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ORIGINAL ARTICLE

Impact on the clinical evolution of patients with COVID-19 from an Intensive Care Unit with isolation of *Candida* spp. in respiratory samples

Impacto na evolução clínica de pacientes com COVID-19 de uma Unidade de Terapia Intensiva com isolamento de Candida spp. em amostras respiratórias

Impacto en la evolución clínica de pacientes con COVID-19 de una Unidad de Cuidados Intensivos con aislamiento de Candida spp. en muestras respiratorias

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ABSTRACT

Background and Objectives: several patients with COVID-19 require hospital admission due to severe respiratory complications and undergo intensive care with mechanical ventilation (MV) support. Associated with this situation, there is an increase in fungal co-infections, which has a negative impact on the outcome of COVID-19. In this regard, this study intended to compare *Candida* spp. incidence in the respiratory tract of patients admitted in the COVID and General Intensive Care Units (ICU) at a teaching hospital in 2021. **Methods:** the results of protected tracheal aspirate samples from 556 patients admitted to the COVID ICU and 260 to General ICU as well as the respective records. **Results:** of the patients analyzed, 38 revealed a positive sample for *Candida* in the COVID ICU and 10 in the General ICU, with an incidence of 68.3/1000 and 38.5/1000, respectively. Males were predominant in both wards. The most affected age group was the population over 60 years old, and the average hospital admission for the COVID ICU was 22.1 years, and for the General ICU, 24.2. **Conclusion:** *Candida albicans* was the most frequently isolated species, and the mortality rate in patients positive for *Candida* was higher in patients with COVID-19 compared to patients in the General ICU, suggesting that patients infected with SARS-CoV-2, admitted to the ICU under MV, are more predisposed to colonization by *Candida* spp., which can have a fatal outcome in these patients.

Keywords: *COVID-19. SARS-CoV-2. Coinfection. Candida. Mechanical Ventilation.*

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RESUMO

Justificativa e objetivos: muitos pacientes com COVID-19 necessitam de hospitalização devido às complicações respiratórias graves, e são submetidos a cuidados intensivos com suporte de ventilação mecânica (VM). Associado a esse quadro, verifica-se o aumento de coinfecções fúngicas, que tem impacto negativo no desfecho da COVID-19. Nesse sentido, este estudo pretendeu comparar a incidência de *Candida* spp. no trato respiratório de pacientes internados nas Unidades de Terapia Intensiva (UTI) COVID e Geral em um hospital escola em 2021. **Métodos:** foram avaliados os resultados de amostras de aspirado traqueal protegido provenientes de 556 pacientes internados na UTI COVID e 260 na UTI Geral, bem como os respectivos prontuários. **Resultados:** dos pacientes analisados, 38 revelaram amostra positiva para *Candida* na UTI COVID e 10 na UTI Geral, com incidência de 68,3/1000 e 38,5/1000, respectivamente. O sexo masculino foi predominante em ambas as alas. A faixa etária mais acometida foi a população acima de 60 anos, e a média de internação para a UTI COVID foi de 22,1 anos, e para a UTI Geral, 24,2. **Conclusão***: Candida albicans* foi a espécie isolada com maior frequência, e a taxa de mortalidade em pacientes com positivos para *Candida* foi maior em pacientes com COVID-19 em relação aos pacientes da UTI Geral, sugerindo que pacientes infectados com SARS-CoV-2, internados em UTI sob VM, são mais predispostos à colonização por *Candida* spp., que pode ter um desfecho fatal nesses pacientes.

Descritores: *COVID-19. SARS-CoV-2. Coinfecção. Candida. Ventilação Mecânica.*

RESUMEN

Justificación y objetivos: muchos pacientes con COVID-19 requieren hospitalización debido a complicaciones respiratorias graves y se someten a cuidados intensivos con soporte de ventilación mecánica (VM). Asociado a esta situación, hay un aumento de las coinfecciones fúngicas, lo que repercute negativamente en el desenlace de la COVID-19. En este sentido, este estudio pretendió comparar la incidencia de *Candida* spp. en el tracto respiratorio de pacientes ingresados en las Unidades de Cuidados Intensivos (UCI) COVID y General de un hospital escuela en 2021. **Métodos:** los resultados de muestras de aspirado traqueal protegidas de 556 pacientes ingresados en la UCI COVID y 260 en el UCI General, así como los respectivos registros. **Resultados:** de los pacientes analizados, 38 presentaron muestra positiva a *Candida* en UCI COVID y 10 en UCI General, con una incidencia de 68,3/1000 y 38,5/1000, respectivamente. Los machos predominaban en ambas alas. El grupo de edad más afectado fue la población mayor de 60 años, y la hospitalización promedio en la UCI COVID fue de 22,1 años, y en la UCI General, de 24,2. **Conclusiones:** *Candida albicans* fue la especie aislada con mayor frecuencia, y la tasa de mortalidad en pacientes positivos para Candida fue mayor en pacientes con COVID-19 en comparación con los pacientes en la UCI General, lo que sugiere que los pacientes infectados con SARS-CoV-2, ingresados en la UCI bajo VM, están más predispuestos a la colonización por *Candida* spp., lo que puede tener un desenlace fatal en estos pacientes.

