Severe Community-Acquired Pneumonia in Eastern China Microbial Etiology and Multidrug-Resistance

Jun She (shejuncn@aliyun.com)
Zhongshan Hospital Fudan University https://orcid.org/0000-0001-5318-0197
Yuli Wang
Zhejiang University School of Medicine First Affiliated Hospital
Xiaoying Ni
Zhongshan Hospital Fudan University
Shenglei Huang
Zhongshan Hospital Fudan University
Ping Jia
Zhongshan Hospital Fudan University
Ping Yang
Mayo Clinic Arizona
Lei Zhu
Zhongshan Hospital Fudan University

Research article

Keywords: Severe community-acquired pneumonia, Microbial etiology, Multidrug-resistance, eastern China

Posted Date: November 14th, 2019

DOI: https://doi.org/10.21203/rs.2.16835/v1

Abstract

Background: Limited information existed about the distributions of microbial etiology and drug-resistance with severe community-acquired pneumonia (CAP) in China, partly attributing to the antibiotics abuse in rearing livestock for Chinese farmers in recent decades. Moreover, the relevant guidelines have not been updated for at least a decade.

Methods: A prospective observational study was carried out in Zhongshan Hospital (Shanghai, China). All consecutive cases of severe CAP diagnosed in Respiratory intensive care unit (ICU) and Emergency ICU were included. We assessed the microbial etiology features and multidrug-resistance (MDR) status. The risk factors were used by multivariate analyses for outcomes.

Results: One hundred and twelve adults with severe CAP in ICUs, mean age of 65.7±15.1 years were studied. Etiological diagnoses were established in 76 (67.9%) cases; Klebsiella pneumoniae was the most frequent pathogen in 27 (35.5%) cases followed by Acinetobacter baumannii (n=15, 19.7%) and Methicillin-resistant Staphylococcus aureus (MRSA) (n=9, 11.8%); While Streptococcus pneumoniae (n=3, 3.9%) was ranked the 6 th in the study. The majority of pathogens were the MDR and the 30-days mortality rate was 43.8% in severe CAP patients. Klebsiella pneumoniae (OR, 6.88; 95%CI, 1.13-41.83), Sequential organ failure assessment (SOFA)≥5(OR, 12.30; 95%CI, 1.79-84.55) was associated to death.

Conclusions: The study indicates a change in the usual pattern of microbiol etiology of severe CAP and the MDR emerged in the majority of pathogens over a decade in eastern China. Enhanced control of using antibiotics to reduce the acquired resistance is urgent.

Introduction

Community-acquired pneumonia (CAP) is one of the leading causes of death due to infection and has considerable implications for healthcare systems worldwide [1, 2]. Approximately 10% of hospitalized patient with severe CAP required admission to intensive care unit (ICU), where 23–47% of them ultimately die [3–6]. Microbiological evaluation is one of the most important clinical decisions for the selection of CAP antibiotic therapy [7]. Indeed, the pathogen responsible for CAP was difficult to identify in many cases. The rate of microbial identification, even in ICU, remained extremely low, ranging 10%–50% [8].

Streptococcus pneumonia (S. pneumonia) was reported to be the main commonly isolated bacterial pathogen [9]. In a large meta-analysis, it was found to be responsible for two thirds of bacteremia pneumonia cases and one third of patients admitted to ICU [10]. *Klebsiella pneumoniae* (*K. pneumoniae)* was reported to be associated with a high mortality [8, 11]. Therefore objective assessment of microbial etiology for patients with severe CAP is important to guide appropriate allocation of resources for management.

It showed that more than 45.3% of *Staphylococcus aureus (S. aureus)* isolated from Chinese patients in surveyed hospitals in 2009 was *Methicillin-resistant Staphylococcus aureus* (MRSA) [12]. Roughly the

highest rate of *Escherichia coli* isolates was resistant to quinolones in the world [13]. The phenomenon may relate to the heavy use of antibiotics in animal husbandry and fisheries, and the weak of the public awareness [14]. Chinese guts had the highest number of antibiotic resistant genes by sequencing gut microbes in Chinese, Danish, and Spanish people. And the genes resisted to tetracycline, which was mostly used in animal feed in China [15].

Currently, limited information existed about the distribution of microbial etiology with severe CAP in China. Moreover, the relevant guidelines, e.g., Chinese Thoracic Society have not been updated for at least a decade. The study was to assess the microbial etiology features and multidrug-resistance (MDR) status in patients admitted to ICU for severe CAP.

