

# Cost-effectiveness of the antimicrobial treatment for inpatients infected with *Klebsiella pneumoniae* carbapenemase: a systematic review protocol

Wendel Mombaquer dos Santos<sup>1,2</sup> • Jessica Yumi Matuoka<sup>1,2</sup> • Silvia Regina Secoli<sup>1,2</sup>

<sup>1</sup>School Nursing, University of São Paulo, São Paulo, Brazil, <sup>2</sup>The Brazilian Centre for Evidence-based Healthcare: a Joanna Briggs Institute Centre of Excellence

**Review question/objective:** The objective of this review is to evaluate the cost-effectiveness of antimicrobial therapy treatment for inpatients infected with *Klebsiella pneumoniae* carbapenemase.

More specifically, the review question is: "What is the best evidence on the cost-effectiveness of the antimicrobial treatment for inpatients infected with *Klebsiella pneumoniae* Carbapenemase?"

**Keywords** cost-effectiveness; costs and cost analysis; health care economics and organizations; *Klebsiella pneumoniae*

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## Introduction

Health expenditures are a global concern, representing a significant share of gross domestic product and having a higher growth rate than the world economy.<sup>1</sup> The financing of health systems has been the object of intense interest due to the constant increase in expenses related to the aging of the population and high cost of technological innovations. Medicines account for 20–30% of overall health expenditures and therefore constitute an important part of health service budgets.<sup>2–4</sup>

In Brazil, approximately R\$424 billion is spent annually on health goods and services, of which R\$190 billion is used by the Federal Government for consumption expenses. Of this total, 20.6% – equivalent to R\$84.8 billion – is exempted for the purchase of medicines.<sup>5–6</sup> Medications are indispensable for the cure and treatment of diseases, as well as the relief of clinical signs and symptoms of patients, and this commodity can directly influence the life expectancy of the population and eradicate diseases, bringing economic and social benefits.<sup>7–8</sup> However, globally, more than half of all medicines are prescribed, dispensed or sold inappropriately and half of patients do not use their medicine as prescribed.<sup>9–13</sup>

The use of antimicrobials, among today's drugs, has a major impact on health expenditures. Incorrect prescription, dose or treatment time of antimicrobials add an average of 36% to treatment costs.<sup>11–15</sup> The main consequences of the indiscriminate or undue use of antimicrobials are changes in the expected therapeutic effect, adverse reactions, drug dependence and the appearance of multi-resistant bacteria.<sup>11–13</sup> The latter requires the use of increasingly potent antimicrobials.<sup>11–15</sup> *Klebsiella pneumoniae* carbapenemase (KPC) is a beta-lactamase that confers resistance to all beta-lactams, including carbapenems.<sup>14–17</sup>

*Klebsiella pneumoniae* carbapenemase is the most common carbapenem in the United States (US). Since the first identification of KPC from clinical isolates in the late 1990s in North Carolina, cases have been identified in all US states as of 2015.<sup>18,19</sup> Worldwide, KPC was responsible for 1% of hospital infections in 2001, rising to 30% in 2008.<sup>20,21</sup> The incidence was 2.93 cases per 100,000 person-years, and the proportion of Enterobacteriaceae that was resistant to carbapenem increased from 1% to 4% between 2001 and 2011, and the proportion of KPC increased from 2% to 10%.<sup>22,23</sup> *Klebsiella pneumoniae* carbapenemase cases have also been reported in other regions of the world, including Europe,<sup>24,25</sup> Asia,<sup>26–28</sup> Australia<sup>29</sup> and South America.<sup>30,31</sup>

*Klebsiella pneumoniae* carbapenemase can cause bloodstream infections, mechanical ventilation-associated pneumonia and urinary tract infection,

Correspondence: Wendel Mombaquer dos Santos, wendel@usp.br

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and infections of central venous catheters have also been described.<sup>14,24,26-28,32-35</sup> Mortality, within 30 days of infections by KPC-producing microorganisms, is greater than 40%. Risk factors for KPC mortality include patients undergoing organ or stem cell transplantation, mechanical ventilation, exposure to antimicrobial agents and long periods of hospitalization, especially in intensive care units.<sup>36-41</sup>

The ideal treatment for infections due to carbapenems-producing organisms is uncertain, and antimicrobial options are limited. Management of patients with infections caused by carbapenems-producing organisms should be done in consultation with a specialist in the treatment of multiresistant bacteria.<sup>42</sup> Therapy for KPC treatment includes a combination of antimicrobials such as tigecycline and polymyxin, in addition to carbapenems and aminoglycoside, which are high-cost antimicrobials. The combination of antimicrobials is associated with reduction of mortality, reduction of resistance to monotherapy and lack of alternatives to single drug efficacy.<sup>14,40,42</sup> Inadequate management of infections caused by KPC prolongs hospitalization time, increases morbidity and mortality, and contributes to higher healthcare costs.<sup>43-47</sup>