Palabras-clave: *COVID-19. SARS-CoV-2. Coinfección. Candida. Ventilacion Mecanica.*

INTRODUCTION

COVID-19 (Coronavirus Disease-2019) is characterized by mild to moderate respiratory illness, with symptoms such as fever, cough, fatigue and breathing difficulties, and, in severe cases, results in Acute Respiratory Distress Syndrome (ARDS). In addition to the harmful effects caused by the virus itself, such as alteration of the immune response and direct damage to pulmonary and extrapulmonary tissues, may be accompanied by infections caused by other microorganisms.[1] The high prevalence of morbidity and mortality in patients with COVID-19 is associated with fungal and bacterial co-infection, especially among those suffering from ARDS.[2]

Often, critically ill patients with COVID-19 who develop ARDS are admitted to Intensive Care Units (ICUs), where invasive monitoring, such as using mechanical ventilators and intravenous catheters, can allow the entry of opportunistic pathogens.[3] Furthermore, the widespread use of immunosuppressive medications, such as systemic corticosteroids, and the prolonged use of broad-spectrum antibiotics, together with the tissue damage caused by SARS-CoV-2 (Coronavirus Severe Acute Respiratory Syndrome-2), increase susceptibility. of these patients to invasion by commensal yeasts, causing deep invasive fungal infections.[4]

According to studies, invasive fungal infection (IFI) associated with COVID-19 had an incidence that varied between 4 and 27.7%, with a higher occurrence in cases admitted to ICUs, candidiasis was one of the most commonly reported IFI, representing an associated mortality rate of 40%.[1, 5, 6]

In healthy individuals, *Candida* species live as commensals, however, in hosts with a weakened immune system, they can cause infections.[7] Bronchial colonization by *Candida* spp. It is prevalent among patients who use mechanical ventilation (MV), being found in approximately 30% of people who use it for more than 48 hours and in 50% of those diagnosed with ventilator-associated pneumonia (VAP). Still in the study by Erami *et al*. (2022), the most common comorbidities among patients colonized

by *Candida* in the respiratory tract included diabetes, renal disorders, malignancies, and cardiovascular diseases.[2]

Due to the complicated medical situations of COVID-19 patients and inadequate collection of clinical samples, most fungal infections in this group of patients are misidentified. Identification and diagnosis of fungal infections have been a challenge for many researchers; therefore, isolation of *Candida* spp. in the lower airways should be interpreted with caution as causative agents of pulmonary disease.[6]

In this regard, secondary fungal infections can complicate the prognosis of patients with COVID-19. Therefore, it is essential to carry out a specific diagnosis as well as understand the antifungal susceptibility profile of *Candida* spp.. The appreciation of these results, together with patients' clinical condition, must be interpreted by the clinician, aiming for an appropriate treatment for a possible fungal co-infection with SARS-CoV-2.[4,8]

Considering the above, this study aims to compare *Candida* spp. incidence in the respiratory tract of patients admitted to the COVID ICU and General ICU in a teaching hospital in 2021.

METHODS

This is a descriptive, documentary and retrospective study, with a quantitative approach, carried out in a public teaching hospital located in the city of Cascavel, Paraná. This hospital has 298 beds, with 60 General ICU beds, and, during the COVID-19 pandemic, 70 beds allocated to COVID ICU.

The criteria for data collection included analysis of medical records of patients admitted to the COVID ICU (with a positive diagnosis for SARS-CoV-2) and General ICU (with a negative diagnosis for SARS-CoV-2) between January and December 2021, without sex restriction, with age including young people, adults and elderly people, who presented a positive diagnosis for yeast isolation in protected tracheal aspirate samples. Cultures with counts ≥105 CFU/mL, without the isolation of another microorganism, were considered positive. Microorganism identification was carried out by automation using VITEK®2 (BioMérieux, France), in accordance with the manufacturer's recommendations. Data were collected in the Philips Tasy® electronic medical record system. The variables collected in the system were comorbidities, use of invasive procedures such as MV, MV length, tracheostomy, orotracheal tube, nasoenteral tube (NET), nasogastric tube (NGT), central venous access (CVA), peripheral venous access (PVA), indwelling urinary catheter (IUC), length of admission, use of antimicrobials and corticosteroids, in addition to sex, age, sector of origin of admission, clinical outcome, and species of *Candida*. Patients who did not have a confirmed or negative result by RT-PCR for SARS-CoV-2 were excluded from the research.

Microsoft Office Excel® version 2010 was used to tabulate the data. The incidence of pulmonary candidiasis was calculated using the ratio, in which the numerator was the number of episodes of pulmonary candidiasis during the study period, and the denominator was the number of patients on MV per day in the same period, multiplying the result by 1,000. To assess the association between qualitative variables, the chi-square test was used, considering a significance level of 5%, with $p < 0.05$ being statistically significant. To define the factors associated with the outcome (death), a mathematical model was adjusted using the binary logistic regression method, using the criterion of $p < 0.10$ of the Odds Ratio being statistically equivalent to 1.

Data collection from patient records occurred after the study was approved by the local Ethics Committee, under Certificate of Presentation for Ethical Consideration (CAAE - *Certificado de Apresentação para Apreciação Ética*) 65827722.2.0000.0107 and favorable Opinion 5.798.336. The research was conducted in accordance with the required ethical standards (Resolutions 466/2012, 510/2016, 580/2018 of the Ministry of Health).

RESULTS

From January to December 2021, protected tracheal aspirate cultures were performed from 556 patients diagnosed with SARS-CoV-2 admitted to the COVID ICU and from 260 patients admitted to the General ICU (with a negative diagnosis for SARS-CoV-2), as, of these, 38 and 10 had positive cultures for *Candida* spp., respectively. The incidence of pulmonary candidiasis was 68.3/1000 patients per day in the COVID ICU and 38.5/1000 patients per day in the General ICU.

In the COVID ICU, 23 (60.5%) were male, and 15 (39.5%) were female. The age of these patients ranged from 39 to 83 years, with a median age of 64.5 years. The interaction time ranged from 3 to 55 days (median = 18). Considering the clinical picture evolution, 24 (63.2%) of patients died and 14 (36.8%) were discharged. In the General ICU, 7 (70%) of patients were male, and 3 (30%) were female, aged between 24 and 75 years (median = 65.5 years). The duration of admission ranged from 13 to 48 days (median = 21.5 days). According to the clinical outcome, 6 (60%) of patients were discharged and 4 (40%) died.