Materials And Methods

Study setting and design

A prospective observational study carried out in Zhongshan Hospital, Fudan University (Shanghai, China), an 2430-bed tertiary institution(15 Respiratory ICU beds and 22 Emergency ICU beds), where located at east of China covering 10 million of Shanghai's population and radiating 150 million people in the surrounding of Yangtze River Delta. The medical system and accessibility to medical care is no different to the other parts of China. All consecutive cases of severe CAP visiting the emergency department or respiratory clinic from August 2017 to December 2018 were included. The study was approved by the Institutional Review Board at Zhongshan Hospital, Fudan University Human Subjects Research Protection Program Office (B2017–061R). All patients were written the informed consents.

Study population

One thousand and three hundred seventeen patients had symptoms suggestive of lower respiratory infection were referred to the emergency department as generally accepted. 806 patients were diagnosis of pneumonia. The diagnosis for CAP was 695 patients with a new chest radiographic infiltrate on computed tomography (CT) scan [16], symptoms including cough and/or sputum productive, fever or hypothermia, and abnormal leukocytes counts [1, 6]. 127 patients were admitted to ICUs according to pulmonologist's judgement. The objective criteria of severe CAP was according to 2007 IDSA/ATS guidelines [1]. The CURB–65 criteria (confusion, uremia, respiratory rate, low blood pressure, age 65 years or greater) [17], and prognostic models, such as the Pneumonia Severity Index (PSI) [18], were also reference. The study profile was shown in Figure 1.

All patients with the exacerbation of chronic respiratory disease (CRD, included chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis and interstitial pneumonia, which have acute worsening of respiratory symptoms to additional therapy without new chest radiographic infiltrate), healthcare associated pneumonia (HCAP, pneumonia in non-ambulatory residents of nursing homes and other long-term care facilities) [1,19], hospital-acquired pneumonia (HAP, any pneumonia contracted by patients in hospital at least 48–72 hours after being admitted) [20], severe immune-compromised

(acquired immune deficiency syndrome, organ transplant, and tumor chemotherapy) [8] and age less than 18 years were excluded.

Data collection and follow up

The clinical information of all patients were carefully collection including age, sex, smoking history (smoking ≥ one cigarette per day for one year), alcohol abuse (consumption≥120 g per day), comorbidity, initial symptoms, the CURB scores and PSI severity, acute physiology and chronic health evaluation-II (APACHEII), sequential organ failure assessment (SOFA) [21], biochemistry and arterial blood gas measurements, chest radiograph features, mechanical ventilation requirement, length of hospital stay, mortality etc. Microbiological evaluation was collected emphasis on diagnostic methods, pathogens distribution, and MDR status. The follow up visit was performed in 30–90 days after discharge from ICUs.

Microbiological evaluation

At least two blood sample and sputum specimens collected within 24 hours after admission were investigated. If the patient's temperature was more than 38.5℃, blood culture was needed. The qualified sputum specimens were screened by microscopy (if < 10 epithelial cells and > 25 leukocytes per field; magnification 100) [22]. The methods of urine antigen were detected *S. pneumoniae* and *Legionella pneumophila.* Nasopharyngeal swabs for respiratory virus and serology for atypical microorganisms were also detection. Paired serology was analyzed by means of at admission and during the third week thereafter for *Mycoplasma pneumoniae, Chlamydophila pneumonia. Legionella pneumophila* and respiratory virus were diagnosed using the indirect immunofluorescence technique for antibodies detection. Pleural fluid culture was performed for patients with significant pleural effusion on chest radiograph. Bronchoalveolar lavage (BAL) and lung tissue were performed by fiberoptic bronchoscopy [8].

All samples were cultured in adequate media that allowed optimal results. The etiology of pneumonia was classified as presumptive if a valid sputum sample yielded one or more predominant bacterial strain; The etiology was considered by blood culture yielding a bacterial or fungal pathogen; High titers of immunoglobulin (Ig)M antibodies in the serum during the acute phase was accepted or four-fold increase in IgG titers for the diagnosis of atypical microorganisms [23].