Given that the irrational use of antimicrobials can increase the cost of treatment by up to four times,<sup>12,13</sup> KPC represents a significant health problem in the hospital environment in that the diversity of antimicrobials used in its treatment may have a clinical and economic impact. The use of high-cost drugs should be evaluated from a perspective where costs and effectiveness are considered. The daily cost for treatment of hospital infections is around R\$158. In a study carried out to evaluate the cost-effectiveness of the treatment of different microorganisms, ceftriaxone was found to be a more cost-effective antibiotic in comparison to levofloxacin.<sup>48,49</sup> In a scenario of rising costs with marginal effectiveness, the discussion of which technology is to be introduced into healthcare systems becomes even more pressing. In this scenario, the importance of KPC economic studies combining these elements stem from the reality of increasing health spending which may affect the sustainability of health systems.

A preliminary search of the CINAHL, Cochrane Database of Systematic Reviews, *JBI Database of Systematic Reviews and Implementation Reports*, MEDLINE and PROSPERO located no systematic reviews that had evaluated the cost-effectiveness

ratio of antimicrobials for treatment of inpatients infected with KPC. To conduct this review, we will use the Joanna Briggs Institute methodology and tools for systematic reviews for economic evidence/cost effectiveness.<sup>50</sup>

## **Inclusion criteria**

### *Participants*

This review will consider studies that have included participants who are 18 years or over, infected by KPC, and have received antimicrobial treatment in a hospital environment. Infection is the invasion of a host organism's bodily tissues by disease-causing organisms, and results from the interplay between pathogens and the defenses of the hosts they infect.

We will exclude studies using antimicrobial treatment for inpatients exclusively colonized by KPC. Colonization is the presence of bacteria on a body without causing disease in the person.

### *Intervention*

This review will relate studies that compare the cost-effectiveness of different antimicrobials for the treatment of KPC infection.

To be included, studies must have estimated the costs relative to the effectiveness of the first antimicrobial therapeutic option compared with the other therapeutic options.

### *Outcomes*

The review aims to identify and synthesize estimates of cost per unit of effect expressed in clinical outcome units. We will consider studies that include cost per avoided deaths, cost per prevention of sepsis, cost per failure avoid, and cost per reduction of length of stay.

### *Context*

The health context is hospital-based independent of the study perspective.

### *Types of studies*

This review will include economic studies with cost-effectiveness design. They may be based on empirical data only or be economic modeling studies.

## **Methods**

### *Search strategy*

The search strategy aims to find both published and unpublished studies. A three-step search strategy

will be utilized in this review. An initial limited search of PubMed will be undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe article (Appendix I). A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference list of all identified reports and articles will be searched for additional studies. Studies published in English, Spanish or Portuguese will be considered for inclusion in this review. Studies published with no restriction of time will be considered for inclusion in this review.

### Information sources

The databases to be searched include:

- CEA (Cost Effectiveness Analysis Registry)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- Embase (Excerpta Medica Database)
- HEED (Health Economic Evaluation Database)
- HTA (Health Technology Assessment Database)
- LILACS (Literature of the Latin American and Caribbean Health Sciences)
- NHS EED (National Health Service Economic Evaluation Database)
- PubMed (US National Library of Medicine National Institutes of Health)
- Science Direct
- Web of Science.

The search for gray literature will include:

- Bank of CAPES for thesis and dissertations
- MedNar
- Google Scholar
- NYAM (New York Academy of Medicine)
- Open Access Theses And Dissertations
- WorldWideScience.org.

### Study selection

Following the search, all identified citations will be collated and uploaded into Covidence software (Covidence, Melbourne, Australia) and duplicates removed. Titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. Studies that meet the inclusion criteria will be retrieved in full and their details imported into Covidence. The full

text of selected studies will be retrieved and assessed in detail against the inclusion criteria. Full text studies that do not meet the inclusion criteria will be excluded and reasons for exclusion will be provided in an appendix in the final systematic review report. Included studies will undergo a process of critical appraisal. The results of the search will be reported in full in the final report and presented in a PRISMA flow diagram. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

### Assessment of methodological quality

Selected studies will be critically appraised by two independent reviewers at the study level for methodological quality in the review using the standardized JBI critical appraisal instrument for Economic Evaluations from the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI). Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Also, methodologic quality of economic studies will be evaluated through critical appraisal of health economic modeling studies.<sup>51,52</sup> Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

All studies, regardless of their methodological quality, will undergo data extraction and synthesis.

