

Risk Factors for Colonization and Infection With Resistant *Pseudomonas Aeruginosa* in Intensive Care Unit: Protocol for a Systematic Review and Meta-analysis

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Abstract

Background: Infection with resistant *Pseudomonas aeruginosa* (RPA) in Intensive Care Unit (ICU) is known to be either endogenous or exogenous or both, but the roles of each of these contamination routes is yet to be clarified. Data regarding prevalence, risk factors and environmental factors associated with RPA in ICU are very scanty and even when they exist, they seem to be contradictory. So, there is a strong interest in understanding both individual and environmental factors associated with RPA infection. This systematic review aims to investigate individual and environmental factors associated with the colonization and infection with RPA in ICU.

Methodology: MEDLINE (Pubmed), EMBASE (OVID), the Cochrane Library (Wiley), Web of Science, CINAHL (EBSCOHost) and LILACS (BIREME) will be searched from inception onwards. Grey literature will be identified through Google Scholar and open Grey. Two reviewers will independently screen all citations, abstracts and full-text articles. Potential conflicts will be resolved through discussion. Methodological quality including bias will be appraised using appropriate approaches. A narrative synthesis will describe quality and content of the epidemiological evidence. Prevalence, Odds ratio, Relative Risk, Hazard ratio with their respective 95% confidence intervals will be calculated. A meta-analysis of data extracted from eligible studies with similar population and RPA testing will be performed. The analysis will evaluate factors influencing the estimates. A random effect model will be used to summarize effect sizes.

Discussion: Two contrasting hypotheses on risk factors of acquisition, colonisation, and infection of RPA are being debated, especially in a context where available data are scanty or exhibit high discrepancy. Indeed, most of the reviews have been focalized on hospitalised patients, and not in ICU, and few of them really address the environmental factors issue. To fill that gap, this review will combine both analysis of individual and environmental risk factors using prevalence study in ICU and evaluation of different methodologies. These two hypotheses will be tested and challenged, and could serve as a basis for a more in-depth studies to fill the methodological gaps that will be identified as part of this current review.

Systematic review registration: This protocol has been submitted registered with Prospective Register of Systematic Reviews (PROSPERO) on 07 march 2021 under number CRD42021233832

Background

Pseudomonas aeruginosa (PA) is ubiquitous gram-negative bacterium with minimal survival requirements in the environment. It has a remarkable ability to colonize surfaces even in the most constraining environments. PA can cause infection in immunodeficient individuals [1]. It is one of the major pathogens involved in healthcare-associated infections in intensive care units (ICU) [2]. The prevalence of hospital-acquired PA carriage was 15.3% in adult French population hospitalized in ICUs [3]. Furthermore, resistance of *P. aeruginosa* to various antibiotics is increasing as it is the case with the global burden of antibiotics resistance. Indeed, it was recently found that 48.7% were multidrug resistant (MDR) [4]. A cohort study conducted in Spain reported more than 80% of isolates susceptible only to

amikacin and colistin, and 9% only to colistin [5]. Infections due to resistant *Pseudomonas aeruginosa* (RPA) have been associated with an increase morbidity and mortality rates [6–7], increased length of stay in ICU, high number of surgeries and invasive procedures [6–8]. Although existing literature demonstrating increased costs related to resistant Gram-negative infections, data focused on *P. aeruginosa* are limited and somewhat inconsistent [8]. Infections with PA in ICU are known to be either endogenous or exogenous or both, but the role of each of these contamination routes is yet to be clarified [9]. Endogenous transmission has been widely described [2, 11], the main source of contamination being the intestinal microbiota under antibiotic pressure [11]. Exogenous transmission occurs from hydrous environments (tap, sink...), invasive medical devices, other patients and health personnel through their hands [13–14]. Most studies lean towards a predominance of the endogenous source, the exogenous source being more often incriminated in outbreaks [3, 10, 13]. Moreover, the source of RPA in ICU is not well established, as well as factors associated with carriage, colonization and infection [9]. Data regarding prevalence, risk factors and environmental factors associated with RPA in ICU are very scanty and even when they do exist, they seem contradictory. For example, a systematic review performed in 2018 demonstrated that there are considerable gaps and inconsistencies in knowledge regarding risk factors associated with RPA or identifying subgroups of patients at increased risk of acquisition of RPA in hospital [14]. Unfortunately, this systematic review did not specifically address the issue in intensive care units and was limited to endogenous risk factors [14]. There is therefore a growing interest in understanding the individual and environmental factors associated with resistant *P. aeruginosa*, particularly in intensive care units where high rates of morbidity and mortality are being observed.[6, 9].

The main objective of this systematic review will be to investigate individual (endogenous) and environmental (exogenous) factors associated with the colonization and infection with resistant *Pseudomonas aeruginosa* in intensive care units. The secondary objectives of this study will be to (i) estimate the prevalence of resistant *P. aeruginosa* colonisation in ICU, (ii) describe the main risk factors of acquisition and colonisation with resistant *P. aeruginosa* in ICU, and (iii) describe the main environmental sources of acquisition and colonisation with resistant *P. aeruginosa* in ICU.