Statistical analysis

Statistical analyses for clinical characteristics and outcomes were reported as means±standard deviation or as percentages. The continuous variables were statistically analyzed by a one-way analysis of variance test. The categorical variables were assessed with *chi*-square test with Fisher's exact test correction. Calculations of odds ratio (OR) and 95% CI values for severe CAP in relation to potential risk factors on mortality were performed with binary logistic regression models [24]; these covariates included age, gender, smoking history, alcohol abuse, comorbidities, APACHE II, SOFA, the most three frequent pathogens (*K. pneumoniae, Acinetobacter baumannii (A. baumannii)*and *S. aureus)* and mixed infections.

All tests were two-sided, and a *P* value of 0.05 was considered statistically significant. Statistical analyses were conducted with IBM SPSS for windows, version 24.0.

Results

Patient Characteristics

Among 127 patients, 15 were excluded the study, e.g. 4 patients had severe immune-compromised, the age of 2 patients was less than eighteen, 9 patients died within 24 hours in ICUs. A total of 112 patients (mean age 65.7±15.1 years, range 21–92) were in enrolled. There were 74 (66.1%) males and 38 (33.9%) females. 59 (52.7%) patients were aged >65 years. The main clinical characteristics of severe CAP in the study were listed in Table 1.

Smoking history was recorded 38 (33.9%) cases and alcohol abuse 17 (15.2%) cases. The common comorbidities were chronic cardiovascular disease 29.5% (n = 33), diabetes mellitus 24.1% (n = 27) and chronic respiratory disease 22.3% (n = 25). A total of 53.6% patients had a chest radiograph with multi-lobar infiltration, and 28.6% cases had pleural effusion. The mechanical ventilation was required in the half of patients, and the length of hospital stay was 18±20 days. The 30-days mortality was 43.8%, while overall (90-days) mortality was 47.3% (Table 1).

The CURB scores and PSI severity for CAP assess clinically important physiologic derangements requiring active intervention [1]. There were 53.6% and 75% patients in CURB scores ≥ 2 and PSI severity class IV-V in the study, respectively. APACHEII and SOFA were used to assess the severity of severe CAP and outcomes [21]. 42.9% patients were APACHEII≥15 and 50% patients were SOFA≥5. The laboratory findings for cell counts, biochemistry and arterial blood gases were listed in Table 2.

Microbial Etiology Distributions

All patients were required to performed microbiological investigation within 24 hours after admission. The etiological identification was obtained in 76 patients (67.9%) (Table 1). The diagnostic methods of microbial etiology were listed in Table S1 (detail in supplemental file). And the Mono and mixed pathogens infection of severe CAP in China was showed in Table S2 (detail in supplemental file).

Microbial Etiology Changes

The distributions of pathogens were substantial variation over a decade. *K. pneumoniae* was one of the most pathogens in the study, which was similar with the previous reports [8, 25], while *A. baumannii* was increased the rank from the 5th to the second compare to Fan et al [25]. *S. aureus* isolated from the study were MRSA, while the *methicillin-sensitive Staphylococcus aureus* (MSSA) had its place in IDSA/ATS 2007 and Chinese research ten years ago. Another surprising result was that *S. pneumoniae* was ranked the 6th in the study compared to IDSA/ATS 2007 [1] and Chinese research reported in ten years ago [25, 26] (Table 3).

MDR and Risk factors

MDR is defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories [27]. The majority of pathogens for patients with severe CAP were MDR in the study. Herein we provided the MDR rate to the main frequent pathogens (*K. pneumoniae, A. baumannii* and *S. aureus)* were shown in Figure 2. More than 50% of *K. pneumoniae* and 60% of *A. baumannii* isolated were drug resistant to the majority of antibiotics, exclude to tigecycline and polymyxin. And *S. aureus* isolated from the study were MRSA.

Also, we analyzed the potential risk factor on clinical outcomes in patients with defined etiology of severe CAP. As shown in Table 4, the logistic regression demonstrated that *K. pneumoniae* (OR, 6.88; 95%CI, 1.13–41.83) and SOFA ≥5 (OR, 12.30; 95%CI, 1.79–84.55) were the independent factors associated with death.

Discussion

It was a prospective observational study of nonimmune-compromised patients with severe CAP in China with emphasis on assessing the microbial etiology features and MDR status. The important findings of our study were: (1) the most three frequent pathogens isolated were *K. pneumoniae, A. baumannii, S. aureus.* Among them, *K. pneumoniae* (OR, 6.88; 95%CI, 1.13–41.83) were the independent factors associated with death, while *S. pneumoniae* (n = 3, 3.9%) was ranked the 6th in the study. (2) The MDR emerged in the majority of pathogens in the study. More than 50% of *K. pneumoniae* and 60% of *A. baumannii* isolated were drug resistant to many antibiotics. *S. aureus* isolated from the study were MRSA.