### Data extraction

Economic data will be extracted from papers included in the review using the standardized data extraction tool from JBI SUMARI.<sup>53</sup> Extracted data will include: firstly, descriptive data on: i) study population/participants, interventions, comparators, and outcomes; ii) study methodology, including type of assessment design, analytical point(s), source of effectiveness data, price and time used for cost; time period of analysis; sensitivity analysis, measures of resource use, cost and clinical and health effects, and cost-effectiveness; iii) context of the study (geographical, healthcare and cultural); secondly, results for resource use and/or cost and/or cost-effectiveness measures; and thirdly, where possible, the authors' conclusions on factors that promote cost-effectiveness of intervention.

The authors of primary studies will be sought for clarifications or for more information.

### Data synthesis

Data extracted from included studies will be analyzed and summarized to address the review objective/answer the review question using narrative, tables and the JBI Dominance Ranking Matrix (DRM). The data analysis will consider what the data on the characteristics, cost effectiveness results and authors conclusions suggest about the circumstances in which the intervention is likely to be more (or less) cost effective than the comparator/s.

The decision matrix has three possible outcomes for the cost of an intervention of interest balanced against the health outcomes:

- Strong dominance is considered appropriate for decisions clearly in favor of either the treatment or control intervention, from both the clinical effectiveness and cost points of view.
- Weak dominance is where the data support either clinical effectiveness or costs, but not both positions.
- Non-dominance is where the intervention of interest is less effective or costlier.

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## Appendix I:- Search strategy for PubMed

Search ID no.	Search formula	Results
#1.	Klebsiella pneumoniae[Title/Abstract] OR Klebsiella pneumoniae[MeSH Terms]	19666
#2.	Klebsiella rhinoscleromatis[Title/Abstract] OR Klebsiella rhinoscleromatis[-MeSH Terms]	11809
#3.	Klebsiella[Title/Abstract] OR Klebsiella[MeSH Terms]	30547
#4.	Enterobacteriaceae[Title/Abstract] OR Enterobacteriaceae[MeSH Terms]	371639
#5.	Enterobacteria[Title/Abstract] OR Enterobacteria[MeSH Terms]	366782
#6.	Enteric Bacteria[Title/Abstract] OR Enteric Bacteria[MeSH Terms]	366735
#7.	Coliform Bacilli[Title/Abstract] OR Coliform Bacilli[MeSH Terms]	365561
#8.	Sodalis[Title/Abstract] OR Sodalis[MeSH Terms]	365600
#9.	Paracolobactrum[Title/Abstract] OR Paracolobactrum[MeSH Terms]	365532
#10.	Ewingella[Title/Abstract] OR Ewingella[MeSH Terms]	365543
#11.	Leclercia[Title/Abstract] OR Leclercia[MeSH Terms]	365563
#12.	Gram-Negative Facultatively Anaerobic Rods[Title/Abstract] OR Gram-Negative Facultatively Anaerobic Rods[MeSH Terms]	415959
#13.	Gram Negative Facultatively Anaerobic Rods[Title/Abstract] OR Gram Negative Facultatively Anaerobic Rods[MeSH Terms]	415959
#14.	Gram-Negative Bacteria[Title/Abstract] OR Gram-Negative Bacteria[-MeSH Terms]	736352
#15.	Gram Negative Bacteria[Title/Abstract] OR Gram Negative Bacteria[MeSH Terms]	736352
#16.	Gammaproteobacteria[Title/Abstract] OR Gammaproteobacteria[MeSH Terms]	494726
#17.	gamma Proteobacteria[Title/Abstract] OR gamma Proteobacteria[MeSH Terms]	494335
#18.	Proteobacteria gamma[Title/Abstract] OR Proteobacteria gamma[MeSH Terms]	493437
#19.	Proteobacteria[Title/Abstract] OR Proteobacteria[MeSH Terms]	632100
#20.	Bacteria, Purple[Title/Abstract] OR Bacteria, Purple[MeSH Terms]	628333
#21.	Purple Bacteria[Title/Abstract] OR Purple Bacteria[MeSH Terms]	627463
#22.	Klebsiella Infections[Title/Abstract] OR Klebsiella Infections[MeSH Terms]	7827
#23.	Infections, Klebsiella[Title/Abstract] OR Infections, Klebsiella[MeSH Terms]	17289
#24.	Klebsiella Infection[Title/Abstract] OR Klebsiella Infection[MeSH Terms]	7825
#25.	Enterobacteriaceae Infections[Title/Abstract] OR Enterobacteriaceae Infections[MeSH Terms]	92141
#26.	Enterobacterial Infections[Title/Abstract] OR Enterobacterial Infections[-MeSH Terms]	92122

