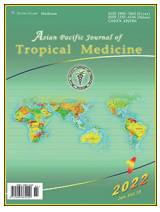

Meta-Analysis

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Antibiotic resistance pattern of *Pseudomonas aeruginosa* wound isolates among Chinese burn patients: A systematic review and meta analysis

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ABSTRACT

Objective: To investigate the resistance profiles to antimicrobial agents of wound-isolated *Pseudomonas* (*P.*) *aeruginosa* among Chinese burn patients.

Methods: Electronic databases and manual search were used to identify eligible studies published since 2010. The objectives were pooled resistance rates for eleven common antimicrobial agents, estimated by a random-effects model. Subgroup analyses were conducted by stratifying the studies into three four-year periods based on year of isolation.

Results: A total of 35 studies were included. Gentamicin had the highest pooled resistance rate (56%, 95% *CI* 48%-64%), while meropenem had the lowest pooled resistance rate (29%, 95% *CI* 20%-40%). There was an increasing trend of resistance to common antimicrobial agents of wound-isolated *P. aeruginosa* over a span of twelve years (2009-2020). There remained the highest risk of gentamicin resistance over time in China. Subgroup analyses indicated significantly higher resistances to ceftazidime and levofloxacin from 2017 to 2020.

Conclusions: Enhanced resistance to common antimicrobial agents in wound-isolated *P. aeruginosa* presents a challenge in burn wound management in mainland China. Effective stewardship programs should be established based on corresponding resistance profiles, thereby optimizing treatment options for hospitalized burn patients.

KEYWORDS: Antibiotic resistance; Burn; Nosocomial infection; *Pseudomonas aeruginosa*

1. Introduction

Burns are a serious public health problem worldwide, accounting for an estimated 180 000 deaths anually. The majority of these fatal cases occur in the South-East Asia regions[1]. Infection following non-fatal burn injuries serves as a leading cause of morbidity and mortality. Hospitalized burn victims are predisposed to infection. It is reported that the incidence density of nosocomial infections (NIs) was 9.6 per 1 000 patient-days in Chinese burn patients and NIs significantly contributed to increased fatal outcomes[2]. Given that thermal injury results in the loss of skin protective barrier against the microbial entry and a concomitant state of immune system dysregulation, the burn wound surface provides a protein-rich environment conducive to the colonization and growth of endogenous and exogenous microorganisms[3,4]. Burn wound infection (BWI) has always been a great challenge of burn care[3].

Pseudomonas (*P.*) *aeruginosa* is one of the most ubiquitous gram-negative pathogens isolated from infected burn wounds, with its large repertoire of virulence factors and antimicrobial resistance traits[3]. *P. aeruginosa* has evolved in parallel with the development of treatment options and enhanced antimicrobial resistance is posing a menace to the lives of burn patients, associated with a more significant global burden on health care[5]. There is no exception for China, where the burnt are also threatened by infections with *P. aeruginosa*. More importantly, there exists a lack of comprehensive studies pertaining to antibiotic resistance in wound-isolated *P. aeruginosa*. Herein, the present systematic scoping review and meta-analysis was undertaken to investigate updated resistance profiles to antimicrobial agents in

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wound-isolated *P. aeruginosa* among Chinese burnt patients through systematically collating findings published in the last decade, thereby providing reference information on the primary use of antibiotics on burn treatment and contributing to bacterial infection control.

2. Materials and methods

This study conformed to the Scoping Review Extension of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISM-ScR guidelines)[6].

2.1. Search strategy

A comprehensive literature search was conducted to retrieve eligible articles in electronic databases supplemented by cross-checking references of relevant papers before April 2021. Given the focus on a more updated resistance profile in our study, searches were limited to publications after 2010. Because there was a gap between the period of study and publication, studies that were carried out in 2009 were also included. The following databases were searched: PubMed, Web of Science, China Wanfang Database, and China National Knowledge Infrastructure (CNKI). The following keywords were used in combinations for searching: 'burn patients', 'burn wound', 'burn wound infection', 'infected burn wound', '*Pseudomonas aeruginosa*', '*P. aeruginosa*', 'drug resistance', 'antimicrobial resistance', and 'antibiotic resistance'. Two independent reviewers initially screened the retrieved searches based on titles and abstracts and made subsequent full-text reviews for potentially eligible articles. Differences were settled through a discussion with a third reviewer.

2.2. Eligibility criteria

Studies were included in the analysis if the following criteria were satisfied: (1) study population are hospitalized burnt patients in mainland China; (2) at least twenty strains of *P. aeruginosa* isolated from clinical burn wound specimens based on standard laboratory tests; (3) mentioning the approach that were used for antibiotic resistance test and it should be up to laboratory standards; (4) reporting sufficient information for analysis of antimicrobial-resistant *P. aeruginosa*, and reporting results of resistance to at least two antibiotics. None but full-length manuscripts written in English or Chinese were considered eligible for the present analysis. Case reports, reviews, editorials, letters, or conference abstracts were rejected.