Methods/design

This systematic review and meta-analysis protocol is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist provided as additional file [15].

Eligibility criteria

Type of studies to be included

This review will include cross-sectional studies, case-control studies (nested or not) and cohort studies (either prospective, retrospective or ambi-directional) conducted in intensive care units (ICUs).

Type of participants

Studies including all patients, admitted in an ICU, whatever the reason of admission and the origin (community, another hospital, or another unit of the same hospital) of patients will be considered. No specific definition of ICU will be applied, and all studies where authors reported as been conducted in an ICU will be considered.

Outcomes

- i. Resistant *P. aeruginosa* is defined as a strain showing intermediate or low susceptibility to an antimicrobial agent.
- ii. Multidrug resistant *P. aeruginosa* is defined as a strain resistant to at least three of the four following drugs: ceftazidime, imipenem, ciprofloxacin, and tobramycin [16].
- iii. Carriage is defined as positive screened specimens. These specimens will be collected from rectal swabs, nasal swabs or tracheal aspiration within 48 hours of patient admission, and once a week during hospitalization [17].
- iv. Colonization is defined as positive clinical specimens and infection as positive clinical specimens with clinical signs confirming infection. In the absence of clinical data, patients with positive clinical specimens will be considered colonised/infected [17].

Inclusion and exclusion criteria

Inclusion criteria for this review are (i) participants admitted in an ICU, (ii) with specimens collected and tested for *P. aeruginosa* (positivity and antimicrobial susceptibility) during hospitalization, (iii) and/or samples collected from the ICU patient's environment (including staff hands and gloves) for *P. aeruginosa* testing.

Search strategy

Six databases will be searched from inception onward, namely MEDLINE (Pubmed), EMBASE (OVID), the Cochrane Library (Wiley), Web of Science, CINAHL (EBSCOHost) and LILACS (BIREME). We will also search for grey literature through Google Scholar and Open Grey.

A search strategy using medical subject headings (MeSH) and text words related to *Pseudomonas aeruginosa*, intensive care units, carriage or colonization or infection will be used as described in Table 1 for MEDLINE (Pubmed), and will be adjusted for the search in other databases cited above. References of articles retrieved will also be manually searched to identify relevant studies which have not been found through initial online searches. For studies that will not be found via internet search, the authors will be directly contacted to have them.

Table 1
Search strategy

Search	Query
#1	Pseudomonas aeruginosa [tw] or Pseudomonas [tw] or P aeruginosa [tw] or Pseudomonadaceae [tw] or Gram-negative bacteria [tw] or gram negative [tw] or bacteria [tw] or Pseudomonas aeruginosa [mesh] or Pseudomonas [mesh]
#2	Intensive care unit [tw] or intensive care units [tw] or ICU [tw] or ICUs [tw] or intensive care [tw] or intensive care units [mesh] or respiratory care units [mesh]
#3	Carriage [tw] or colonization [tw] or colonisation [tw] or acquisition factors [tw] or infection [tw] or contamination [tw] or infected patients [tw] or asymptomatic Infections [mesh] or infections [mesh]
#4	Water [tw] or water tap [tw] or tap [tw] or bed [tw] or gloves [tw] or hands [tw] or environmental [tw] or environment [tw] or exogenous factors [tw] or Sink [tw] or care material [tw] or drains [tw] or surfaces water [mesh] or beds [mesh] or protective gloves [mesh] or environment [mesh]
#5	#3 or #4
#6	#1 and #2 and #5
#7	Date: from inception to December 31th, 2020
#8	No language restriction
#9	#6 and #7 and #8

The search will be conducted by an experienced information specialist, with no language restriction. For studies published in a language other than English, Google translate will be used for translation. The result of electronic searches will be uploaded to Rayyan software [18] for duplicates identification and titles and abstracts' screening [19]. Prisma-P flow diagram template will be used to describe the number or article retrieved and screen at each step [15].

Study selection

Two reviewers will independently screen all studies yielded by the search to confirm and exclude duplicates identified using Rayyan. Then, they will screen the studies against inclusion and exclusion criteria for eligibility. Full texts of eligible studies will therefore be retrieved for deep analysis to decide whether the study will be included or not. When full text will not be available online, they will be requested from author by email or phone call. Disagreement between the two reviewers will be resolved through discussion and consensus. If the disagreement persists after discussion, a third experienced reviewer will act as referee for the final decision. The Kappa statistics will be reported to describe the interrater agreement.