The majority of patients had underlying risk factors, 81.6% from COVID ICU and 100% from General ICU. The most prevalent were systemic arterial hypertension and diabetes *mellitus* in both wards analyzed. Other comorbidities that were equally present among patients were alcohol consumption, smoking, dyslipidemia, obesity, among others (Figure 1).

Table 1 describes the invasive procedures to which patients were subjected. It is observed that invasive devices were widely used, resulting in 100% use by patients. The most frequent were orotracheal tube (OTT), NET, CVA, IUC and MV, whose time ranged from 3 to 40 days (median = 15.5) in COVID ICU and from 10 to 29 days in General ICU (median = 18.5).

Table 2 demonstrates predictive factors for the outcome of death. The variables considered significant by the logistic regression method were admission days,

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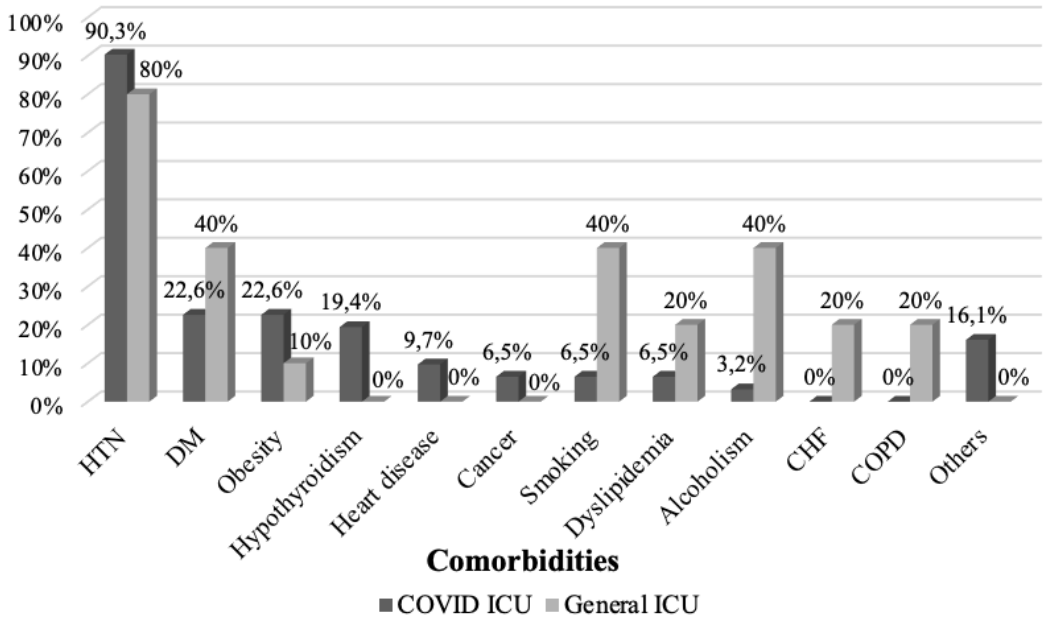

Figure 1. Comorbidities of patients admitted to the COVID ICU and General ICU of a teaching hospital in western Paraná in 2021.
Caption: HTN - systemic arterial hypertension; DM – diabetes mellitus; CHF – congestive heart failure; COPD – chronic obstructive pulmonary disease.

Table 1. Invasive procedures used in patients with positive *Candida* culture admitted to the COVID and General ICUs of a teaching hospital in western Paraná in 2021.

	Admission wards	
Invasive procedures	**COVID ICU N (%)**	**General ICU N (%)**
Mechanical ventilation	38 (100)	10 (100)
Orotracheal tube	38 (100)	10 (100)
Tracheostomy	13 (34.2)	7 (70)
Nasoenteral tube	38 (100)	9 (90)
Nasogastric tube	8 (21.1)	4 (40)
Central venous access	38 (100)	10 (100)
Peripheral venous access	34 (89.5)	8 (80)
Indwelling bladder catheter	38 (100)	10 (100)
Total	38 (100)	10 (100)

Table 2. Factors associated with the outcome of death in patients with *Candida* isolated from pulmonary secretions of patients admitted to the COVID and General ICUs of a teaching hospital in western Paraná in 2021.

Variables	**p-value**	**Odds Ratio [95%CI]**
Admission days	0.0124*	0,3811
Mechanical ventilation days	0.0077*	3,7439
General ICU	0.0701	38,2022
COVID ICU		
Without tracheostomy	0.0718	0,0010
With tracheostomy		

** Indicate significant differences (p<0.05).*

Table 3. Absolute (n) and relative frequencies (%) of the number of *Candida* spp. cases in patients admitted to the COVID and General ICUs of a teaching hospital in western Paraná in 2021.

	COVID ICU		**Adult ICU**		
Tests	**n**	**%**	**n**	**%**	***p-value***
Negative	518	93.17	251	96.54	0.0540
Positive	38	6,83	9	3.46	

days of MV and tracheostomy. Among these factors, it was observed that patients with more days on MV were 3.74 times more likely to die (p = 0.007), and patients admitted to the COVID ICU were 38.2 times more likely to die than those admitted to the General ICU.

The percentage of deaths comparing the number of positive and negative cases of *Candida* spp. among patients admitted to COVID ICU and General ICU it was 6.83% and 3.46%, respectively, not being statistically significant (p = 0.0540). However, a trend towards significance was observed, with the COVID ICU tending to present more positive cases of *Candida* spp. than the General ICU (Table 3).

Regarding the patients who presented tracheal secretion culture with isolation of *Candida*, all (100%) used antimicrobials. Among the most prescribed were piperacillin/tazobactam, ceftriaxone, azithromycin, meropenem and linezolid (Table 4).

