | * | 125 (98.4) |
| Vancomycin | * | * | * | * | 125 (98.4) |
| Quinoprptin / daptoptin | * | * | * | * | 117 (92.1) |
| Total | 546 | 243 | 163 | 139 | 127 |

MDR = multidrug-resistant bacteria, MRSA = Methicillin-resistant *Staphylococcus aureus*. "*" represents that this antibiotic is not included in the antibiotic susceptibility kit.

Discussion

MDR infection as a global public health event brings great challenges to clinicians, and they often face the situation that no sensitive antibiotics are available. The colonization of MDR is the basis for infection,

which is widespread. Infection occurs when the body's resistance and immunity decline, so MDR infections are more common in elderly patients and pediatric patients. As we have shown, patients with MDR infection were mostly distributed in departments dominated by elderly patients and pediatrics, with an average age of 61.3 years. ICU contributed the most to MDR, which is consistent with the previous report [12]. Compared with general patients, patients in ICU have more chronic coexisting diseases and more severe acute physiological disorders, so they are in a state of relative immunosuppression [13]; the frequency of indwelling catheter is very high in ICU patients, which provides a path for microorganisms to invade; patients in ICU are faced with higher pressure of bacterial selection and colonization; these are the main reasons. Geriatrics, respiratory department, and rehabilitation department are mainly based on elderly patients who have been hospitalized for a long time, often accompanied by lung infections, so MDR frequently appears in these departments. The high incidence of MDR in cardiac and macrovascular surgery is unexpected, which may be related to the large surgical trauma, long operation time, and high proportion of patients admitted to ICU for a brief transition after operation. Many patients in the dermatology and burns department are chronic wounds of skin and soft tissues, contributing most of the multidrug-resistant MRSA [14]. MDR derived from sputum specimens accounted for three quarters, which was the main source of *Acinetobacter baumannii* and *Klebsiella pneumoniae*. Therefore, the lung is the most vulnerable organ to MDR, and long-term bed rest and ventilator application are the susceptible factors [15]. Urinary tract infection account for a large part of all nosocomial infections [16], urine becomes the second largest source of MDR, which mainly is *Escherichia coli*. As a regional central hospital, patients with various acute and chronic wounds are often treated, which has become a wide source of secretions isolated for MDR [14]. In addition, MDR can originate from almost all systems, such as blood, chest, abdomen, and biliary tract.

The MDR acquired from the community was significantly higher than that in hospital, indicating that the prevalence of MDR in the community should also be paid attention to [17]. Nonstandard use of antibiotics in community or primary medical institutions is an important reason for the prevalence of MDR [18]. Comparing the mortality of patients infected with MDR in hospital and patients infected with common bacteria in hospital, the mortality of the former was significantly higher than that of the latter, which further confirmed that the infection of MDR is an independent risk factor for death [19], so reducing the infection of MDR is to reduce the mortality.

Gram-negative bacilli accounted for nearly 90% of all MDR, of which the main bacterial species were *Acinetobacter baumannii*, *Klebsiella*, *Pseudomonas aeruginosa*, and *Escherichia coli*. In recent years, the prevalence of ESBL producing organisms and carbapenemase producing organisms are increasing rapidly [20, 21]. ESBL is a class of enzymes that make bacteria resistant to most of the β -lactam antibiotics. Carbapenems are the most effective against infections caused by ESBL producing organisms [22]. Therefore, carbapenems play an important role in the field of anti-infectives. However, β -lactamases that can hydrolyze carbapenems have emerged, which seriously threatens the clinical utility of these antibiotics and "Extreme drug resistance" in Gram-negative bacilli leaves us helpless [23]. In this research, *Acinetobacter baumannii* were resistant to almost all carbapenems, and only had a high sensitivity to tigecycline, but 10% were resistant to all kinds of antibiotics. It is reported that this part of the bacteria is

still sensitive to polymyxin [24], but not available in mainland China. ESBL-producing *E. coli* and ESBL-producing *K.pneumoniae* were highly sensitive to carboxycycline, penicillin, ceftazidime and piperacillin tazobactam, but carbapenemase producing enterobacteriaceae were only sensitive to tigecycline. *Pseudomonas aeruginosa* were highly sensitive to amikacin, and the sensitivity rate to other antibiotics was not more than 50%. Therefore, besides amikacin, quinolones, piperacillin, ceftazidime, and meropenem can still be selected to anti-*Pseudomonas aeruginosa* based on antibiotic sensitivity tests. In general, multidrug-resistant Gram-negative bacilli infections often leave us rare antibiotics to choose. MRSA as the most common multidrug-resistant Gram-positive bacteria were highly sensitive to vancomycin, linezolid, and quinoprtin / daptoptin, 70% of MRSA were sensitive to quinolones and were resistant to all other antibiotics. The emergence of MRSA resistant to vancomycin and linezolid needs to be vigilant, which makes clinicians helpless.

Prevention of the emergence and spread of MDR is an urgent international task. Measures are mainly divided into two types of strategies, one is to control the use of antibiotics, the other is to take a variety of infection control measures [25]. In China, the standardized use of antibiotics has only been emphasized in recent years, but the situation in primary and community hospitals is still worrying. Strictly maintaining good hand hygiene is the simplest and effective infection control measure. At the same time, strengthening the active monitoring of MDR and decolonizing when necessary are also effective measures.

In conclusion, MDR are mainly Gram-negative bacteria, which are distributed in almost all departments of the hospital. ICU contributes most of MDR and other departments dominated by elderly patients also have a large number of MDR. Pulmonary infection is the main origin of MDR. The five most common MDRS are *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli* and MRSA. MDR infection is an independent risk factor for death. Carbapenems are the most effective antibiotics for ESBL-producing Enterobacteriaceae, but tigecycline is the only effective one for carbapenemase producing Enterobacteriaceae. Vancomycin, linezolid, and quinoprtin / daptoptin are very effective against MRSA, but we need to be alert to the emergence of vancomycin-resistant MRSA. This study is helpful to understand the distribution of MDR in hospital and the extent of antibiotic resistance. The lack of susceptibility factors, underlying diseases, antibiotic application, and follow-up after discharge are the limitations of this article and need to be further studied.

Declarations

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