It seems to have been some changes of pathogens distribution in China over a decade [28]. *K. pneumonia* was one of the most isolated pathogens in severe CAP and it was the independent risk factors related to the mortality (OR, 6.88; 95%CI, 1.13–41.83) in our study. The results were similar to the study of Paganin F. et al [8] and 593 patients with CAP in 36 hospitals in China from 2004 to 2005 showed the four most isolated pathogens were *S. pneumonia, Haemophilus influenza, K. pneumonia* and atypical pathogens [29].

In the study, *A. baumannii* isolated in severe CAP was increased really astonishing. Although, isolation of *A. baumannii* from patients with CAP was rare (range 1.3%–25.9%) [30, 31]. The severe CAP with *A baumannii* increased gradually in the Asia–Pacific [32]. *A. baumannii* is believed an important hospital-derived infection and is suspected to patients with constant use of antibiotics [33].Indeed, some antibiotics that used in animals were also used in human. A survey showed that nearly half of the 210,000 tons of antibiotics produced in China end up in animal feed [34]. And the use of antibiotics in livestock farming probably was a main source of antibiotics in the rivers was reported [35]. It was urgent to control the release of animal-originated antibiotics into the environment.

S. pneumoniae was showed to be the main isolated bacterial pathogen in severe CAP. It is usually penicillin-sensitive and the incidence of resistance appears to be decreasing in the United Kingdom [36]. However *S. pneumonia* was not rank the most microbial etiology in the study compared to the study reported in ten years ago [25]. The result was similar to a recent study that the proportion of CAP attributable to *S. pneumonia* had been declining in Australian adults. The proportion of *S. pneumonia* CAP cases declined from 26.4% in 1987–1988 to 13.9% in 2004–2006 [37]. The confirmation from other studies is required.

The MDR emerged in the majority of pathogens in the study. A report from CHINET surveillance system in China from 2005 to 2014 showed increased carbapenem resistance of clinical isolated *K. pneumoniae* and *A. baumannii* strains were up to 13.4% and 66.7%, while the carbapenem resistances were 73–81% and 80% compared to our study, respectively. MRSA is increasing in severe CAP [38] and its MDR is a serious public health threat in China. Antibiotics resistance was the most in densely populated cities in the east and the resistances were not just in adults. It appeared in 85% of erythromycin-resistant *S. pneumoniae* isolated from children tested in 2016 [39]. Enhanced the control of using antibiotics to reduce the acquired resistance was imperative.

China's health ministry tried to prevent calamitous outbreaks of MDR. They formulate "guidelines for clinical application of antibiotics" in 2004 and the ambitious program to combat the overdue of antibiotics [40]. But the measures have limited success. It needs the attention of the whole society, not just for doctors. The Chinese population lacks general knowledge about the damage of antibiotics abuse and the antibiotics were available over the counter in rural without prescription [14]. The weak of the public awareness were in need of changing and enhance to education.

The limitation of the study was the small enrollment and not multi-centers. Moreover, the bronchoscopy was not the routinely performed for patients. Some pathogens such as *A. baumannii* are often colonization bacteria may interference the sputum detection. However, as consideration of the alarming results, it needs to made more people realize the seriousness issues. Further study should be validated to confirm the results in severe CAP and mechanism research.

Conclusion

The study showed that *K. pneumoniae* was not only a most frequent microbial etiology, but also an independent risk factor for mortality in the population. The MDR emerged in the majority of pathogens in the study. It is urgent that increasing public awareness to the damage of antibiotics abuse on education. For the Chinese government and medical care provider timely interventions need to be implemented to control of using antibiotics to reduce the acquired resistance.

Declarations

Abbreviations

AB: *Acinetobacter baumannii;* CAP: Community-acquired pneumonia; ICU: intensive care unit; IDSA/ATS: Infectious Diseases Society of America/American Thoracic Society; MDR: multidrug-resistance; MRSA: Methicillin-resistant Staphylococcus aureus; MSSA: Methicillin-sensitive Staphylococcus aureus; ESBL: Extended-spectrum β-lactamase; MAP: Mean artery pressure; PaO2/FiO2: Pressure of arterial oxygen /Fraction of inspired oxygen; BUN: blood urea nitrogen; WBC: white cell counts; PSI: Pneumonia Severity Index; CRD: chronic respiratory disease; COPD: chronic obstructive pulmonary disease; HCAP: healthcare associated pneumonia; HAP: hospital-acquired pneumonia; APACHE II: acute physiology and chronic health evaluation-II; SOFA: sequential organ failure assessment; BAL: Bronchoalveolar lavage; OR: odds ratio.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board at Zhongshan Hospital, Fudan University Human Subjects Research Protection Program Office (B2017–061R). All patients were written the informed consents.