<i>(Continued)</i>		
Search ID no.	Search formula	Results
#27.	Infections, Enterobacterial[Title/Abstract] OR Infections, Enterobacterial[-MeSH Terms]	92567
#28.	Enterobacterial Infection[Title/Abstract] OR Enterobacterial Infection[-MeSH Terms]	92109
#29.	Infection, Enterobacterial[Title/Abstract] OR Infection, Enterobacterial[-MeSH Terms]	92102
#30.	Infections, Enterobacteriaceae[Title/Abstract] OR Infections, Enterobacteriaceae[MeSH Terms]	96270
#31.	Enterobacteriaceae Infection[Title/Abstract] OR Enterobacteriaceae Infection[MeSH Terms]	92112
#32.	Infection, Enterobacteriaceae[Title/Abstract] OR Infection, Enterobacteriaceae[MeSH Terms]	92102
#33.	Gram-Negative Bacterial Infections[Title/Abstract] OR Gram-Negative Bacterial Infections[MeSH Terms]	334760
#34.	Gram Negative Bacterial Infections[Title/Abstract] OR Gram Negative Bacterial Infections[MeSH Terms]	334760
#35.	Infections, Gram-Negative Bacterial[Title/Abstract] OR Infections, Gram-Negative Bacterial[MeSH Terms]	335657
#36.	Bacterial Infection, Gram-Negative[Title/Abstract] OR Bacterial Infection, Gram-Negative[MeSH Terms]	349127
#37.	Gram-Negative Bacterial Infection[Title/Abstract] OR Gram-Negative Bacterial Infection[MeSH Terms]	334600
#38.	Infection, Gram-Negative Bacterial[Title/Abstract] OR Infection, Gram-Negative Bacterial[MeSH Terms]	334409
#39.	Infections, Gram Negative Bacterial[Title/Abstract] OR Infections, Gram Negative Bacterial[MeSH Terms]	335657
#40.	Bacterial Infections, Gram-Negative[Title/Abstract] OR Bacterial Infections, Gram-Negative[MeSH Terms]	346204
#41.	Bacterial Infections, Gram Negative[Title/Abstract] Bacterial Infections, Gram Negative[MeSH Terms]	11801
#42.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41	867253
#43.	Cost Effectiveness[Title/Abstract] OR Cost Effectiveness[MeSH Terms]	92668
#44.	Effectiveness, Cost[Title/Abstract] OR Effectiveness, Cost[MeSH Terms]	69591
#45.	Cost-Utility Analysis[Title/Abstract] OR Cost-Utility Analysis[MeSH Terms]	70227

<i>(Continued)</i>		
Search ID no.	Search formula	Results
#46.	Analyses, Cost-Utility[Title/Abstract] OR Analyses, Cost-Utility[MeSH Terms]	70115
#47.	Analysis, Cost-Utility[Title/Abstract] OR Analysis, Cost-Utility[MeSH Terms]	69588
#48.	Cost Utility Analysis[Title/Abstract] OR Cost Utility Analysis[MeSH Terms]	70227
#49.	Cost-Utility Analyses[Title/Abstract] OR Cost-Utility Analyses[MeSH Terms]	69812
#50.	Economic Evaluation[Title/Abstract] OR Economic Evaluation[MeSH Terms]	73247
#51.	Economic Evaluations[Title/Abstract] OR Economic Evaluations[MeSH Terms]	71175
#52.	Evaluation, Economic[Title/Abstract] OR Evaluation, Economic[MeSH Terms]	69587
#53.	Evaluations, Economic[Title/Abstract] OR Evaluations, Economic[MeSH Terms]	80049
#54.	Marginal Analysis[Title/Abstract] OR Marginal Analysis[MeSH Terms]	69738
#55.	Analyses, Marginal[Title/Abstract] OR Analyses, Marginal[MeSH Terms]	72469
#56.	Analysis, Marginal[Title/Abstract] OR Analysis, Marginal[MeSH Terms]	89582
#57.	Marginal Analyses[Title/Abstract] OR Marginal Analyses[MeSH Terms]	69614
#58.	Cost-Effectiveness Analysis[Title/Abstract] OR Cost-Effectiveness Analysis[MeSH Terms]	71678
#59.	Analysis, Cost-Effectiveness[Title/Abstract] OR Analysis, Cost-Effectiveness[MeSH Terms]	69588
#60.	Cost Effectiveness Analysis[Title/Abstract] OR Cost Effectiveness Analysis[MeSH Terms]	71678
#61.	economics, pharmaceutical[Title/Abstract] OR economics, pharmaceutical[MeSH Terms]	2702
#62.	pharmacoeconomics[Title/Abstract] OR pharmacoeconomics[MeSH Terms]	3438
#63.	#43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62	127797
#64.	#42 OR #63	1520