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Review

Prevalence of *Pseudomonas aeruginosa* and antimicrobial-resistant *Pseudomonas aeruginosa* in patients with pneumonia in mainland China: a systematic review and meta-analysis

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SUMMARY

Objective: To estimate the prevalence of *Pseudomonas aeruginosa* and antimicrobial-resistant *P. aeruginosa* in ventilator-associated pneumonia (VAP), hospital-acquired pneumonia (HAP), and community-acquired pneumonia (CAP) in mainland China.
Methods: Meta-analyses of 50 studies published from 2010 to 2014 were conducted, followed by predefined subgroup analyses and meta-regressions.
Results: *P. aeruginosa* accounted for 19.4% (95% confidence interval (CI) 17.6–21.2%) of all isolates in VAP, which was similar to the proportion in HAP of 17.8% (95% CI 14.6–21.6%), but significantly greater than the proportion in CAP of 7.7% (15/195, $p < 0.001$). Regarding VAP, the prevalence of *P. aeruginosa* has decreased since 2007. *P. aeruginosa* exhibited varying resistance to agents recommended for the initial management of VAP, with a high level of resistance to gentamicin (51.1%, 95% CI 37.7–64.4%) and a low level of resistance to amikacin (22.5%, 95% CI 14.3–33.6%). The prevalence of *P. aeruginosa* isolates resistant to agents recommended for the treatment of HAP ranged from 22.2% (95% CI 13.8–33.6%) for amikacin to 50.0% (95% CI 30.2–69.8%) for cefoperazone.
Conclusions: *P. aeruginosa* was highly prevalent among patients with VAP and HAP in mainland China. The initial empirical treatment of these patients remains challenging because of the strikingly high prevalence of antimicrobial resistance.

1. Introduction

Pneumonia is an acute inflammation of the lungs caused by a wide spectrum of pathogens, which can be divided into two main types: hospital-acquired pneumonia (HAP) and community-acquired pneumonia (CAP). HAP is a respiratory infection that develops more than 48 h after hospital admission, occurs at a rate of 5–10 cases per 1000 hospitalizations, and is the second most common nosocomial infection in the USA.[1] HAP is also associated with mechanical ventilation, in which case it is termed ventilator-associated pneumonia (VAP). The global incidence of VAP ranges from 8% to 28%,[2] while the mortality varies from 24% to 76%.[3] CAP arises in those infected by pathogens who have not been recently hospitalized. In studies from Europe and North America, the annual incidence of CAP is 34–40 cases per 1000 children,[4] and the condition accounts for about 500 000 hospital admissions annually.[5]

Pseudomonas aeruginosa is one of the most frequent Gram-negative pathogens responsible for nosocomial pneumonia.[6] According to data reported by the National Healthcare Safety Network (NHSN), *P. aeruginosa* (16.6%) ranked second in the USA among the pathogens isolated from VAP patients from 2009 to 2010.[7] In comparison, the prevalence of *P. aeruginosa* in CAP is much lower. *P. aeruginosa* was the pathogen in only 0.05% of patients with CAP.[8]

Initial empirical antimicrobial therapy is commonly recommended in guidelines for the management of pneumonia.[1,9–12]

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The initial management of a suspected *P. aeruginosa* infection should include a selected β-lactam plus either an antipseudomonal quinolone or an aminoglycoside.[10–12] However, *P. aeruginosa* pneumonia is becoming difficult to treat because of the increasing prevalence of drug resistance and the resultant limited therapeutic options.[13] Terms such as 'multidrug resistance' (MDR), 'extensive drug resistance' (XDR), and 'pan-drug resistance' (PDR) are used to characterize the different patterns of multiple drug resistance exhibited by *P. aeruginosa*. According to the definitions proposed by the European Centre for Disease Prevention and Control (ECDC), MDR refers to an organism's non-susceptibility to at least one agent in three or more antimicrobial categories, XDR indicates non-susceptibility to at least one agent in all but two or fewer antimicrobial categories, and PDR suggests non-susceptibility to all agents in all antimicrobial categories.[14] In Asia, the MDR, XDR, and PDR rates of *P. aeruginosa* involved in nosocomial pneumonia are reportedly 42.8%, 4.9%, and 0.7%, respectively.[15] In addition, resistant and MDR *P. aeruginosa* infections have been firmly associated with an increased mortality and a longer length of hospital stay.[13] To achieve optimal empirical antimicrobial therapy, it is therefore important to understand the pathogen distribution and drug susceptibility patterns of pneumonia.[9]

