THE RELATIONSHIP BETWEEN THE INCREASED INCIDENCE OF INFECTIOUS AND CONTAGIOUS BACTERIAL DISEASES AND COVID-19 PANDEMIC: SYSTEMATIC LITERATURE REVIEW

A RELAÇÃO ENTRE O AUMENTO DA INCIDÊNCIA DE DOENÇAS BACTERIANAS E CONTAGIOSAS E A PANDEMIA DE COVID-19: REVISÃO SISTEMÁTICA DA LITERATURA

CAROLINA DE MARQUI MILANI

Graduando em Medicina pela Faculdade Ceres – FACERES, em São José do Rio Preto/SP.

RAFAELA DO NASCIMENTO THOMÉ

Graduando em Medicina pela Faculdade Ceres – FACERES, em São José do Rio Preto/SP.

ALEXANDRE DANTAS GIMENES

Doutor e Mestre em Ciências pelo programa de Biologia Estrutural e Funcional da Universidade Federal de São Paulo (UNIFESP-EPM). Graduado em Farmácia Bioquímica pelo Centro Universitário da Fundação Educacional de Barretos. Professor do curso de medicina da Faculdade Ceres – FACERES, em São José do Rio Preto/SP.

FLÁVIO AUGUSTO NAOUM

Pós-doutor em hemoglobinopatias pelo North Middlesex University Hospital e Royal London Hospital, Inglaterra. Doutor em Medicina Interna pela Faculdade de Medicina de São José do Rio Preto. Mestre em Medicina na área de Hematologia pela Universidade de São Paulo. Graduado em Medicina pela Faculdade de Medicina de Marília e Residência Médica em hematologia e hemoterapia pela Santa Casa de São

Paulo. Professor do curso de medicina da Faculdade Ceres – FACERES, em São José do Rio Preto/SP.

ABSTRACT

Introduction: Infectious and contagious bacterial diseases are the main cause of mobility and mortality worldwide and are related to pathogens such as *Streptococcus pneumoniae, Haemophilus influezae*, and *Neisseria meningitidis* reside in healthy people upper respiratorytract, and it's transmitted by direct contact, by respiratory ways. Substantial increase in hospitalizations, the absence off systemized protocol for appropriate attendance, the lack of diagnosis tests and indiscriminate use of antimycobacterial in hospitals during the sanitary emergency, specially broad-spectrum antibiotics, culminated in substantial increase on COVID-19 secondary infection cases by multiresistant bacteria.

Aims and Objectives: To understand the relation between the increase of bacterial infectious and contagious diseases and the pandemic scenario, identify most frequent infectious diseases, their transmission patterns and control and predict what will be the consequences of this new pathological scenario in the future.

Methods: Systematic Literature Review using Pubmed/Medline, Cochrane Library and BVS (Biblioteca virtual em saúde) database.

The following terms, their synonyms and combinations were used in this study.: "communicable", "bacterial", "diseases", "AND" "COVID-19". The quality of the articles was evaluated using the Quality Assessment Tool from the Department of Health and HumanServices (NHLBI).

Results: 258 references were found during electronic research, 9 (nine) of them being eligible and included in this study. In 100% of studied articles (nine) were observed indiscriminate use of antibiotics during the study period. In most articles, were observed increase on the incidence of multidrug resistant bacterial infections. Four of the isolated bacteria were more expressive: *K. pneumoniae*, *Acinetobacter spp.*, *S. aureus* e *E. coli*. Importance of vigilance and potential increase in multidrug resistant bacterial infection incidence in COVID-19 pandemic era, related to antibiotic general usage increasement were recognized.

Conclusion: Indiscriminate antimicrobial prescription during pandemic period related to bacterial resistance increasement justify contagious respiratory infection increasement. The concern about bacterial resistance related to excessive antibiotic usage in this period and indication to alternative treatments that replaces first choices is emphasized. Surveillance protocols are highlighted.

Keyword: Communicable; bacterial; diseases; AND covid-19.

