The dynamics of *Klebsiella pneumoniae* drug-resistant profile in a regional burn center: a retrospective study between 2009 and 2018

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Abstract

BACKGROUND: The aim is to observe drug-resistant trends of *Klebsiella pneumoniae* (*K.pneumoniae*) isolated from Jiangxi burn center in recent 10 years, and to analyze its causes and provide general information on preventive measures.

METHODS: All data were collected by Hospital Laboratory Information System (LIS) and electronic cases. SPSS23.0 software was used to analyze bacterial isolation rate and drug-resistant trend. A chi-square test had been adopted to observe drug-resistant difference of *K.pneumoniae* in ICU ward and non-ICU ward.

RESULTS: During 10 years, 593 *K.pneumoniae* isolates were acquired from the burn center, which mainly from wound secretion, bloodstream, sputum. The resistance rate of *K.pneumoniae* to many drugs, including 3 or 4 generation cephalosporins, carbapenems, fluoroquinolones, aminoglycosides, and even tegacycline showed an obvious upward trend ($P < 0.05$) in this period. The isolated *K.pneumoniae* was mainly concentrated in 1-3 weeks and carbapenem-resistant *K.pneumoniae* was mostly acquired in later stage after their hospitalization.

CONCLUSION: We should pay attention to the increasing trend of *K.pneumoniae* in the burn center. Some measures should be taken to reduce isolated rate and drug-resistant rate in the future.

Background

Infections are a serious medical problem in burn patients, leading more than 70% death [1,2]. The destruction of protective skin barrier is benefit for displacement of skin microorganism located in peripheral tissue of burn area [3,4]. In addition, gastrointestinal bacteria usually transfer into bloodstream, respiratory tract and burn wound, etc., because of stress injury originating in humoral and cellular immunity, which also contributes to a higher rate of infection in burn patients [5,6]. Compared with common hospitalized patients, burn patients are more prone to nosocomial infection because of skin damage, longer hospitalization period and multiple interventional therapeutic procedures [2,6]. It is very necessary to know distribution of pathogen and drug-resistant status in order to available usage of antibiotics timely [7,8].

In our burn center, *Kneumoniae pneumoniae* (*K.pneumoniae*) still is one of the most common infectious pathogen in recent years, isolated rate just behind *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, similar to other literature reports [9,10]. However, *K.pneumoniae* infection has suddenly risen and carbapenem-resistant *K.pneumoniae* (CRKP) was a major clone, which should be paid sufficient attention to. Because treatment caused by CRKP infection had a long cycle, increasing morbidity and mortality, therefore, some measures must be taken to prevent the spread of CRKP infection [11]. Because CRKP is usually developed from non-CRKP, it is necessary to control the epidemics of *K.pneumoniae* in order to effectively inhibit the epidemic of CRKP. In addition to standard usage of antibiotics and normative prevention of nosocomial infection, it is also important to understand the

dynamic changes of drug resistance of *K.pneumoniae* in burn center for better differentiated management [12].

In this study, we have statistically explored *K.pneumoniae* by retrospectively collecting data over the past 10 years (2009–2018). The aim is to understand the reasons for the rapid increase of isolation rate and drug resistance rate of *K.pneumoniae*.

Methods

Setting and study design

Jiangxi Burn Center was located in the First Affiliated Hospital of Nanchang university, which was approved by Jiangxi Health Department in 1990. The burn center was a 6-story building with 70 hospital beds, including ordinary burn ward, burn intensive care unit (ICU) and burn laboratory. This center received more than 20,000 outpatients and 1,400 inpatients from all over the province every year. Because of the particularity of burns, patients' hospitalization time was approximately 20 days. There were including more than 2,400 burn surgeries per year, nearly each patient underwent two operations on average during their hospital time.