Data extraction

An online google form will be used by two independent reviewers to extract data from each included study. Disagreement between the reviewers will be resolved by discussion and consensus. In case of any uncertainty or when some data will be missing, a request will be sent to authors by email or phone call for clarifications and / or completion of missing data. If two reports contain data from the same study, only the most complete report will be considered. If necessary, more precision will be requested from authors. The following data will be extracted from each report:

- **Information about data selection and extraction:** name of extractor, date of data extraction, confirmation of eligibility of the study.
- **Study characteristics:** First author name, year of publication, hospital level (primary, secondary, or tertiary hospitals), number of recruitment center, study design, enrolment start and end dates and sampling method.
- **Participants:** number of participants, region (s) and country/countries from which participants were recruited, study eligibility criteria, reasons of admission in ICU, age, gender, hospital length of stay.
- ***P. aeruginosa* carriage, colonisation or infection data:** number, type and timing of patients' specimens (both screening and clinical), number and type of environmental specimens, result of *P. aeruginosa* testing and antimicrobial susceptibility, prevalence of *P. aeruginosa* carriage, colonisation and infection.
- **Factors associated with resistant *P. aeruginosa*:** All factors reported in studies will be collected with their corresponding effect estimates (Odds Ratios, Relative risk or Hazard ratios).

Quality of studies and evidence assessment

The methodological quality of studies will be assessed using the Joanna Briggs Institute (JBI) critical appraisal tools for each corresponding study design (cross-sectional, case-control, cohort) [19]. Potential bias in design, conduct and analysis of each study will be appraised by two independent reviewers, with a third experienced reviewer serving as referee in case of disagreement. The quality of the evidence will be judged using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [20]. The grades of evidence will be categorized as follow (1) high "further research is unlikely to change our confidence in the estimate of effect", (2) moderate "further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate", (3) low "further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate" and (4) very low "any estimate of effect is very uncertain". The confidence in evidence will be discussed among authors. A narrative synthesis of the results will be provided according to the grading quality of evidence and strength of recommendations [20].

Data synthesis and management

Prevalence, Odds ratio, Relative Risk, Hazard ratio with their 95% confidence intervals will be calculated from the compiled data. A meta-analysis of data from eligible studies with similar population and *P. aeruginosa* testing will be performed. The analysis will evaluate factors influencing the estimates. A

random effect model will be used to summarize effect sizes. This multivariable analysis will be adjusted for potential confounders.

Heterogeneity between combined studies will be tested using the standard Chi-square test with the Q statistic ($p < 0.10$ statistically significant). The extent of heterogeneity will be quantified using the I² statistics; I² > 50% will be deemed as representing substantial inconsistency or significant statistical heterogeneity [21]. Funnel plots and Egger's regression asymmetry test will be used to perform a publication bias and sensitivity analyses if needed [22]. Where statistical pooling will not be possible, results will be presented in a synthetic narrative form. All the analysis will be performed using Stata version 15 (StataCorp, College Station, Texas).

Discussion

Two contrasting hypotheses are being debated as to the origin of resistant *P. aeruginosa* infection in intensive care unit. The first one suggests that the origin would be endogenous and related to the patient himself [3, 10, 13]. The second one stipulates that the source would be related to the hospital environment [13–14]. The role of the health staff is also considered to be important because they act as a vector through their hands or by care they provide to patients [23]. Data on risk factors of acquisition, colonisation, and infection of resistant *P. aeruginosa* in ICU are scanty, and a high discrepancy exist in available data. Although most of the studies were performed amongst hospitalised patients, studies that assess this risk factors in ICU are very scanty, and few systematic reviews address the issue of environmental factors. To fill that gap, this review will combine analysis of both individual and environmental risk factors with prevalence study of this infection in intensive care units.

In addition, this systematic review will enable establishing the state of art by combining data series and evaluating the different methodologies used in various studies that will be identified. A trend from the two hypotheses could therefore emerge and could serve as a basis for more in-depth studies, especially to fill the methodological gap that will be identified as part of this current review.

The main limitation of the present systematic review will be the restricted access to unpublished data, or to more detailed information when data will be too aggregated. The authors of these studies will be contacted to provide missing information. Another limitation could be the limited number of studies dealing with this quite specific topic. Nevertheless, it is still possible to get heterogenous outcomes in these studies.

Abbreviations

CDBPH: Centre for Development of Best Practices in Health

CRFiMT: Centre for Research on Filariasis and other Tropical Diseases

GRADE: Grading of Recommendations Assessment, Development and Evaluation

ICU (s): Intensive care unit (s)

PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

PROSPERO: Prospective Register of Systematic Reviews

Declarations

Ethics approval and consent to participate

Not applicable as all the data will be secondary data.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study will be available and could be shared with the readers.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

ES, HCND, GSW, and JRZ designed the study and drafted the protocol. CDE critically review and adjusted the search strategy. MGF, MZV, ACZ, SM, POZ reviewed the article for intellectual content. SE and JRZ are the guarantor of this study. All the authors approved the final version of this protocol.

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