Regarding antifungal medications, the frequency of use in COVID ICU patients was 31.6%, with fluconazole being the most prescribed drug, with 91.7%, followed by echinocandins (anidulafungin and micafungin 8.3%, respectively). Meanwhile, in the General ICU, the frequency was 50%, with anidulafungin present in the majority of prescriptions (80%), followed by fluconazole, with 40%.

Regarding the use of steroidal anti-inflammatory

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Table 4. List of antimicrobials prescribed to patients admitted to the COVID and General ICUs of a teaching hospital in western Paraná in 2021.

Antimicrobials	Admission wards	
	COVID ICU N (%)	General ICU N (%)
Piperacillin/tazobactam	35 (92.1)	9 (90)
Ceftriaxone	30 (78.9)	8 (80)
Azithromycin	27 (71)	-
Meropenem	25 (65.8)	9 (90)
Linezolid	21 (55.3)	5 (50)
Polymyxin B	17 (44.7)	3 (30)
Amikacin	15 (39.5)	1 (10)
Levofloxacin	13 (34.2)	-
Vancomycin	11 (28.9)	4 (40)
Cefepime	6 (15.8)	1 (10)
Teicoplanin	5 (13.2)	1 (10)
Tigecycline	5 (13.2)	-
Moxifloxacin	4 (10.5)	-
Clindamycin	4 (10.5)	3 (30)
Amoxicillin/clavulanic acid	3 (7.9)	-
Imipenem	3 (7.9)	-
Imipenem/cilastatin	3 (7.9)	-
Metronidazole	3 (7.9)	3 (30)
Ampicillin	2 (5.3)	1 (10)
Clarithromycin	2 (5.3)	-
Gentamicin	2 (5.3)	-
Sulfamethoxazole/trimethoprim	1 (2.7)	-
Daptomycin	1 (2.7)	-
Oxacillin	1 (2.7)	-
Ceftazidime	-	2 (20)
Moxifloxacin	-	1 (10)
Total	38 (100)	10 (100)

drugs, 100% of patients admitted to the COVID ICU used these medications. Dexamethasone was prescribed to 100% of patients, followed by hydrocortisone, 10.5%, prednisone, 5.3%, and methylprednisolone, 7.9%. In the Adult ICU, 40% of patients used steroidal anti-inflammatory drugs, with hydrocortisone prescribed in 75% of cases, followed by methylprednisolone and prednisone, with 25% both. Dexamethasone, contrary to what was observed in the COVID ICU, was not prescribed in this unit.

Regarding the isolated yeasts, it was observed that C. *albicans* was the prevalent species in both wards, representing 60.5% in the COVID ICU and 40% in the General ICU. In COVID ICU, there was greater diversity among the isolated species, with five different species, such as *C. tropicalis*, *C. lusitaniae*, *C. dubliniensis* and *C. parapsilosis*. In the Adult ICU, the isolated species were *C. tropicalis*, *C. glabrata*, *C. parapsilosis* and *C. famata* (Table 5).

Table 5. Invasive procedures used in patients with positive *Candida* culture admitted to the COVID and General ICUs of a teaching hospital in western Paraná in 2021.

Yeasts	Admission wards	
	COVID ICU N (%)	General ICU N (%)
Candida albicans	23(60.5)	4 (40)
Candida tropicalis	9 (23.7)	3 (30)
Candida lusitaniae	2 (5.3)	-
Candida dubliniensis	2 (5.3)	-
Candida parapsilosis	1 (2.6)	1 (10)
Candida sp.	1 (2.6)	-
Candida famata		1 (10)
Candida glabrata		1 (10)
Total	38 (100)	10 (100)

DISCUSSION

Although there are few studies on the lung microbiome, growing evidence indicates that the fungal microbiota is altered in critically ill patients; however, in patients with COVID-19, lung fungal colonization/infection represents a major concern.[9] Although microbial colonization is an important factor in the development of secondary infections, *Candida* pneumonia is rarely reported in ICUs. In the present study, it was observed an incidence of pulmonary candidiasis of 68.3/1000 patients per day in the COVID ICU and 38.5/1000 patients per day in the Adult ICU.

Some studies have reported that the development of VAP is independent of *Candida* colonization in the airways. Therefore, the meaning of *Candida* colonization in the airways remains controversial, requiring caution when interpreting many clinical conditions. [2]

With regard to gender, there was a higher prevalence of males in admissions, corresponding to 60.5% in the COVID ICU and 70% in the General ICU, corroborating findings from other studies. A study carried out in a university hospital in Italy also showed a predominance of males, compared to females. This occurrence may be related to the greater number of men admitted to hospital in these sectors.[9]

According to patients' age, the median was 64.5 years for COVID ICU patients and 65.5 for General ICU patients, which were close to the study by Viciani *et al.* (2022), demonstrating that the median age was 64 years for patients without COVID-19 and 68 for individuals with COVID-19.[9]

According to Taylor (2021), hospital admission rates for COVID-19 were higher in patients over 65 years of age, requiring ICU admission. This predominance can be justified by the fact that older patients are more vulnerable to complications when subjected to prolonged stays, medical interventions, immune system imbalance, or when they have diseases or comorbidities. As the population ages, the frequency of older patients with health problems requiring treatment in the ICU also increases.[10-12]

Related to the period of stay in the ICU, it was found that COVID ICU patients had a median stay of 18 days, and General ICU patients had a median of 21.5 days. These data were close to what was presented in a retrospective study, carried out in a tertiary hospital in Spain, where the median length of stay for patients was 20 days.[13] Studies have shown that increased hospital and ICU stays increase the risk of co-infections. The combination of factors associated with treatment, prolonged stays in the ICU, medical interventions, such as the use of MV and