RESUMO

Introdução: As doenças bacterianas infecciosas e contagiosas são a principal causa de mobilidade e mortalidade em todo o mundo e estão relacionadas a patógenos como Streptococcus pneumoniae, Haemophilus influezae e Neisseria meningitidis residem no trato respiratório superior de pessoas saudáveis, e são transmitidas por contato direto, por vias respiratórias. Aumento substancial de internações, ausência de protocolo sistematizado para atendimento adequado, falta de exames diagnósticos e uso indiscriminado de antimicobacteriano nos hospitais durante a emergência sanitária, especialmente antibióticos de amplo espectro, culminaram em aumento substancial de casos de infecção secundária por COVID-19 por multirresistentes bactérias.

Objetivos: Compreender a relação entre o aumento de doenças infecciosas e contagiosas bacterianas e o cenário pandêmico, identificar as doenças infecciosas mais frequentes, seus padrões de transmissão e controle e prever quais serão as consequências deste novo cenário patológico no futuro.

Métodos: Revisão Sistemática da Literatura utilizando Pubmed/Medline, Biblioteca Cochrane e base de dados BVS (Biblioteca virtual em saúde).

Os seguintes termos, seus sinônimos e combinações foram utilizados neste estudo.: "transmissível", "bacteriano", "doenças", "AND", "COVID-19". A qualidade dos artigos foi avaliada por meio da Ferramenta de Avaliação de Qualidade da Departamento de Saúde e Serviços Humanos (NHLBI).

Resultados: foram encontradas 258 referências durante a pesquisa eletrônica, sendo 9 (nove) elegíveis e incluídas neste estudo. Em 100% dos artigos estudados (nove) foi observado uso indiscriminado de antibióticos no período estudado. Na maioria dos artigos, observou-se aumento na incidência de infecções bacterianas multirresistentes. Quatro das bactérias isoladas foram mais expressivas:K. pneumoniae, Acinetobacter spp., S. aureus e E. coli. A importância da vigilância e o potencial aumento da incidência de infecção bacteriana multirresistente na era da pandemia de COVID-19, relacionados ao aumento do uso geral de antibióticos, foram reconhecidos.

Conclusão: A prescrição indiscriminada de antimicrobianos durante o período de pandemia relacionada ao aumento da resistência bacteriana justifica o aumento da infecção respiratória contagiosa. Ressalta-se a preocupação com a resistência bacteriana relacionada ao uso excessivo de antibióticos neste período e a indicação de tratamentos alternativos que substituam as primeiras escolhas. Os protocolos de vigilância são destacados.

Palavra-chave: Transmissível; bacteriana; doenças; covid - 19.

1 INTRODUCTION

Infectious and contagious bacterial diseases such as pneumonia, meningitis and sepsis are the main causes of mobility and mortality worldwide, in all age groups, according to available data from the World Health Organization (WHO).[1,2]. Most times isolated bacteria in serious cases are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*. Those bacteria reside in healthy people upper respiratory tract, and it's transmitted by direct contact, through respiratory ways.[2]

Lower respiratory bacterial infections take sixth place in mortality causes in all ages, being the most common in children under 5 years old. Around 400 million lower respiratory bacterial infections are filed all years, that leads to 2,5 million deaths per year. [3,4]

New studies have shown an increasing number of infections by these pathogens, along with changes in the infection patterns, especially in the last years, since the beginning of COVID-19 pandemic, in the end of 2019 when were also observed higher number of cases of multi resistant bacteria infections in these new listed cases.[5]

Multi resistant bacteria infections besides being the main cause of child mobility and mortality worldwide, represents great impact for the economy.[6] There for, considering the increase of antimicrobial prescription, the priority concerns from the World Health Organization (WHO) regarding multi resistant bacteria are emphasized, [1,2] and shows the necessity of further studies that can identify the new scenario for infectious diseases after the beginning of COVID-19 pandemic.