In mainland China, data from the National Nosocomial Infection Surveillance System (NNISS) indicated that *P. aeruginosa* ranked top among pathogens identified from the lower respiratory tract, at 12.82% from 1999 to 2001, 12.31% during the period from 2002 to 2004, and 13.37% from 2005 to 2007.[16] In addition, of the 7270 *P. aeruginosa* isolates collected from 15 teaching hospitals in 2012, 13.5–34.5% were resistant to at least one of the agents tested and 80 isolates showed PDR.[17] Despite descriptions of the epidemiological characteristics of *P. aeruginosa* in previous studies, substantial uncertainty remains in the epidemiology of *P. aeruginosa* pneumonia. It appears that there is only one systematic review dealing with the prevalence of *P. aeruginosa* in VAP, with an estimate of 20.6% for the period 2007–2012;[18] none has been conducted to investigate the antimicrobial resistance patterns in relation to *P. aeruginosa* pneumonia. In this regard, the present systematic review aimed to provide further details in this field and to promote appropriate empirical antimicrobial therapy by estimating the prevalence of *P. aeruginosa* and antimicrobial-resistant *P. aeruginosa* in different types of pneumonia in mainland China.

2. Methods

2.1. Literature search and eligibility criteria

The following five electronic databases were searched systematically for relevant studies: MEDLINE, EMBASE, Chinese BioMedical Database (CBM), China National Knowledge Infrastructure (CNKI), and Wanfang Database. Given the focus on the recent epidemiological characteristics of *P. aeruginosa* pneumonia in this review, searches were limited to studies published between January 2010 and December 2014. The searches were based on the following terms related to this review: '*Pseudomonas aeruginosa*', 'Pneumonia OR Pneumon*(truncated term)' and 'China OR Chinese OR Han Chinese'. Combinations of medical subject heading (MeSH) and free-text terms were applied to MEDLINE, EMBASE, and CBM, and free-text terms were used to search CNKI and Wanfang Database. The full search strategies for each database are listed in the **Supplementary Material** (Table S1).

Reviewers were divided into two groups that worked in parallel. The reviewers independently screened each record by title, keywords, and abstract against the eligibility criteria. Full texts were referred to when information in the records was inadequate for determination. Any disagreement between the two groups of reviewers was resolved by an additional reviewer. A flow chart for study inclusion was developed in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[19]

Studies were included if they met all of the following criteria: (1) Study patients with any type of pneumonia (VAP, HAP, or CAP) infected by *P. aeruginosa*. (2) Study reporting available and sufficient data to calculate the prevalence of *P. aeruginosa*, the prevalence of MDR/XDR/PDR *P. aeruginosa*, or the prevalence of *P. aeruginosa* isolates resistant to a given agent in a specific type of pneumonia. Based on the clinical practice guidelines prepared by the Chinese Medical Association,[10–12] the agents were limited to those recommended for the initial management of suspected *P. aeruginosa* pneumonia in a Chinese population, which included β-lactams (cefoperazone, cefepime, ceftazidime, piperacillin, imipenem, meropenem, cefoperazone–sulbactam, and piperacillin–tazobactam), antipseudomonal quinolones (levofloxacin and ciprofloxacin), and aminoglycosides (amikacin and gentamicin). (3) Data collected in a prospective manner with a study design of surveillance, ambispective or prospective cohort study, nested case–control study, cross-sectional study, or baseline of randomized controlled trial (RCT). (4) Studies conducted in mainland China. (5) Investigations published in Chinese or English.

2.2. Data extraction

An extraction form was pre-designed using EpiData 3.1 (The EpiData Association, Odense, Denmark) and then modified following a pilot test. The revised extraction form comprised four parts: general information, methodological quality, clinical characteristics, and data for calculating the prevalence of *P. aeruginosa* and corresponding antimicrobial-resistant isolates. The data extraction procedure was also implemented independently by the two parallel groups of reviewers. Any disagreement was resolved by an additional reviewer.

2.3. Risk of bias assessment

The methodological quality of each included study was assessed using the modified Leboeuf-Yde and Lauritsen tool,[20] which consists of 10 items addressing two study dimensions (external validity and internal validity) plus a summary risk of bias assessment (**Supplementary Material**, File S1).[21] Each item can be judged as having a low or a high risk of bias. One point was awarded if an item was judged to have a low risk of bias, and the maximum score was 10 points. Studies with a score of $\geq$8, 6–7, and $\leq$5 points were considered to have a low, moderate, and high risk of bias, respectively.[22] Graphs of the summary of the risk of bias were developed using RevMan 5.3 (Cochrane Informatics and Knowledge Management Department, London, UK).

2.4. Statistical analysis

All analyses were performed with R 3.2.1 (Bell Laboratories, Inc., Madison, WI, USA), and all statistical tests were two-sided. The prevalence of *P. aeruginosa* and antimicrobial-resistant *P. aeruginosa* isolates in a specific type of pneumonia were calculated using the following formulae for each study included, when applicable:

$$\text{Prevalence of } P.\ aeruginosa = \frac{\text{Number of } P.\ aeruginosa \text{ isolates}}{\text{Number of all the detected isolates}} \times 100\%$$