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intravenous catheters, increase the risk of candidiasis.[7]

Considering the comorbidities presented among patients, systemic arterial hypertension and diabetes *mellitus* were the most prevalent. These data coincide with a cross-sectional study carried out in a tertiary hospital in Egypt, which analyzed patients with COVID-19 under MV admitted to the ICU, which presented hypertension (62.4%) and diabetes *mellitus* (56.3%) as the main underlying diseases. In addition to these, obesity, hypothyroidism, lung disease and heart disease were observed in both the present study and the one mentioned. The presence of cancer/malignancy was also observed in other studies. [7, 14] Patients with underlying chronic diseases and advanced age tend to be more likely to acquire infections due to their weaker immune conditions.[15]

In this study, the invasive devices most used by patients were MV, OTT, CVA, IUC, NET and PVA. Patients admitted to the ICU often require central venous catheterization and parenteral nutrition, while those for whom MV is not necessary receive peripheral venous catheters. In recent decades, urinary catheters have been identified as risk factors for the development of invasive candidiasis.[7,5] These data coincide with those of another study carried out in a university hospital in Spain, where patients positive for *Candida* spp. were admitted to the ICU and required orotracheal intubation. The treatment received was with parenteral nutrition and nasogastric catheters and central and bladder access routes.[3] Using these medical devices provides a direct route into the host by penetrating the skin barrier. *Candida* species can form biofilms on these devices and act as physical barriers to protect antifungal treatment and host immune system defenses, already weakened due to COVID-19.[7]

In our study, patients with more days on MV were 3.74 times more likely to die ($p = 0.007$), and patients admitted to the COVID ICU were 38.2 times more likely to die than those admitted in General ICU. However, this result must be interpreted with caution, as the value obtained for "p" is not significant ($p = 0.07$), but indicates a tendency towards significance. Isolation of *Candida* spp. via the respiratory tract is associated with longer periods of MV and ICU admission, with unfavorable outcomes.[7] As in the present study, Meawed *et al*. (2021) found, in their research, that longer duration of MV proved to be a highly significant risk factor for candidiasis ($p < 0.001$).[14]

In this research, antibiotic therapy was present in 100% of prescriptions in ICUs, with all patients using more than one class of antibiotics. Patients with COVID-19 are more likely to acquire bacterial co-infections, and the most commonly prescribed antibiotics were ceftriaxone and azithromycin, observed in a single-center retrospective analysis, similar to the current study.[8] In another retrospective observational study, carried out in a tertiary hospital in Spain, ceftriaxone was also the most used antibiotic among patients as well as piperacillin/tazobactam, carbapenems, linezolid and levofloxacin, corroborating the data from this research.[13]

Prolonged use of broad-spectrum antibiotics is associated with microbiota imbalance, creating a favorable environment for the proliferation and transformation of commensal to pathogenic *Candida* morphogenesis.[15] The dysbiosis caused by using these medications allows *Candida* spp. overcome other microorganisms, providing their colonization and dissemination.[7]

Regarding the use of steroidal anti-inflammatory drugs, it was observed that, in COVID ICU, there was 100% use of these medications. Patients with COVID-19 develop a cytokine storm syndrome that is characterized by an increase in pro-inflammatory cytokines and a decrease in anti-inflammatory cytokines. In this sense, systemic corticosteroids are frequently used as treatment, such as dexamethasone, which is a well-known medication used to reduce the dysregulation of the inflammatory state.[5]

Although this glucocorticoid reduces the risk of a hyperinflammatory response in patients with COVID-19, its use is a risk factor for the development of opportunistic fungal co-infection, as the hyphae are protected from phagocytic attack. A study demonstrated that treatment with corticosteroids is associated with a 3.33 times greater risk of developing an IFI, when compared to other patients who did not receive this type of medication.[10]

In this study, the mortality rate of patients diagnosed with COVID-19 and admitted to the COVID ICU (63.2% 24/38) was significantly higher than that observed among negative patients admitted to the Adult ICU (40% 4/10), similar to the study by Calderaro *et al*. (2021), who analyzed infectious agents in lower respiratory tract samples from patients positive and negative for SARS-CoV-2 admitted to the ICU of a tertiary hospital located in Parma, Italy. According to study reports, infections caused by *Candida* and other fungal species tend to affect patients with severe viral infections, and may be associated with increased morbidity and mortality.[17, 18]

Regarding the yeasts isolated, C. *albicans* was the most frequently isolated species in both wards. *Candida* spp. are recognized as opportunistic microorganisms that cause serious infections in immunocompromised individuals. An important characteristic of *Candida* virulence is biofilm formation, which involve the ability to adhere to tissues and surfaces, and are extremely resistant to routine antifungals. Biofilm formation involves the adhesion of yeast cells, which promotes their proliferation, extracellular matrix material accumulation and yeast cell dispersion, which can establish new biofilms.[19] The extracellular matrix assists in fungal colonization and invasion, by acting as a protective barrier, increasing adhesion and production of hyphae; thus, it protects the cell from immune attack by increasing resistance to antifungal agents.[7]

These data corroborate data from the study by Erami *et al*. (2022), in which C. *albicans* was the prevalent species, isolated from bronchoalveolar lavage (BAL) samples from patients with COVID-19 pneumonia who used MV for more than four days, admitted to a hospital in Iran.[2]

The exact pathogenesis of candidiasis associated with COVID-19 is not clear, however several factors have been proposed to explain how patients with COVID-19 are more predisposed to *Candida* infection. SARS-