2.3. Data items

Two reviewers independently extracted the following data from included studies into a pre-established Excel form: first author, year of publication, geographic location, time of enrollment, characteristics of enrolled subjects (mean age, sex, total body surface area, *etc*.), total number of pathogens found in burn wound and the number of *P. aeruginosa* strains detected, the approach used to determine *P. aeruginosa*, method and criteria used for antimicrobial resistance test, the number of wound-isolated *P. aeruginosa* resistant to antipseudomonal antibiotics. Based on international guidelines, we chose the following eleven widely prescribed antibiotics for investigation of resistance profiles in the setting of meta-analysis: imipenem (IPM), meropenem (MEM), cefepime (FEP), ceftazidime (CAZ), piperacillin (PIP), piperacillin-tazobactam (TZP), aztreonam (ATM), amikacin (AMK), gentamicin (GEN), ciprofloxacin (CIP), and levofloxacin (LVX)[7]. Plus, data for polymyxin B (PMB) or colistin (CST) was also extracted when available. Intermediate isolates were included in the resistance rate calculation. For studies reporting year-stratified results, their analyses were considered separate reports. Two reviewers checked with each other after data were captured and any difference was solved through discussion.

2.4. Quality assessment

Two independent reviewers evaluated the methodological quality of included studies using a risk of bias tool provided by Hoy *et al*[8]. The tool modified based on our application comprises ten items plus a summary evaluation. An individual study was awarded one point in each item if judged to have a low risk of bias. In summary assessment, articles with a total point ranging from 8-10, 6-7, or 0-5 were deemed to have an overall low, moderate, or high risk of bias, respectively. The summary risk of bias graph was generated using RevMan version 5.3[9]. Consultation was conducted with a third reviewer in case of any disagreement.

2.5. Data synthesis

Data synthesis was conducted using Stata version 15.0 (Stata Corp, College Station, TX). A random-effect model was developed to calculate pooled prevalence for resistance to each antimicrobial agent with corresponding 95% confidence intervals (*CI*s). The Freeman-Tukey's double arcsine transformation was adopted in case of studies with estimated proportions of 0% or 100%[9]. Heterogeneity across studies was quantified by the I^2 statistics, with an I^2>50% regarded as having a significant degree of heterogeneity[9]. Subgroup analyses were generated according to year of isolation. We stratified studies into three four-year subgroups: (1) 2009-2012; (2) 2013-

2016; (3) 2017-2020. If a study reported cumulative data spanning two four-year periods, the midpoint of study duration was used for stratification. For example, a study reporting a cumulative resistance profile for strains isolated between 2011 and 2015, was classified into the '2013-2016' subgroup based on its midpoint mainly lying on 2013. Results of subgroup analyses were managed and used for chart making, using Microsoft Excel software. Test of interaction was employed to compare effect estimates between subgroups and a *P*-value<0.05 demonstrated that there was proof of statistical significance[10]. Additional sensitivity analyses were performed to explore the impact of an individual study by omitting one each time. Publication bias was evaluated under the Egger's test if the number of included studies was at least ten, with a *P*-value <0.05 as suggestive of significant bias[9].

3. Results

3.1. Study selection

A total of 813 records were retrieved through prior searches of four electronic databases. Reviewers scanning by titles and abstracts after removal of duplicated entries resulted in 189 publications receiving a subsequent full-text assessment for inclusion. Finally, 35 articles were selected in the enrollment of meta-analysis. Figure 1 sets out the flow diagram of study selection.

3.2. Study characteristics and quality assessment

Table 1 displays the main characteristics among included studies. These observational studies, written in Chinese, reported descriptive data provided by single-centres localized in three chartered cities and 18 provinces in mainland China[11–45]. Thus, most of the included studies were ranked as having a high risk of bias in terms of Item 1-3 presented in Figure 2. The vast majority of selected studies made use of Kirby-Bauer (K-B) disk diffusion for testing antimicrobial resistance. The mean age among enrolled burnt victims ranged from 23.7 to 62.5 years, except for three studies only contributing data of pediatric burn cases[14,25,30]. Twenty-eight studies performed tests following the guidelines provided by Clinical and Laboratory Standards Institute (CLSI; formerly NCCLS), while 6 articles[14,18,19,24,25,42] failed to mention guidelines and were considered having a high risk of bias with regard to Item 7 (Figure 2). Additionally, studies that did not well-describe the mode of sample collection were awarded a 'No' answer for Item 8. As shown in Figure 2 which illustrates a summary of quality appraisal, there is an overall moderate risk of bias among included studies.