An example that justifies those needs are the New Delhi samples of *Klebsiella* pneumoniae that were observed and are becoming completely resistant to last generation carbapenem antibiotics, the last resort available nowadays to fight super resistantbacteria. [1,7]

It is valid to append interrogatives about the increase in the number of bacterial infections that pandemic scenario generated by SARS-COV-2 virus has caused, leading to numerous social and economical impacts, and especially health impacts. Substantial increase in hospitalizations, the absence off systemized protocol for appropriate attendance, the lack of diagnosis tests and indiscriminate

use of antimicrobacterial in hospitals during the sanitary emergency, specially broad-spectrum antibiotics, culminated in substantial increase on COVID-19 secondary infection cases by multi resistant bacteria, mainly in severe cases patients with invasive interventions. [8,9,10]

Studies have shown that antimicrobials were prescribed to at least 70% of hospitalized COVID-19 patients. Around 3,6% of hospitalized COVID-19 patients tested positive to secondary bacterial diseases, versus 20% after 48 hours of hospitalization. In 47% of confirmed secondary infections patients were observed multi resistant bacterial infection, being *K. pneumoniae* and *Acinetobacter spp.* the most common on those cases. [9,10]

Currently there is little data available regarding the perspective of infectious and contagious bacterial diseases incidence for the years to come. However, there is evidence that sustains the theory that substantial increment in multi resistant bacterial infection cases is to come all around the world and this topic has been part of the clinical practice, in hospitals and in ambulatory attendance. In that regard, the aim of this study was, by a systematic literature review, to understand the relation between the increase of bacterial infectious and contagious diseases and the pandemic scenario, identify most frequent infectious diseases, their transmission patterns and control and predict what will be the consequences of this new pathological scenario in the future.

METHODS

STUDY DESIGN

Systematic literature review study registered in PROSPERO, international systematic review database in health and social assistance of *Center for Reviews* and *Dissemination of University of York*.

SEARCH STRATEGY

Three online databases were selected to participate in this study: Pubmed/Medline, Cochrane Library and BVS (Biblioteca virtual em saúde). The following terms, their synonyms and combinations were used in this study.:

"communicable", "bacterial", "diseases", "AND" "COVID-19", with controlled vocabulary on the search strategy in each database, Pubmed/Medline (MeSH terms), Cochrane Library (DeCs terms) amd BVS (Biblioteca virtual em saúde). (DeCs terms).

STUDY SELECTION

The following interrogative was made to accomplish this literature review research: Why has there been an increase in the incidence of infectious and contagious bacterial diseases in COVID-19 pandemic?

Study population includes multi resistant bacteria in patients infected or not by COVID-19 during the pandemic. The interventions studied were the excessive prescription of antibiotics and the lack of tracking and data about the incidence of infectious and contagious bacterial diseases during the pandemic. Those results include both quantity and quality results. (Table 1).

Table 1. Eligibility criteria PICOT.

| PICOT Interrogative | Why has there been an increase in the incidence of infectious and |
|------------------------|---|
| | Contagious bacterial diseases in COVID-19 pandemic? |
| Population | Infectious and contagious bacterial diseases |
| Intervention | Drug treatments offered to patients diagnosed with COVID-19 |

| Compare | - |
|---------------|--|
| Outcome | Explanations for the increased incidence of infectious |
| | diseases ofbacterial origin in the COVID19 pandemic. |
| Type of study | Experimental and observational. |

All studies identified by the initial research on the databases were filed in a database in Excel software (Version 16.4). The following eligibility criteria were adopted: (1) studies published in the last 5 years (2017 to April 2022); (2) studies written in English or Portuguese; (3) studies that included antibiotic prescription; (4)

studies with full texts available; and (6) gray literature, review studies, serial cases, case studies, abstracts of proceedings and conferences, studies protocols, comment articles, letters to the editor and policy briefs were excluded. By the end of this process, the full texts of the studies considered potentially relevant and independently selected by three study authors were obtained for final inclusion or exclusion based on the present criteria. The quality evaluation tools from the study of the Department of Health and Human Services [11] were used to evaluate the quality of included articles.

STAGE 1: IDENTIFICATION OF THE ARTICLES BY ELECTRONIC DATABASE RESEARCH.

Two independent reviewers made the electronic database research. Posteriorly, the titles and identified study abstracts were independently evaluated as to suitability for the aims of the research. Were excluded the studies that did not approach the incidence of infectious and contagious bacterial diseases. Disagreements were resolved by consensusbetween the two reviewers, or by a third reviewer when necessary. Duplicate studies were removed.