CoV-2 infection can cause a reduction in lymphocytes and, consequently, the impairment of immune defense against fungal agents, including *Candida*. Elevated blood lactate and acidosis is associated with greater severity of COVID-19, allowing restructuring of the yeast cell wall to mask β-glucans and escape host immunological recognition. Additionally, *Candida*'s ability to form biofilms may be triggered through oxidative stress and pH imbalance observed in COVID-19 patients.[1] In our study, although the outcome of death and positive tracheal secretion culture for *Candida* is not statistically significant, the COVID ICU tended to present more positive cases of candidiasis in relation to the General ICU. Delisle *et al*. (2008) showed, based on regression analysis, that there is a significant association between respiratory tract colonization by *Candida* and hospital mortality.[20]

Disseminated candidiasis has become more prevalent as COVID-19 has progressed.[2] However, isolation of *Candida* spp. should be valued in all critical patients, due to the potential virulence factors produced by this microorganism, which corroborate the successful colonization or invasive infection of the host's tissues.[21] As there are controversies regarding the interpretation through the isolation of yeasts in samples from the respiratory tract, since the diagnostic criteria for candidiasis for this site are not well established.[6] Therefore, it is important to question whether it is possible *Candida* pneumonia or just colonization, with more laboratory and clinical interaction studies needed to determine cut-off points and establish the use of antifungal prophylaxis in a population at risk.

We conclude that patients admitted to the ICU for COVID-19 share some risk factors and underlying diseases, such as chronic respiratory diseases, corticosteroid therapy and invasive devices. To our knowledge, this is the first case series reported of a possible correlation of respiratory tract candidiasis after COVID-19 in critically ill patients. More studies are needed to understand the association between isolation of *Candida* in the respiratory tract and its clinical importance. An accurate and rapid diagnosis of candidiasis will provide adequate treatment for patients, in addition to representing an improvement in the mortality rates resulting from these infections not only in patients with severe COVID-19, the target of this study, but also in other critical patients mainly in ICUs.

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Mariangela Cauz and **Lilian Cristiane Baeza** contributed to laboratory identification of the isolates, data analysis and interpretation and manuscript writing.

All authors approved the final version to be published and are responsible for all aspects of the work, including ensuring its accuracy and integrity.

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ORIGINAL ARTICLE

Impact of the national shortage of polymyxin B in critically ill patients during the COVID-19 pandemic

Impacto da escassez nacional de polimixina B em pacientes gravemente enfermos durante a pandemia de COVID-19

Impacto del desabasto nacional de polimixina B en pacientes críticos durante la pandemia de COVID-19

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ABSTRACT

Background and Objectives: during the COVID-19 pandemic, the number of critical patients requiring intensive care increased considerably, resulting in an increase in infections due to multi-resistant microorganisms. In Brazil, in 2021, due to the high demand for polymyxin B use, there was a national shortage of the medication. One strategy used to overcome this situation was aminoglycoside use. The work aimed to analyze the impact of replacing polymyxin B with amikacin and gentamicin in the final stage of patients. **Method:** an analytical study with an observational, cross-sectional design, with a quantitative approach, through a retrospective analysis through the analysis of medical records, with the primary stages being discharges or deaths. **Results:** mortality was similar between the group treated with aminoglycoside and the group treated with polymyxin B. Within the aminoglycoside group, mortality was higher in the group that had bacteria resistant to the drug than in the group that had infection with an organism sensitive to this drug. Mortality was not affected by comorbidities, age, or number of hospital infections. The main factor that led to the need for dialysis was the combination of two nephrotoxic medications. **Conclusion:** two hypotheses emerged: the first would be that replacing polymyxin B with aminoglycosides did not impact mortality; the other would be that, regardless of the antibiotic group used, patients had a high risk of death. Despite sample limitations, the study corroborates the adoption of strategies for the rational use of antimicrobials.

Descriptors: *Polymyxin B. Aminoglycosides. COVID-19.*

RESUMO

Justificativa e Objetivos: durante a pandemia de COVID-19, o número de pacientes críticos que necessitaram de cuidados intensivos aumentou consideravelmente, resultando em aumento de infecções por microrganismos

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multirresistentes. No Brasil, em 2021, devido à grande demanda pelo uso da polimixina B, houve escassez nacional do medicamento. Uma estratégia utilizada para superar essa situação foi o uso de aminoglicosídeos. O trabalho teve como objetivo analisar o impacto da substituição da polimixina B por amicacina e gentamicina na fase final dos pacientes. **Método:** estudo analítico com desenho observacional, transversal, com abordagem quantitativa, por meio de análise retrospectiva por meio de análise de prontuários, sendo as etapas primárias as altas ou óbitos. **Resultados:** a mortalidade foi semelhante entre o grupo tratado com aminoglicosídeo e o grupo tratado com polimixina B. Dentro do grupo aminoglicosídeo, a mortalidade foi maior no grupo que apresentava bactérias resistentes ao medicamento do que no grupo que apresentava infecção por organismo sensível a este medicamento. medicamento. A mortalidade não foi afetada por comorbidades, idade ou número de infecções hospitalares. O principal fator que levou à necessidade de diálise foi a combinação de dois medicamentos nefrotóxicos. **Conclusão:** surgiram duas hipóteses: a primeira seria que a substituição da polimixina B por aminoglicosídeos não impactou a mortalidade; a outra seria que, independentemente do grupo de antibióticos utilizado, os pacientes apresentavam alto risco de morte. Apesar das limitações amostrais, o estudo corrobora a adoção de estratégias para o uso racional de antimicrobianos.