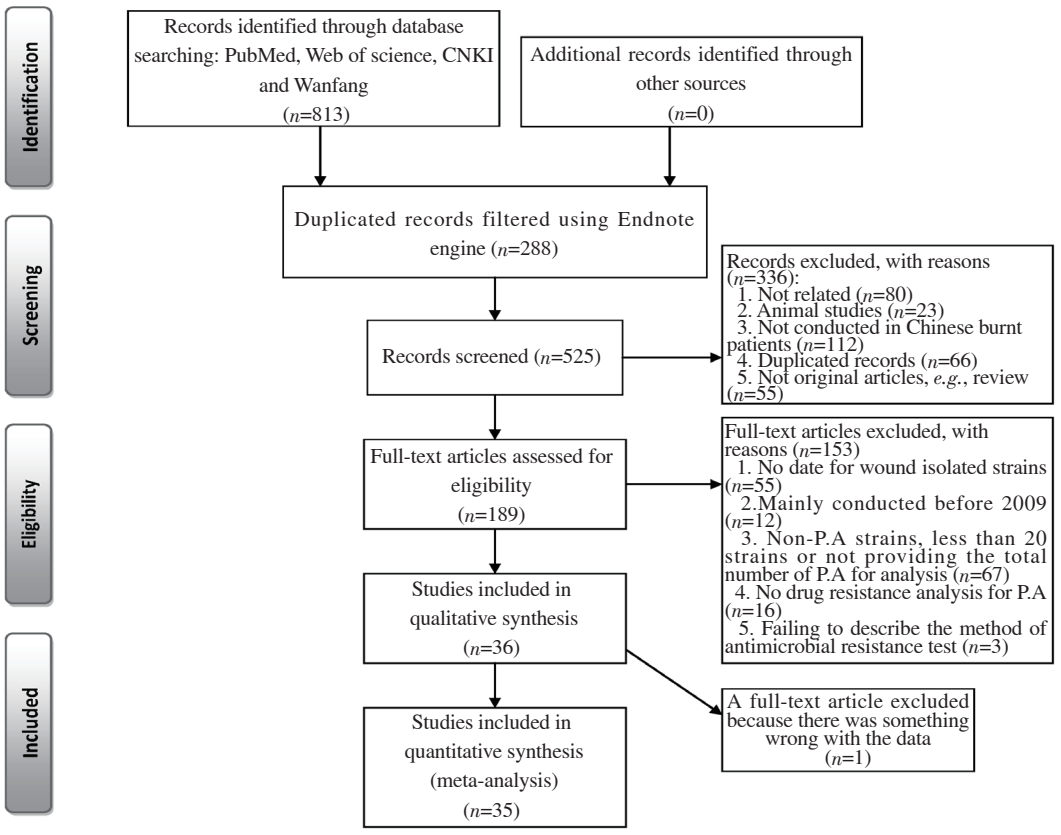


Figure 1. PRISMA flowchart of study identification. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; P.A: *Pseudomonas aeruginosa*.

Table 1. Baseline characteristics of included studies.