Consent for publication

Not applicable.

Availability of data and material

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

Competing interests

The authors declare no conflict of interest.

Funding

This work was sponsored by the National Natural Science Foundation of China [81873420]; Shanghai Top-Priority Clinical Key Disciplines Construction Project [2017ZZ02013]; The Special Fund for Clinical Research of Zhongshan Hospital, Fudan University [2016ZSLC11]; Jun She was supported by Shanghai Pujiang Program [16PJD012].

Author contributions

Study concept and design (LZ, JS), data acquisition (YLW, XYN, SLH), data analysis and interpretation (JS, LHS, JP), drafting (JS), revision (PY). All authors read and approved the final manuscript.

Acknowledgement

We thank Prof. Yuanlin Song and Prof. Huaying Li, Zhongshan Hospital, Fudan University, China for their improvement of the work.

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Tables

Table 1. Clinical characteristics of Severe CAP.

Characteristic	Number
Patients	112
Mean Age (year)	65.7±15.1
Range	21-92
Sex - Male	74(66.1)
- Female	38(33.9)
Smoking history	38(33.9)
alcohol abuse	17(15.2)
Comorbidities	
Chronic respiratory disease	25(22.3)
Chronic cardiovascular disease	33(29.5)
Neurological disease	12(10.7)
Diabetes mellitus	27(24.1)
Renal insufficiency	14(12.5)
Chronic hepatic disease	9(8)
Malignancy	11(9.8)
Single organ	39(34.8)
Two organs	36(32.1)
≥three organs	16(14.3)
Mechanical ventilation use	54(48.2)
Defined microbial aetiology	76(67.9)
Positive blood culture	13(10.7)
Chest CT scan	
Multilobar infiltration	60(53.6)
Pleural effusion	32(28.6)
Length of hospital stay (days)	18±20
30-days mortality	49(43.8)

Table 2. Severity and laboratory findings of severe CAP at admission.

Characteristic	n
Mean BodyTemperature°C	37.3±0.9
MAP	92.6±16.4
Confusion State	17（15.2）
PSI	
PSI IV-V	84（75.0）
CURB-65	
CURB-65≥2	60（53.6）
APACHEII	
APACHEII≥11	67（59.8）
APACHEII≥15	48（42.9）
SOFA	
SOFA≥5	50（44.6）
Laboratory	
Hemoglobin	109.4±21.8
Platelet	200.6±111.4
WBC count (*10^9/L)	10.7±6.4
Neutrophils (*10^9/L)	9.16±5
Lymphocyte (*109/L)	1.1±2.6
C reactive protein （mg/dl）	102.2±78.5
Procalcitonin（ng/ml）	3.3±11.4
Fibrinogen（mg/dl）	417.3±170.5
D-dimer（mg/l）	6.3±7.4
Serum sodium（mmol/l）	141.1±7.8
Serum potassium（mmol/l）	4.0±0.8
BUN （mg/dl）	11.6±9.6
Serum creatinine（mmol/L）	107.7±111.9
Arterial blood gas	
PH	7.4±0.1
PaO_2 （mmHg）	70.2±27.5
$PaCO_2$ （mmHg）	40.4±13.4
PaO_2/FiO_2	204.3±99.1

MAP, Mean artery pressure;

APACHEII, Acute physiology and chronic health evaluation-II;

SOFA, Sequential organ failure assessment

WBC, White cell count

BUN, Blood urea nitrogen

Table 3. The distribution of microbial etiology of severe CAP in ICU vs. CAP outpatient over a decade.