STAGE 2: ELIGIBILITY ASSESSMENT OF FULL-TEXT ARTICLES

Studies selected according to eligibility criteria were read in full text. Throughout the selection process, uncertainties were discussed among the authors until a consensus was reached. In the different phases of the systematic review, a flow of information is originated. As for information related to eligibility, studies that did not specifically address possible explanations for the increase in infectious diseases during the pandemic were excluded. Assessment of the methodological quality of the reviewed articles was performed using the quality assessment tools available from the US Department of Health and Human Services.[11]

STAGE 3: STUDIES INCLUDED IN THE QUALITATIVE SYNTHESIS

The number of articles identified, screened, assessed for eligibility and included in this review was recorded, as were the reasons for exclusion. The characteristics (location, design, sample size, methods, results and conclusions) of each study were recorded and summarized. The methodology of the studies and the measures of evaluation of the results were varied, therefore it was chosen to carry out a qualitative synthesis, instead of combining the data in a meta-analytical statistical approach.

This systematic review was performed based on the guidelines proposed by the Preferred Reporting Items for Systematic Reviews (PRISMA).[12] A flowchart with the different phases of a systematic review, and the description of information regarding the number of articles identified, included and excluded and the reasons for exclusions, originated in this review (Figure 1).

RESULTS

In the article identification stage, 258 references were found during the electronic search: 174 (Pubmed/Medline), 11 (Cochrane Library) and 73 (BVS (Biblioteca virtual em saúde)). After reading the title, 73 articles were eliminated due to duplicity. In the selection ofarticles, of the 185, five were eliminated because they did not have full texts available. A total of 180 abstracts were evaluated for adequacy to the established eligibility criteria, with 171 full-text articles excluded, with justification (Figure 1).

The nine selected articles followed to the bibliographic reading stage, proceeding with their complete reading, and included in the present study. These articles were analyzed regarding the aime of the study, study design, the population studied, the most frequent bacterial infectious and contagious diseases related to the pandemic, the relationship with the indiscriminate use of antibiotics and its consequences. Table 2 presents the analyzed characteristics of the selected articles.

Two studies were published in England (2,13), one in the United States of

America (5), South Korea (6), one in Australia (14), one in Iran (9), one in Belgium (4), one in Qatar (8), and one in India (10). Most studies were observational case-control studies (2, 4, 5, 6, 8, 9, 10, 14). There was one randomized clinical trial (13). Among analytical studies, the largest sample was 362,581 subjects (6), and the smallest sample was 38 subjects (9).

In 100% of the articles studied (nine) studies, indiscriminate use of antibiotics was observed during the study period (2, 4, 5, 6, 8, 9, 10, 13, 14). In most articles, an increase in the incidence of infections caused by antibiotic-resistant bacteria was observed. Of the bacteria isolated, four were more expressive: *K. pneumoniae, Acinetobacter spp., S. aureus* and *E. coli* (2, 6, 8, 9, 10, 13, 14).

On the other hand, only one article did not observe an increase in the incidence of infections caused by antibiotic-resistant bacteria, due to the social isolation measures adopted during the pandemic (5), and one states that the observed reduction was due to the interruption of surveillance and surveillance documentation of these diseases during the pandemic (4). The method of transmission of the infections mentioned in all articles was the transmission of the infection through direct contact with an infected person, for example, during a handshake followed by touching the eyes, nose or mouth, or with contaminated objects and surfaces. (2, 4, 5, 6, 8, 9, 10, 13, 14).

The nine articles recognized the importance of surveillance and the potential increase in the incidence of infections caused by antibiotic-resistant bacteria in the era of the COVID-19 pandemic, resulting from the increase in the widespread consumption of antibiotics, immune deregulation and lower adherence to measures. of infection control and prevention (2, 4, 5,6, 8, 9, 10, 13, 14).

All included studies were analyzed using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (U.S. Department of Health & Department (Table 3).