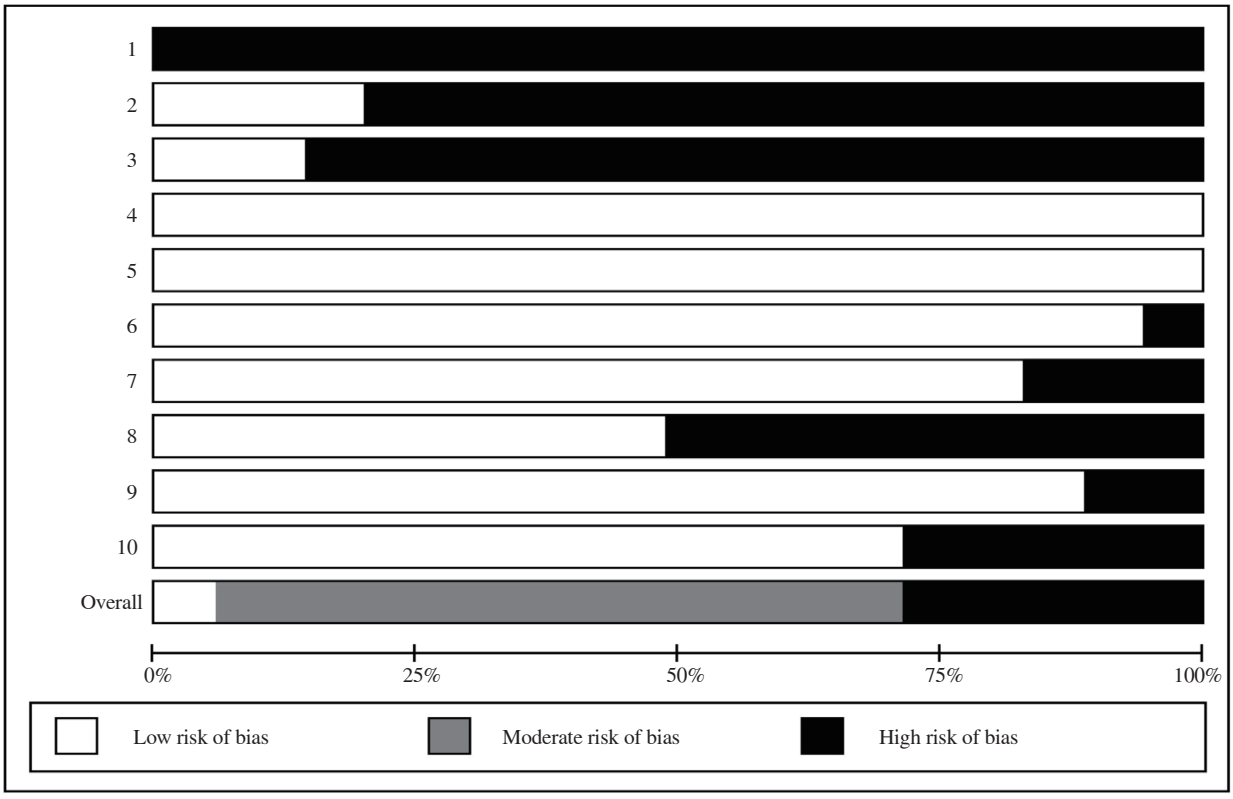
Study	Time of isolation	Location	Enrolled burnt subjects			Burn wound isolates		
			Total (*n*)	Male (%)	Mean age (y)	Total pathogens (*n*)	P.A (*n*)	Method for drug resistance test
Chen *et al*. 2014[11]	2012.10-2013.3	Zhejiang	100	64.0	47.0	520	200	K-B disc diffusion
Chen *et al*. 2017[12]	2014-2015	Qinghai	369	68.8	24.7	329	71	K-B disc diffusion
Cheng *et al*. 2021[13]	2017.6-2020.6	Hainan	100	75.0	33.8	108	35	K-B disc diffusion
Dai *et al*. 2012[14]	2009-2010	Zhejiang	1226	/	2.3	379	46	K-B disc diffusion
Han *et al*. 2016[15]	2012.1-2015.12	Inner Mongolia	671	/	/	795	126	K-B disc diffusion
Han et al. 2017[16]	2013.1-2014.4	Hebei	65	70.8	46.8	83	22	K-B disc diffusion
Han, 2020[17]	2017.12-2019.12	Shanxi	50	58.0	62.5	260	100	K-B disc diffusion
Han *et al*. 2014[18]	2012.7-2013.10	Anhui	200	60.0	33.1	436	51	Auto system (BD)
Huang *et al*. 2019[19]	2017.1-2018.6	Guangdong	245	64.9	46.3	245	66	Auto system (Vitek)
Li *et al*. 2013[20]	2009.3-2012.12	Shanghai	/	/	/	446	77	Auto system (Vitek)
Liu *et al*. 2013[21]	2012	Yunnan	/	/	/	666	154	Disc agar diffusion
Liu, 2019[22]	2016.6-2018.6	Shandong	510	/	/	534	194	Disc agar diffusion
Luo *et al*. 2015[23]	2012.9-2013.9	Zhejiang	326	66.9	(4-87)	315	81	K-B disc diffusion
Lv, 2015[24]	2009.7-2014.7	Hubei	300	53.3	39.6	318	101	K-B disc diffusion
Ma *et al*. 2017[25]	2011-2015	Zhejiang	/	/	/	673	75	Auto system (Vitek), disc agar diffusion
Meng *et al*. 2012[26]	2010.3-2011.3	Henan	425	66.1	(6 m-79)	1 050	118	K-B disc diffusion
Peng *et al*. 2014[27]	2011.1-2013.12	Guizhou	530	55.3	42.9	559	181	K-B disc diffusion
Qin *et al*. 2013[28]	2010-2013	Guangxi	267	61.0	42.5	449	102	K-B disc diffusion
Qiu *et al*. 2014[29]	2012.1-2014.1	Beijing	596	47.1	47.4	1 088	192	K-B disc diffusion
Song *et al*. 2019[30]	2010.1-2017.12	Anhui	170	61.8	4.6	138	39	K-B disc diffusion
Sun *et al*. 2015[31]	2010-2013	Henan	280	66.1	46.0	186	48	K-B disc diffusion
Sun, 2014[32]	2011.1-2014.3	Shandong	/	/	/	370	42	Auto system (Dade Behring)
Wang *et al*. 2014[33]	2010.5-2012.5	Jiangsu	/	/	/	310	22	K-B disc diffusion
Wang *et al*. 2013[34]	2011.11-2012.4	Liaoning	87	/	/	156	45	K-B disc diffusion
Wang *et al*. 2013[35]	2011.12-2012.12	Jiangxi	108	79.6	1-59	94	24	Auto system (Sensititre)
Wang *et al*. 2015[36]	2012.6-2014.6	Guizhou	150	54.0	43.2	217	37	K-B disc diffusion
Xia *et al*. 2017[37]	2011-2015	Zhejiang	/	/	/	200	53	K-B disc diffusion, Broth microdilution
Yang *et al*. 2015[38]	2012-2014	Inner Mongolia	454	/	1-87	281	65	K-B disc diffusion
Zeng *et al*. 2017[39]	2014.1-2014.12	Sichuan	326	54.0	23.7	213	33	Auto system (Vitek)
Zhang *et al*. 2018(1)[40]	2012	Chongqing	1 310	66.3	30.0	256	39	K-B disc diffusion
Zhang *et al*. 2018(2)[40]	2013					537	58	
Zhang *et al*. 2018(3)[40]	2014					593	85	
Zhang *et al*. 2018(4)[40]	2015					416	72	
Zhang *et al*. 2018(5)[40]	2016					225	35	
Zhang et al. 2018(6)[40]	2017					156	27	
Zhang, 2012[41]	2010.1-2011.6	Henan	/	/	/	124	41	Auto system (Sensititre)
Zhang, 2018[42]	2015.3-2017.5	Zhejiang	200	64.0	36.6	186	58	Auto system (Vitek)
Zhou, 2014[43]	2012,8-2013.8	Hunan	67	71.6	43.4	172	58	K-B disc diffusion
Zhou *et al*. 2014[44]	2010.4-2013.4	Guangdong	510	63.7	31.2	515	115	K-B disc diffusion
Zou *et al*. 2018[45]	2015.1-2016.12	Jiangxi	572	/	/	391	36	Auto system (Vitek)