Descritores: *Polimixina B. Aminoglicosídeos. COVID 19.*

RESUMEN

Antecedentes y Objetivos: durante la pandemia de COVID-19, el número de pacientes críticos que requirieron cuidados intensivos aumentó considerablemente, resultando en un aumento de infecciones por microorganismos multirresistentes. En Brasil, en 2021, debido a la alta demanda del uso de polimixina B, hubo escasez nacional del medicamento. Una estrategia utilizada para superar esta situación fue el uso de aminoglucósidos. El trabajo tuvo como objetivo analizar el impacto de la sustitución de la polimixina B por amikacina y gentamicina en la etapa final de los pacientes. **Método:** estudio analítico con diseño observacional, transversal, con enfoque cuantitativo, mediante un análisis retrospectivo mediante el análisis de historias clínicas, siendo las etapas primarias las altas o defunciones. **Resultados:** la mortalidad fue similar entre el grupo tratado con aminoglucósido y el grupo tratado con polimixina B. Dentro del grupo de aminoglucósido, la mortalidad fue mayor en el grupo que tenía bacterias resistentes al fármaco que en el grupo que tenía infección con un organismo sensible a este. droga. La mortalidad no se vio afectada por las comorbilidades, la edad o el número de infecciones hospitalarias. El principal factor que llevó a la necesidad de diálisis fue la combinación de dos medicamentos nefrotóxicos. **Conclusión:** surgieron dos hipótesis: la primera sería que la sustitución de polimixina B por aminoglucósidos no impactó la mortalidad; la otra sería que, independientemente del grupo de antibióticos utilizado, los pacientes tenían un alto riesgo de muerte. A pesar de las limitaciones de la muestra, el estudio corrobora la adopción de estrategias para el uso racional de antimicrobianos.

Descriptores: *Polimixina B. Aminoglucósidos. COVID-19.*

INTRODUCTION

In recent decades, due to indiscriminate antimicrobial use and the selective pressure exerted by them, infections related to multi-resistant microorganisms have emerged. These microorganisms can range from bacteria, fungi, viruses and other parasites, which have the ability to render antimicrobials ineffective.[1]

Antimicrobial resistance (AMR), which occurs when a pathogen shows resistance to one or more AMR from three or more tested categories,[1-3] is a situation of worldwide concern and impact, so much so that the World Health Organization estimates that, by 2050, resistance to AMR will lead to the death of around one person every three seconds (more than ten million people per year). This prediction was made in 2019, before the emergence of the coronavirus pandemic, COVID-19.[4-7] COVID-19, one of the greatest pandemics in history, originated in China at the end of 2019,[7, 8] and its causal agent is SARS-CoV-2, a strain of coronavirus that causes an upper respiratory tract infection, which can progress to pneumonia as a secondary infection and severe acute respiratory syndrome. With so many patients suffering from severe respiratory conditions, hospital admissions have increased, mainly in an intensive care environment, with a significant increase and indiscriminate antibiotic use throughout the country, resulting in antimicrobial resistance as a public health consequence.[5, 6]

With increasing rates of antimicrobial resistance due to indiscriminate AMR use (such as azithromycin) to combat healthcare-associated infections, one of the antibiotics used against organisms resistant to carbapenems was polymyxin B. Due to the high demand for this drug, a national shortage of the drug occurred during 2021.[8]

Based on previous studies to restrict broad-spectrum antibiotic use, replacing polymyxin B with aminoglycosides, the strategy adopted by many institutions to overcome the national shortage crisis was to use aminoglycosides, mainly amikacin and gentamicin, as an alternative. However, these studies were carried out in ideal situations, where drug replacement was a choice and not a necessity, as observed during the pandemic.[9-14]

Taking into account this historical moment and the public health crisis that has taken place, the hypothesis of this work is that the replacement of polymyxin B with aminoglycosides did not lead to greater mortality among critically ill admitted to hospital patients, provided

that the multidrug-resistant bacteria were sensitive to amikacin and/or gentamicin. Regarding the outcome of renal failure, using both drugs is expected to harm the organ, as both classes are known to be nephrotoxic.[15] However, there is still no comparison in the literature between polymyxin B and aminoglycoside and the greater possibility of using one or the other leading to renal replacement therapy.

Therefore, the study's main objective was to analyze the impact that replacing polymyxin B with amikacin and gentamicin had on patient outcomes. To this end, the mortality of patients who received aminoglycoside versus polymyxin B and the recovery duration from the infectious condition for each of the antibiotics used were assessed. Data on progression to renal replacement therapy and length of stay in a critical environment were also collected.

METHOD

This is an analytical study with an observational, cross-sectional design, with a quantitative approach, through a retrospective analysis, which was carried out based on data obtained from medical records of critically ill patients admitted to a small tertiary hospital in the Metropolitan Region of Curitiba, in the drug shortage period, from August and September 2020 and August and September 2021.[16, 17]

Critical patients who required polymyxin B use during 2020 and those who used amikacin or gentamicin during 2021 were included. Patients who used AMR concomitantly and who were only over 18 years of age were also included. Incomplete medical records and those of patients who died within 24 hours of using antibiotics or being admitted to hospital were excluded.

Data were collected and tabulated in spreadsheets using Excel®. For descriptive analysis, categorical variables were presented according to their frequencies, prevalence and percentages, while quantitative variables were described according to means, deviation and standard error. Participants were divided into groups according to drug use. In most analyses, the sample was composed of two groups: 1) aminoglycosides (AM); and 2) polymyxin (PL). In other analyses, a subdivision of the drug was carried out, with four groups: 1) sensitive aminoglycoside (SAM); 2) aminoglycoside resistance (AMR); 3) PL; and 4) PL + AM (PLAM).[18, 19]

For inferential analyses, data tabulated in Excel® were transferred to the Statistical Package for the Social Sciences (SPSS, IBM Statistics, v.23, 2015). The Mann-Whitney U test was used to compare, between AM and PL groups, age, total length of stay, length of stay in a critical environment, duration of use and number of antibiotic cycles. With the aim of investigating the primary outcome, which is equivalent to the patient being discharged from hospital or death, and the secondary outcome, which is equivalent to progressing to dialysis, the chi-square test was used to compare the frequency of occurrence of these variables between groups.[18, 19]