The frequent pathogen	Severe CAP in ICU			CAP outpatient	
	Present study, China	Fan et al. China ten years ago[25]	IDSA/ATS in 2007	Liu et al.China ten years ago[26]	IDSA/ATS in 2007
First	***Klebsiella pneumoniae***	***Klebsiella pneumoniae***	***Streptococcus pneumoniae***	*Mycoplasma pneumoniae*	***Streptococcus pneumoniae***
Second	***Acinetobacter Bauman***	***Streptococcus pneumoniae***	***Staphylococcus aureus***	***Streptococcus pneumoniae***	*Mycoplasma pneumoniae*
Third	***MRSA***	*Pseudomonas aeruginosa*	*Legionella species*	*Haemophilus influenzae*	*Haemophilus influenzae*
Fourth	*Pseudomonas aeruginosa*	***Staphylococcus aureus***	*Gram-negative bacilli*	*Chlamydia pneumoniae*	*Chlamydia pneumoniae*
Fifth	*Mycoplasma pneumoniae*	*Acinetobacter Bauman*	*H.influenzae*	*Klebsiella pneumoniae*	*Respiratory viruses*

MRSA, *Methicillin-resistant Staphylococcus aureus*.

Table 4. The potential risk factors in patients with defined etiology of severe CAP.

Characteristic	Death	Survivors	Odds ratio	95%CI	P value
Age	46	30	-	-	0.188
Gender	53	23	-		0.696
smoking history	26	50	-	-	0.980
alcohol abuse	13	63	-	-	0.528
Chronic respiratory disease	19	57	-	-	0.693
Chronic cardiovascular disease	23	53	-	-	0.251
Neurological disease	11	65	-	-	0.242
Diabetes mellitus	20	56	-	-	0.767
Renal insufficiency	6	70	-	-	0.572
Chronic hepatic disease	6	70	-	-	0.686
Malignancy	9	67	-	-	0.383
Single organ	30	46	-	-	0.955
Two organs	26	50	-	-	0.485
≥three organs	8	68	-	-	0.641
APACHE II ≥11	26	50	-	-	0.987
APACHE II ≥15	21	55	-	-	0.705
SOFA≥5	23	53	12.302	1.790-84.546	0.011
Klebsiella pneumoniae	27	49	6.876	1.130-41.828	0.036
Acinetobacter Bauman	15	61	-	-	0.372
MRSA	9	67	-	-	0.081
Mono-pathogens infection	30	46	-	-	0.555
Double infection	4	72	-	-	0.129
Triple infection	2	74	-	-	0.888

APACHEII, acute physiology and chronic health evaluation-II;

SOFA, sequential organ failure assessment;

MRSA, *Methicillin-resistant Staphylococcus aureus*.