K-B: Kirby-Bauer; m: month; P.A: *Pseudomonas aeruginosa*; y: year.

3.3. Resistance profile for wound-isolated P. aeruginosa

A total of 14 598 strains of pathogens causing bacterial infection were isolated from burn wound specimens, of which 2 988 strains of *P. aeruginosa* were detected. The total isolation rate of *P. aeruginosa* collected from burn wounds was 20.5% and the overall prevalence pooled by 35 studies was 21% (95% *CI* 18%-24%, I^2=94.4%) among Chinese burn victims between 2009 and 2020. Table 2 summarizes antimicrobial-resistant *P. aeruginosa* reported in each included study and Table 3 shows the overall combined prevalence of wound-isolated *P. aeruginosa* resistant to 11 commonly prescribed antimicrobial agents. The highest level of pooled resistance was observed against GEN (56%), while the lowest degree of resistance was found against MEM (29%). Forest plots for overall estimates of each agent are provided in supplementary figures. High heterogeneity was suggested through the analysis but no individual study was found to neither decrease the significant degree of heterogeneity nor affect the general outcomes based on leave-one-out sensitivity analyses, which demonstrated the robustness of results. According to the Egger's test, no potential bias was observed except for the analysis of CIP (P=0.035) (Table 3).

Summarized outcomes regarding subgroup analyses stratified by 3 four-year periods are shown in Table 4, illustrating the change in consolidated resistance of wound-isolated *P. aeruginosa* to the most important antibiotics over time. Moderately high resistances to antibiotics were seen during the period from 2009-2012,



1. Was the study's target population a close representation of the national population in relation to relevant variables?
2. Was the sampling frame a true or close representation of the target population?
3. Was some form of random selection used to select the sample, or was a census undertaken?
4. Was the likelihood of nonresponse bias minimal?
5. Were data collected directly from the subjects (as opposed to a proxy)?
6. Was an acceptable method of determining pathogens isolated from bum wound used in the study?
7. Was the study instrument that measured drug resistance shown to have validity and relability? *e.g.* based on guidelines such as CLSI, EUCAST?
8. Was the same mode of data collection used for all subjects?
9. Was the length of analysis for antimicrobial-resistant *Pseudomonas aeruginosa* appropriate?
10. Were the numerator(s) and denominator(s) for proportion of antimicrobial-resistant *Pseudomonas aeruginosa* appropriate?

Figure 2. Quality assessment of the included studies.

where there was the highest proportion of GEN-resistant strains (61%) and the lowest proportion of MEM-resistant strains (30%) among *P. aeruginosa* isolates. Compared with the first four-year period, an overall decreased trend in resistances to commonly used antimicrobial agents was observed in the second four-year period (2013-2016), despite no significant differences between two subgroups (P=0.15). The pooled resistance to GEN (48%) remained the highest during 2013-2016, but a declined trend in GEN resistance in this period could be observed when it was compared to that during 2009-2012 (P=0.058). Except for AMK, all of the antibiotics were subject to increased drug resistance in the third four-year period (2017-2020) comparing with those in 2009-2012 and 2013-2016, where the highest and lowest level of resistance was found against GEN (72%) and AMK (31%), respectively. Of note, pooled resistance rates of CAZ and LVX were significantly elevated in the third period, compared with the first and second periods (P<0.05).