DISCUSION

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Personalidade Acadêmica Homenageada: Ivan Dias da Motta (Universidade Estadual de Maringá – UEM)

It can be observed, in the nine articles included in this literature review, that the indiscriminate administration of antibiotics during the pandemic period with a consequent increase in bacterial resistance represents the explanation for the increase in contagious infections of bacterial origin after the beginning of the COVID19 pandemic. Severely hospitalized COVID patients were most associated with over dosage of antibiotics during treatment, even those without secondary infections. [8,9,10] B-lactamase-b-lactamase inhibitors (piperacillin-tazobactam, cefoperazone sulbactam) and carbapenems were the most prescribed antibiotics for COVID patients, even though there are no data to support the administration of broad-spectrum antibiotics for these patients.[14]

As a possible consequence of the overuse of these drugs, increases were observed in the rates of infections with multidrug-resistant bacteria and in the rates of carbapenem resistance among pathogens isolated in the studies. The majority of prescriptions were for antimicrobials in the reserve category in the WHO AWare classification, that is, antibiotics of last resort, leading to a worsening of already alarming levels of antibiotic resistance.[10]

There was not an exclusive association of improvement in COVID-19 patients treated with antibiotics and those who did not, when not associated with secondary infections.[9]

The interpretations of the articles reveal a potential increase in cases of infections by multidrug-resistant bacteria in the coming years. [2,10] In addition to the excessive use of antibiotics, especially those of broad spectrum, social isolation during the pandemic can be cited as responsible for the possible increase in multidrug-resistant bacterial infections.[9]

In this way, it can be inferred that we will be dealing in the coming years with the consequences of the increase in bacterial resistance and the fragility of the immune system, especially in preschool children, resulting from the protocols adopted during the pandemic.

Another situation that we consider answering our research question of the present study and that is not mentioned by the articles analyzed in this literature review is the lack of supply of medicines in developing countries. Routinely used

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and first-choice drugs for the treatment of contagious infectious respiratory diseases of bacterial origin, such as amoxicillin and azithromycin, have become difficult to access due to shortages.

It is being observed in developing countries that the shortage of medicines represents a problem for patients with diseases dependent on outpatient medicines. In addition, there are also reports of household stockpiling of drugs identified with potential for treating COVID19 and personal protective equipment.[15]

The shortage has contributed to the indication of other drugs that would not be the first choice, that is, the lack of first choice drugs leads to the use of second or third choice alternatives, usually with a broader spectrum. An example that can be used to highlight the consequences of this scenario is the shortage of the antimicrobial penicillin between 2014 and 2019 in Brazil, the main drug for the treatment of syphilis. When the prescription of penicillin was replaced by Benzylpenicillin and this alternative treatment, in addition to being a longer and less effective treatment, ended up providing an increase in the selective pressure of bacteria and a consequent contribution to an increase in bacterial resistance.[15]

Therefore, there is a clear need for efficient screening and surveillance to monitor the growth of infections with multidrug-resistant bacteria, as well as clearer and stricter protocolsfor the administration of antibiotics in all sectors.[13]

Most infectious diseases of bacterial origin reported in the studies were secondary hospital infections, highlighting poor infection control and poor hygiene practices and prevention of cross-infection in these environments. The importance of concern about the transmission of infections among hospitalized patients with COVID-19 by health professionals is highlighted, highlighting the need to reinforce hygiene protocols and prevention of cross-infection in all health services.[10]

This study had some limitations. This is a systematic review; although the main search strategy was broad, our selection criteria may have missed articles. We excluded gray literature, case series, case studies, proceedings abstracts, parts of commentary, and protocols. The theme, the time of the pandemic and the emergency situation experienced restricted the performance of clinical trials. More studies are needed to measure the future impact of justifications for the increase in

infectious diseases of bacterial origin during the COVID19 pandemic.

CONCLUSION

The evidence found indicates that the indiscriminate administration of antibiotics during the pandemic period with a consequent increase in bacterial resistance is considered the justification for the increase in contagious respiratory infection of bacterial origin. The concern about bacterial resistance is highlighted, which, in addition to being related to the excessive use of antibiotics in this period, is also related to the indication of alternative treatments that replace the first choices. More efficient surveillance and dosage protocolsneed to be established, as well as diagnostic practices aimed at using specific spectrum antimicrobials, reducing mortality, hospitalization time and the growth of bacterial resistance.

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