Figures

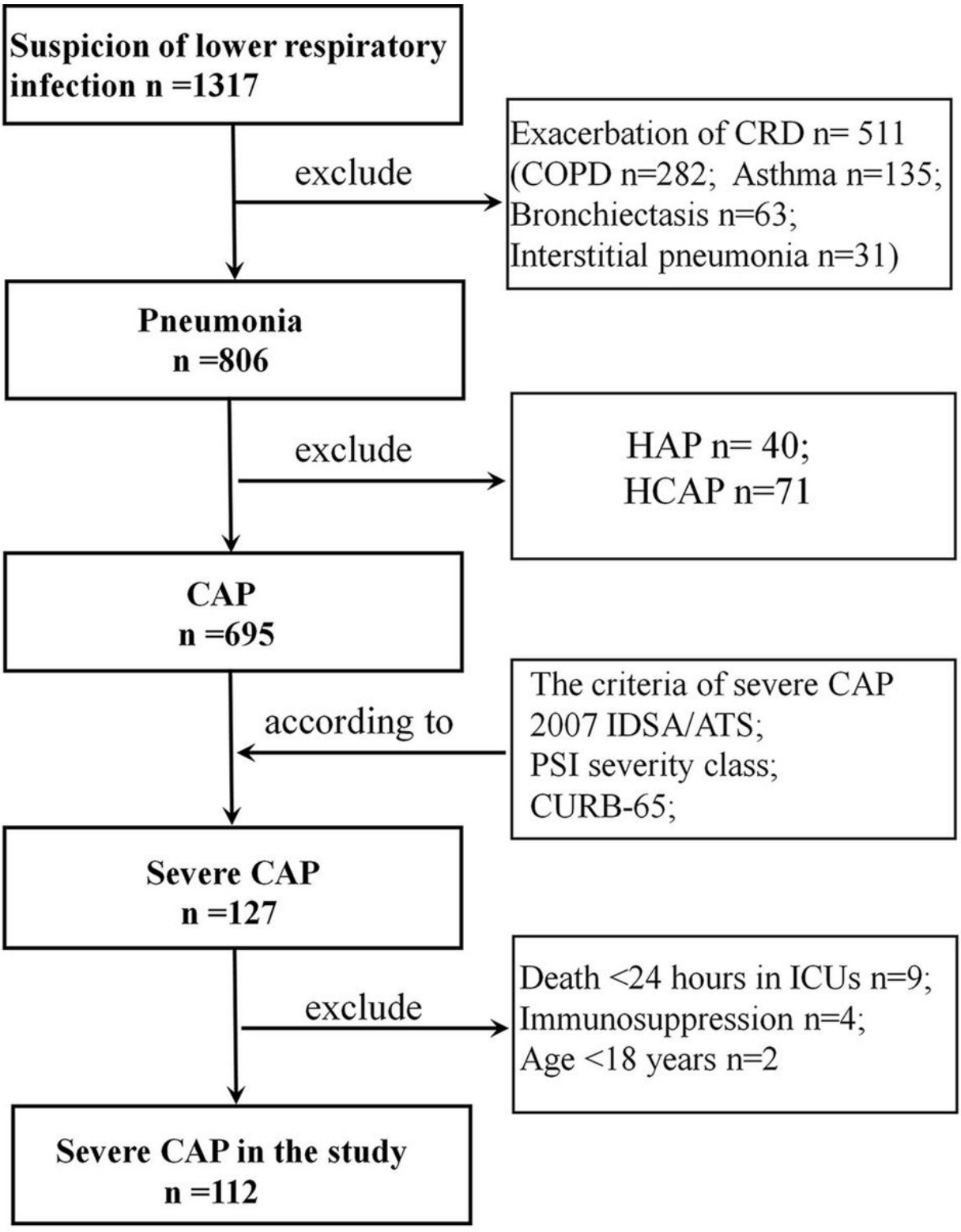

Figure 1

Study profile: number of people who were enrolled and analyzed in the study.

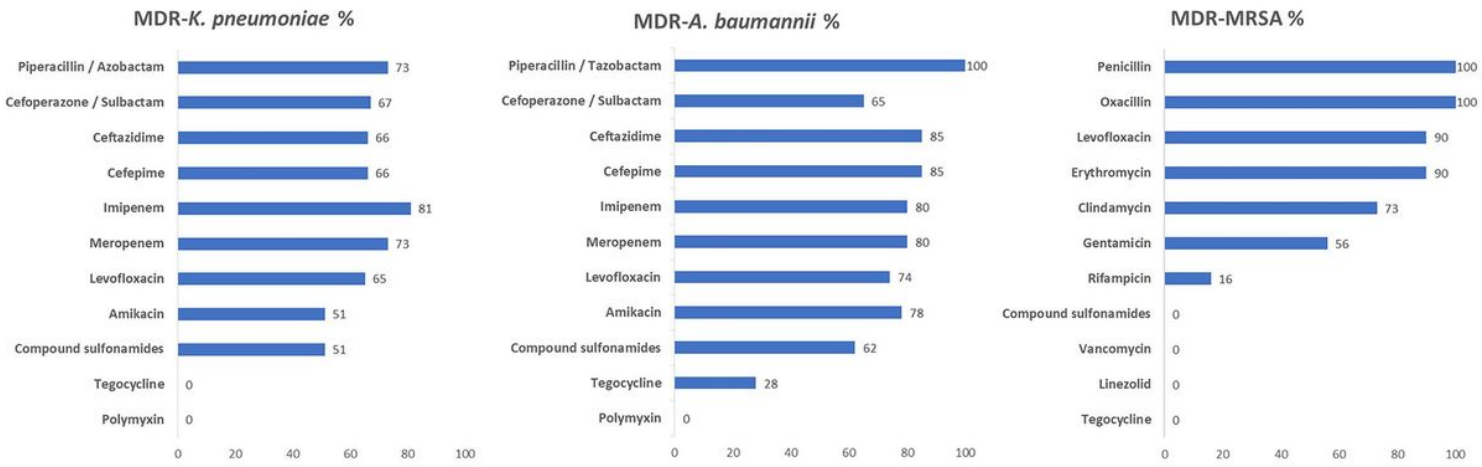

Figure 2

The rate of MDR in K. pneumoniae, A. baumannii and MRSA.

Supplementary Files

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- Supplementalfile.docx