In addition, there was a considerably lower proportion of wound-isolated *P. aeruginosa* resistant to PMB (pooled resistance: 1%, 95% *CI* 0%-3%), based on four included studies[29–31,40]. Two articles[16,37] contributed data to the analysis of CST resistance and the pooled result was 31% (95% *CI* 19%-44%).

4. Discussion

Antimicrobial resistance in China has become a serious public health issue, with increased resistance rates of most prevalent bacteria in clinically important antimicrobial agents[46]. To our knowledge, this is the first scoping review and meta-analysis investigating the antimicrobial resistance profile of wound-isolated *P. aeruginosa* among Chinese burn patients referring to publications in the recent decade. Based on 2 988 strains of *P. aeruginosa* collected from wound samples of hospitalized burn patients during 2009-2020 in China, we found a prevalence of more than 28% in resistance to commonly used antipseudomonal drugs. Subgroup analyses indicated that there was an increasing trend of antimicrobial

Table 2. Summary of antimicrobial agents tested among included studies.

Study	IMP	MEM	CAZ	FEP	PIP	TZP	ATM	AMK	GEN	CIP	LVX
Chen *et al*. 2014[11]	√		√			√		√			
Chen *et al*. 2017[12]	√			√	√			√	√	√	
Cheng *et al*. 2021[13]	√	√	√	√	√	√	√	√	√	√	√
Dai *et al*. 2012[14]	√		√			√	√		√	√	√
Han *et al*. 2014[18]	√	√	√	√			√	√	√	√	√
Han *et al*. 2016[15]	√	√	√	√	√	√	√	√	√	√	√
Han *et al*. 2017[16]	√	√		√	√		√				√
Han, 2020[17]	√		√		√			√			
Huang *et al*. 2019[19]	√	√		√	√		√				√
Li *et al*. 2013[20]	√		√	√				√	√	√	
Liu *et al*. 2013[21]	√	√	√	√	√	√	√	√		√	√
Liu, 2019[22]	√		√	√		√	√		√	√	√
Luo *et al.* 2015[23]	√	√	√	√	√	√	√	√	√	√	√
Lv, 2015[24]	√		√				√	√	√	√	
Ma *et al*. 2017[25]	√	√	√	√		√		√	√	√	√
Meng *et al.* 2012[26]	√		√			√	√				√
Peng *et al.* 2014[27]			√		√			√	√	√	
Qin, 2013[28]	√		√			√	√	√	√		
Qiu *et al*. 2014[29]	√	√	√	√			√	√			√
Song *et al*. 2019[30]	√	√	√	√		√			√		
Sun, 2014[32]	√	√	√	√	√	√	√	√	√	√	√
Sun *et al*. 2015[31]	√	√	√	√	√	√	√	√	√	√	√
Wang *et al*. 2013[34]	√		√	√	√			√	√	√	
Wang *et al*. 2013[35]	√	√							√		√
Wang *et al*. 2014[33]	√	√	√	√	√	√	√	√	√	√	√
Wang *et al*. 2015[36]	√		√	√			√	√	√	√	
Xia *et al*. 2017[37]	√	√	√	√	√	√	√	√	√	√	√
Yang *et al*. 2015[38]	√	√	√	√		√	√	√	√	√	√
Zeng *et al*. 2017[39]			√	√		√	√	√	√	√	
Zhang, 2012[41]			√	√	√		√		√		√
Zhang *et al.* 2018[40] (1)	√	√	√	√	√	√	√	√	√	√	√
Zhang *et al*. 2018[40] (2)	√	√	√	√	√	√	√	√	√	√	√
Zhang *et al*. 2018[40] (3)	√	√	√	√	√	√	√	√	√	√	√
Zhang *et al*. 2018[40] (4)	√	√	√	√	√	√	√	√	√	√	√
Zhang *et al*. 2018[40] (5)	√	√	√	√	√	√	√	√	√	√	√
Zhang *et al*. 2018[40] (6)	√	√	√	√	√	√	√	√	√	√	√
Zhang, 2018[42]					√		√	√	√		√
Zhou *et al*. 2014[44]	√	√	√			√		√	√		√
Zhou, 2014[43]	√		√		√			√	√		
Zou *et al*. 2018[45]	√			√		√	√	√			

AMK: amikacin; ATM: aztreonam; CAZ: ceftazidime; CIP: ciprofloxacin; FEP: cefepime; GEN: gentamicin; IPM: imipenem; LVX: levofloxacin; MEM: meropenem; PIP: piperacillin; TZP: piperacillin-tazobactam.

resistance of wound-isolated *P. aeruginosa* over time.