Microbiology data

According to the Rules for the Use of Antibiotics issued by Ministry of Health, PRC (the People's Republic of China). The burn center routinely transmitted blood, burn wound, sputum and urinary tract samples, etc., to the clinical laboratory for microbial culture, identification and antimicrobial susceptibility test after patients were hospitalized. Compact-2-VITEK automatic system (BioMerieux, France) was applied for bacterial identification and drug sensitivity test. The drug-susceptible results were compared with the latest standards issued by the Clinical and Laboratory Standards Institute (CLSI). The following drugs would be used for susceptibility testing in *Enterobacteriaceae*, included meropenem (MEM), imipenem (IMP), ertapenem (ETP), cefepime (FEP), ceftazidime (CAZ), ceftriaxone (CRO), cefazolin (KZ), piperacillin/tazobactam (TZP), ampicillin/sulbactam (SAM), ampicillin (AMP), aztreonam (AZT), gentamicin (CN), amikacin (AK), tobramycin (TOB), ciprofloxacin (CIP), levofloxacin (LEV), cotrimoxazole (SXT), nitrofurantoin (F). Cefoperazone/sulbactam (SCF) was also adopted to detect drug-sensitivity by Kirby-Bauer (K-B) method, the diameter of inhibition zone being less than 18mm for considering antimicrobial resistance as well as the diameter more than 18mm for judging sensitivity. *Escherichia coli* ATCC 25922 was used as a reference strain. In addition, drug susceptibility testing to tigecycline (TGC) was evaluated by E-test (Oxoid, England) when it was resistant to carbapenems since January 1, 2014. The interpretation of results was referred to the latest CLSI criteria.

Statistical analysis

All data were retrospectively collected from the Hospital Laboratory Information System (LIS) and electronic cases. Information on patients of positive culture for *K.pneumoniae* had been included in the statistics in burn wards in recent years. In addition, the initiative bacterial isolated time, infecting sites, and drug-resistance was also collected depending on the hospital information section. All statistical analyses were done with WPS (Word Processing System) (Jinshan Co., Ltd, China) and SPSS 23.0 (IBM, USA) software. The linear regression model was utilized to analyze the trend of drug-resistant rate in different years. A chi-square test was adopted to know different drug-resistant levels between ICU and non-ICU wards. $P < 0.05$ was considered statistically significant.

Results

General information

Over the decade period, 14,346 inpatients were admitted, which included 8874 (61.86%) males and 5472 (38.14%) females, with a male-to-female ratio of 1.62:1. Scald was the most common mechanism of burn (86.02%), followed by flame (9.28%), electrical injury (2.07%) and other burns (2.63%). The proportions of mild, moderate, severe, and critical burn injuries categorized on the basis of the Excess Mortality Ratio-Adjusted Injury Severity Score (EMR-ISS) [13] were 5.12%, 73.09%, 11.02%, and 10.68%, respectively. During the hospitalization period, surgery was performed in 9054 (63.11%) patients and conservative treatment was done in 5292 (36.89) patients. The isolation rates of *K.pneumoniae* in 2009–2018 were 0.89% (11/1235), 1.69% (21/1243), 2.03% (25/1230), 2.72% (35/1289), and 3.98% (54/1355), 4.69% (69/1472), 3.82% (55/1441), 5.09% (83/1630), 4.56% (74/1624), 9.09% (166/1827), respectively.

Drug-resistant trends of *K.pneumoniae* during 2009 to 2018

A total of 593 *K.pneumoniae* were collected during the study period. As shown in Table 1, the resistance rate of ampicillin was the highest each year, similar to cefazolin. The resistance rate of tigecycline was very low, but it had still been on the rise since 2014 (0% in 2014 to 16.15% in 2018). Regression analysis model showed that ampicillin and cefazolin were long-term high level drug resistance, and the resistance rates of most other antibiotics were increased significantly ($P < 0.05$), among which, the fastest and highest growth rate was carbapenems (including meropenem, imipenem, ertapenem), followed by cephalosporins and tigecycline. The growth rate of quinolones, amikacin, tobramycin and nitrofurantoin was relatively slower compared with carbapenems, cephalosporins and tigecycline. However, by 2018, the resistance rate of nitrofurantoin was approximately 80%, even reached up to 95%.

Comparison drug resistance of *K.pneumoniae* in ICU and non-ICU ward

The results were shown in Table 2. The resistance rate of *K.pneumoniae* isolated from ICU was significantly higher than that of non-ICU ward. Except for ampicillin/sulbactam, ampicillin, tigecycline and

nitrofurantoin in the two wards, there were marked by differences in other antibiotics ($P < 0.05$).