Regarding resistance to aminoglycosides, pooled results suggested the highest risk of GEN resistance among Chinese burn patients infected with *P. aeruginosa*, irrespective of time. In comparison to other common antibiotics, continuously higher resistances to GEN were found during 2009-2020, ranging from 48% to 61%. According to Xiao *et al*[46], the resistance rates of *P. aeruginosa* to GEN were high in China over the past decade (2000-2009), and our results indicated that GEN resistance remained prevalent in the subsequent years. Subgroup comparison suggested a nearly significant trend in declined GEN resistance from the first four-year to the second one (P=0.058), which might be attributed to effective control to the use of GEN at that time based on its resistance profile as showed before. The resistance rates to GEN, however, greatly rose again in recent years. In contrast, there existed relatively lower pooled 12-year resistances to AMK in the range of 31%-42%, which is also consistent with the trend in 2000-2009[46,47]. Given the higher resistance to GEN, reduced use of this antibiotic should be taken into account in the setting of treating burn wounds without knowledge of results of drug resistance testing, whereas AMK can act as the first choice because of its low resistance potential when considering using aminoglycosides.

The increasing rates of carbapenem-resistant *P. aeruginosa* isolated from infected wounds represent a challenge to antibiotics therapy for burn wound infection in China. IPM and MEM resistances against *P. aeruginosa* collected from various types of samples were reported to be 28% and 24.4% on average, respectively, in the period of 2000-2009[47]. The pooled resistance for the subsequent 12 years was 33% and 29%, respectively, in the present analysis. The synergistic effect of multiple mechanisms of chromosomal resistance mainly

contributes to carbapenem resistance[46]. Carbapenem exhibits a notable stability to most ß-lactamases without high toxicity, thereby serving as the primary choice for severe Gram-negative infections currently[31,48]. Increased therapeutic exposure affected by the easier access to this kind of antibiotics also led to furtherance. Despite increased resistance showed in the overall results, it is still plausible to take carbapenem into account for the first-line treatment of severe burn wound infections when there is a lack of drug sensitivity test, based on its potent antibacterial activity and our results showing relatively high sensitivity to carbapenems compared with other antibiotics. PMB and CST comprise a last-line therapy for life-threatening infections, such as carbapenem-resistant *P. aeruginosa*, yet their universal application is limited by their important toxicity issues[49]. We observed that wound-isolated *P. aeruginosa* presented higher susceptibility to PMB (pooled resistance: 1%) and moderately high susceptibility to CST (pooled resistance: 31%), The latter might be affected by the very small number of included studies. Polymixins can be considered in the case of burn wounds severely infected by carbapenem-resistant *P. aeruginosa*.

In the pooling analysis of resistance to LVX and CAZ, statistical significance was observed among year-stratified subgroup comparisons. It was noted that the pooled resistance to CAZ in the most recent four-year period (2017-2020) was significantly higher than that in 2009-2012 (69% versus 38%, $P<0.05$) and 2013-2016 (67% versus 31%, $P<0.01$), respectively. Similarly, the pooled resistance to LVX in 2017-2020 was remarkably elevated, as compared to that in 2009-2012 (67% versus 37%, $P<0.05$) and 2013-2016 (67% versus 28%, $P<0.01$), respectively. Factors at play could lie in the compromised use of CIP and resultant increased LVX exposure in recent years. Additionally, the production of ß-lactamase contributed to elevated CAZ resistance[46].

Table 3. Summary of overall prevalence of resistance to eleven antimicrobial agents.

Drugs	Total (*n*)	Resistant (*n*)	Pooled resistance (95% *CI*)	I^2 (%)	Egger (*P*)
ß-lactam					
Imipenem	2747	977	0.33 (0.25-0.41)	94.95	0.471
Meropenem	1526	469	0.29 (0.20-0.40)	94.25	0.918
Ceftazidime	2571	1059	0.38 (0.30-0.47)	94.91	0.874
Cefepime	1925	917	0.46 (0.36-0.56)	94.50	0.464
Piperacillin	1482	802	0.52 (0.42-0.62)	93.63	0.126
Piperacillin-tazobactam	1904	817	0.38 (0.28-0.48)	95.37	0.145
Aztreonam	2025	971	0.47 (0.37-0.57)	95.02	0.683
Aminoglycosides					
Gentamicin	2176	1234	0.56 (0.48-0.64)	91.84	0.187
Amikacin	2514	957	0.35 (0.27-0.43)	93.87	0.350
Fluoroquinolones					
Ciprofloxacin	1893	797	0.35 (0.25-0.46)	95.75	0.035
Levofloxacin	1949	768	0.37 (0.27-0.47)	95.03	0.404

Note: Egger's test was performed to assess publication bias. *CI*: confidence intervals.