Analysis of *K.pneumoniae* drug resistance isolated from different specimens

In this decade study, 224 strains from wound secretions, 216 from bloodstream, 79 from sputum, 50 from urine and 22 from catheter, two from pleural fluid and drainage fluid, respectively (Figure 1). When *K.pneumoniae* was isolated at multiple time points, the original isolated strain would be included in the statistical analysis. In order to know the different drug resistance among strains from different sources, we analyze these groups. The results showed that *K.pneumoniae* isolated from bloodstream showed the highest resistance to β -lactam drugs, and relatively low-level drug-resistant strains originated from wound secretions, catheters, etc. The resistance levels of different origin's strains to quinolones (CIP and LEV) and aminoglycosides (CN, AK and TOB) were similar. The exact results were shown in Table 3.

Distribution of *K.pneumoniae* in different isolated time

As shown in Figure 2, the highest isolated time was 8–21 days (31.03%, 184/593), of which CRKP was mainly been isolated in 15–21 days (38.26%, 158/413), while non-CRKP separation was mainly concentrated in 4–14 days (62.78%, 113/180). With the extension of hospitalization period, the isolated rate of CRKP showed an upward trend. The results were consistent with that of CRKP isolated 22 days later.

Discussion

K.pneumoniae is one of important pathogens in burn wards. In recent years, the infectious rate has shown an increasing trend, and its drug resistance has grown up to be an important issue, which has attracted great attention of clinical and microbiologists [14,15]. The main reason is that *K.pneumoniae* can cause respiratory tract, urinary tract, and even sepsis, etc [16], moreover, *K.pneumoniae* are widely distributed in hospital environment and can survive for a long time, which is a great threat to critically ill patients [17,18]. Due to the large number of CRKP, especially hypervirulent strains with high mucinous phenotype, they can avoid host immunity and antagonizing immune killing function, resulting in severe invasive infections and high lethal rate [19,20].

From 2009 to 2018, 593 strains of non-repetitive *K.pneumoniae* were isolated from burn center in the first affiliated hospital of Nanchang university. The proportion of isolates to the total number of strains showed an increasing trend, accounting for 0.89% (11/1235), 1.69% (21/1243), 2.03% (25/1230), 2.72% (35/1289), and 3.98% (54/1355), 4.69% (69/1472), 3.82% (55/1441), 5.09% (83/1630), 4.56% (74/1624), 9.09% (166/1827), respectively. Burn patients have skin barrier damage, long hospitalization period, ventilator and other interventional operations, which can easily lead to burn wound, bloodstream, respiratory tract and urinary tract infection [2,3,6,7,21,22]. From the sites of infection, *K.pneumoniae*

mainly were isolated from wound secretion, bloodstream and sputum during the past 10 years, and the proportion of isolation almost being no change. This may be related to the fact that *K.pneumoniae* was a common nosocomial bacterium, which could easily lead to opportunistic infection. At the same time, doctors of burn department regularly timely applied antibiotics according to clinical practice and laboratory epidemiological data. During this 10-year period, the resistance rate of common antibiotics in burn center had shown an increasing trend. For example, the resistance rate of the third generation cephalosporins was 50–60% in 2009, and it increased to 80–90% in 2018. That was also higher than the average level of resistance from other departments in our hospital, and also higher than the average level in China [23]. Except for the first generation of cephalosporins and aminopenicillin, other β -lactam antibiotics had shown an obvious upward trend, and resistance to aminoglycosides and fluoroquinolones have also increased significantly ($P < 0.05$) (Table 1). In order to observe whether the increase of antibiotic resistance was related to the usage of antibiotics, we had statistics in drug resistance from ICU to non-ICU. The results showed that drug-resistant rate of strains in ICU was significantly higher than that in non-ICU isolates (Table 2) [24]. Because ICU patients had serious and deeper tissue damage, and interventional procedures and the exposure of antibiotics was significantly higher than that in non-ICU patients, this was related to the increase of antibiotic usage leading to increased drug resistance [25,26]. Previous data of drug-resistance in *Staphylococcus aureus* also confirmed this opinion [27].

To further understand whether *K.pneumoniae* infection was related to the length of hospitalization, we investigated the original data and found that the isolated rate increased following with the length of hospitalization, even reached a peak in 1–3 weeks (Figure 2). This was related to the early infection of burn patients with Gram-positive bacteria, Gram-negative bacteria in the middle and late stages [3]. Because CRKP had the characteristics of low cure rate and high mortality rate, we wanted to know whether infectious site was different between CRKP and non-CRKP patients [28]. We found that CRKP infection in ICU was obviously higher than that in non-ICU, and there was also a significant difference in drug resistance. According to the time point of isolation, we found that there was no significant difference in the proportion of CRKP in the early stage of admission, while CRKP were the main isolates in the middle and late stage. Tigacycline was a drug usually adopted in the treatment of severe burn patients in recent years [29]. Since 2014, we had included it in drug sensitivity monitoring. The results showed that CRKP strains didn't show any drug resistance in that year. However, the drug-resistant rate showed an obvious upward trend in the following years ($P = 0.02$) (Table 1). Because we justly detected these carbapenem-resistant strains, the overall drug resistance rate may be below that level, however, the future development of drug resistance is not optimistic accordance with current trends. Furthermore, there was no difference in drug resistance among ICU and non-ICU isolates. The possible reason was that doctors apply tigacycline to treat patients much specifically in our hospital.

In summary, the isolated and drug-resistant rate of *K.pneumoniae* in our burn center showed an increasing trend during 2009 to 2018, and the infecting sites mainly focused on burn wound and bloodstream. How to reduce the incidence and drug resistance of *K.pneumoniae* is of great significance to reduce the morbidity and mortality. Therefore, hospital infection control department should continue to strengthen drug resistance surveillance, grasping its epidemic and drug resistance changes in burn

department, conducting an epidemiological investigation, understanding its transmission rule as well as emphasizing rational usage of antibiotics. The aim is to avoid further increase and spread of drug-resistant bacterium.

This study has several limitations. At first, this study was conducted in a single burn center, as a result, these findings may not completely comply with other burn wards, however, it was certain that there were obviously increasing antimicrobial resistance trends in the burn center. Secondly, we conducted a statistical analysis for all isolated *K.pneumoniae*, without distinguishing infection from colonial status, which might increase the number of infectious bacteria and even drug resistance. Finally, our study was a retrospective consequence, and collected data was no clear causal relationship, even no uniform tests and evaluation standard in this period, and it was possible that there were some deviations in our results. However, our findings provided valuable information on the dynamics of *K.pneumoniae* infection and drug resistance. In particular, it was clear that high antibiotic exposure increased bacterial resistance.

Declarations

Abbreviations

CLSI: Clinical and Laboratory Standards Institute; ICU: Intensive care unit; Non-ICU, ordinary burn ward; OR, odds ratio; χ^2 , chi-square; CRKP: carbapenem-resistant *K.pneumoniae*; PRC: the People's Republic of China; MEM: meropenem; IMP: imipenem; ETP: ertapenem; FEP: cefepime; CAZ: ceftazidime; CRO: ceftriaxone; KZ: cefazolin; TZP: piperacillin/tazobactam; SAM: ampicillin/sulbactam; AMP: ampicillin; AZT: aztreonam; CN: gentamicin; AK: amikacin; TOB: tobramycin; CIP: ciprofloxacin; LEV: levofloxacin; SXT: cotrimoxazole; F: nitrofurantoin; SCF: Cefoperazone/sulbactam; TGC: tigecycline; LIS: Hospital Laboratory Information System; EMR-ISS: Excess Mortality Ratio-Adjusted Injury Severity Score.

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Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KS Chen conceived and designed the experiments. Wei Wang, Lijin Zou performed the experiments: Lijin Zou provides a part of information from burn department; Wei Wang analysed the data and wrote the paper. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

All participants were informed about the study's purposes. Prior to sample collection, written informed consent was obtained from the study participants. The study was performed at the First Affiliated Hospital of Nanchang University and was approved by the ethics committee of the First Affiliated Hospital of Nanchang University (Approval number: 2015018). All study information was kept confidential.

Disclosure statement

No competing financial interest exist.

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Tables

Due to technical limitations, Tables 1 - 3 are only available for download from the Supplementary Files section.

Figures

Figure 1 *K.pneumoniae* isolated from different sources

Figure 1

K.pneumoniae isolated from different sources.

Figure 2 Distribution of *K.pneumoniae* in different isolated times

Figure 2

Distribution of *K.pneumoniae* in different isolated times.

Supplementary Files

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