An awareness of the importance of drug control should be noted in burn wound management. Constant evaluation of wound samples and careful monitoring of antimicrobial resistance is needed to help physicians select the best treatment options for burn patients to avoid treatment failure. Besides, more effective antibiotic stewardship programs should be established. Each burn unit has its own system of surveillance and should be thoroughly sterilized periodically.

We acknowledged that the present study possessed some key limitations. Circumspection should be in order when interpreting these data because it remained unclear whether or not enrolled subjects among included studies could be representative of the national population as shown in our quality assessment. There existed a lack of studies conducted in other places in China and studies that were conducted in the more recent period. The study design of included studies was also limited to our study, as most of them were retrospective single-centre studies. More multicenter

Table 4. Summary of subgroup analyses according to year of isolation.

Drugs	2009-2012[a]		2013-2016[b]		2017-2020[c]		Subgroup comparison[¶]		
	Pooled resistance (95% *CI*)	I^2 (%)	Pooled resistance (95% *CI*)	I^2 (%)	Pooled resistance (95% *CI*)	I^2 (%)	a *vs* b	a *vs* c	b *vs* c
ß-lactam									
Iimipenem	0.37 (0.20-0.41)	97.03	0.28 (0.22-0.35)	84.61	0.40 (0.16-0.66)	96.15	0.15	0.82	0.36
Meropenem	0.30 (0.08-0.58)	96.64	0.27 (0.18-0.36)	89.35	0.37 (0.16-0.62)	86.05	0.82	0.69	0.43
Ceftazidime	0.38 (0.26-0.51)	94.77	0.31 (0.24-0.38)	86.07	0.69 (0.44-0.89)	94.42	0.34	0.02*	<0.01*
Cefepime	0.52 (0.32-0.72)	94.79	0.38 (0.29-0.47)	89.64	0.66 (0.42-0.86)	92.96	0.21	0.35	0.02
Piperacillin	0.55 (0.38-0.73)	94.23	0.47 (0.35-0.60)	90.47	0.57 (0.26-0.86)	95.42	0.47	0.91	0.55
Piperacillin-tazobactam	0.43 (0.23-0.65)	96.91	0.32 (0.21-0.43)	92.49	0.50 (0.18-0.81)	94.25	0.36	0.72	0.29
Aztreonam	0.50 (0.30-0.70)	96.48	0.43 (0.32-0.55)	92.45	0.53 (0.29-0.77)	93.44	0.55	0.85	0.46
Aminoglycosides									
Gentamicin	0.61 (0.51-0.71)	89.7	0.48 (0.39-0.57)	87.75	0.72 (0.32-0.98)	96.04	0.058	0.53	0.17
Amikacin	0.42 (0.28-0.56)	94.7	0.31 (0.22-0.41)	92.64	0.31 (0.07-0.62)	92.16	0.20	0.48	1.00
Fluoroquinolones									
Ciprofloxacin	0.44 (0.28-0.60)	94.85	0.26 (0.16-0.37)	92.12	0.52 (0.25-0.80)	92.23	0.07	0.62	0.08
Levofloxacin	0.37 (0.23-0.52)	93.29	0.28 (0.20-0.37)	87.87	0.67 (0.43-0.87)	93.70	0.29	0.03*	<0.01*

[¶]: Estimates of each subgroup were compared using 'test of interaction', with results expressed as *P*-values. *: *P*-value less than 0.05 indicating statistical significance. 'a/b/c' represent three time periods. *CI*: confidence interval; *vs*: versus.

studies in a prospective design are encouraged in the future. Another limitation was high heterogeneity throughout the analysis. Intrinsic geographic differences unavoidably generated heterogeneous antimicrobial-resistant patterns. The drugs indicated for burn wound management were likely to vary from region to region and drug delivery patterns could change according to the prescription of local physicians. Moreover, those drugs they used might come from multiple pharmaceutical manufacturers. In addition, when analyzing the pooled resistance to CIP, we noticed the existence of publication bias. The reason for that might be that the investigators selectively examined the resistance to fluoroquinolones.

In summary, increasing antimicrobial-resistant strains of *P. aeruginosa* isolated from burn wounds remain a challenge for burn caring in mainland China. It is therefore considered prudent to make the constant monitoring of wound-isolated *P. aeruginosa* and establish more effective antibiotic stewardship programs according to corresponding antimicrobial resistance profile, to prevent treatment failure and select the best treatment options. Meanwhile, more publications are encouraged for better surveillance of resistant patterns and illumination of therapeutic options.

Conflicts of interest statement

The authors declare that there are no conflict of interest statement.

Authors' contributions

GLJ designed the study, performed the literature search, extracted data, and wrote the manuscript. XH performed the literature search, extracted data, done the quality assessment and assisted in manuscript review. YZG was responsible for study design, quality assessment, and revision of manuscript. All the authors analyzed the data and approved the manuscript draft.

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