The Spearman correlation test was used to correlate Polymerase Chain Reaction (PCR), creatinine and urea values on D3, total length of stay and length of stay in a critical environment, duration of use and number of antibiotic cycles with hospital discharge/death outcomes. The correlation between palliative care and age was also analyzed.[18, 19]

Generalized Estimating Equation (GEE) models with appropriate link function (identity or log) and (linear, gamma or tweedie) distribution assumed were used to compare the quantitative variables (PCR, creatinine and urea) between groups (AM and PL) and length (D0, D3, D7, D10 and D14). Thus, group and duration were the effects analyzed as well as their interaction. The distribution model was selected (best overall fit) based on the lowest value of Quasi-likelihood under Independence Model Criterion (QIC, 2007). AR1 structure matrix was used, and, when necessary, Bonferroni post-hoc for subsequent comparisons. The significance of all analyzes was set at 5% ($p < 0.05$).[18, 19]

As it involves reviewing medical records, the project was previously submitted to the Research Ethics Committee of São José dos Pinhais, under Consubstantiated Opinion 5,549,515 (CAAE (*Certificado de Apresentação para Apreciação Ética* - Certificate of Presentation for Ethical Consideration): 58850522.9.0000.9587), in compliance with the Standards for Conducting Research on Human Beings of the Brazilian National Health Council, in accordance with Resolution 466/12.

RESULTS

Thus, 22 patients comprised the sample of this study. Depending on drug use, the AM group had 10 patients (69.9 ± 7.82 years, 8 men, 2 women), and the PL group had 12 (70.4 ± 8.26 years, 8 men, 4 women). There was no significant difference in age between groups ($U = 56.000$; $p = 0.791$).

The main point researched, which was to compare the outcome of discharge or death between groups, is presented in Tables 1 and 2. For this result, two analyzes are presented, dividing patients into 2 (Table 1 – PL and AM) or 4 groups (Table 2 - SAM, AMR, PL and PLAM), in order to try to remove the influence of the low sample number. The chi-square test found no difference in the frequency of death and discharge in either of the two analyzes.

However, it is noteworthy that, when observing the groups of patients who received only AM, mortality was higher in those who were sensitive to the drug (75%) than in those who were not resistant to it (33%).

Table 3 presents different outcomes. It was observed that there was no difference between length of stay, number of antibiotic cycles, number of care-related infections or number of antibiotics between AM and PL groups.

According to table 3, it can be seen that there was a statistical difference in relation to length of stay in a critical environment, which was longer for patients in the PL group as well as a longer period of antibiotic use. In

Table 1. Comparison of frequency of hospital admission outcome between AM and PL groups.

	Discharge	Death	Death for other causes	X^2	p
AM (n = 10)	2 (20%)	8 (80%)	-	0.078	0.781
PL (n = 12)	3 (25%)	9 (75%)	-		

Source: the authors.

Table 2. Comparison of frequency of hospital admission outcome among AMR, PL and PLAM groups.

	Discharge	Death	Death for other causes	X^2	p
SAM (n = 4)	0 (0%)	4 (100%)	-	3.731	0.292
AMR (n = 6)	2 (33%)	4 (67%)	-		
PL (n = 4)	2 (50%)	2 (50%)	-		
PLAM (n = 8)	1 (12%)	7 (88%)	-		

Source: the authors.

Table 3. Comparison of length of stay and use of antibiotics between groups.

	AM (n = 10)	PL (n = 12)	U	p
Length of stay (days)	24.4 ± 7.97	39.8 ± 20.51	31.50	0.060
Length of stay in a critical environment (days)	17.8 ± 11.23	38.7 ± 18.88	23.50	0.016*
Antibiotic use duration (days)	6.9 ± 3.31	12.66 ± 7.37	28.50	0.037*
Antibiotic cycles (n)	4.7 ± 1.49	5.92 ± 2.06	41.00	0.200
Care-related infections (n)	3.1 ± 1.66	2.75 ± 1.05	55.50	0.757
Comorbidities (n)	2.3 ± 1.64	1.9 ± 1.24	50.00	0.491

*Note: data presented as mean ± standard deviation; n = number; *indicates statistical difference when comparing groups.*
Source: the authors.

order to justify these results, the duration between the start of treatment and the outcome of death was also compared between groups in the hypothesis that there was a positive correlation in relation to the duration of antibiotic use with greater survival. However, the Mann-Whitney test did not observe a significant difference in this variable (U = 21.00; p = 0.147), possibly due to the variability of values and the reduced number of patients, since the mean number of days is descriptively longer in the PL group (AM = 8.5 ± 5.75 vs. PL = 15.2 ± 11.2 days).

Mortality was high in both groups. A complementary analysis to assess whether older age would be a predisposing factor for a worse outcome was performed. The Mann-Whitney test did not identify a difference in age (U = 28.00; p = 0.254) nor in the number of infections (U = 35.50; p = 0.567) among patients who were discharged or died.

When comparing the frequency of need for dialysis (Table 4), the chi-square test identified a significant difference between groups, such that patients in the PL group needed dialysis more than those in the AM group. When analyzing patients divided into 4 groups (Table 5 - SAM, AMR, PL and PLAM), SAM, AMR and PL groups were very similar in terms of the need for dialysis, however, when there was a combination of two drugs (PLAM), the frequency of dialysis was much higher, showing that using two nephrotoxic medications had a more significant impact on the dialysis outcome.

Another analysis was carried out with patients divided between the discharge and death groups, regardless of the medication used, to assess how much comorbidities influenced the outcomes. The comorbidities asses-

Table 4. Comparison of dialysis use between AM and PL groups.

	With dialysis	Without dialysis	X^2	p
AM (n = 10)	2 (20%)	8 (80%)	4.791	0.029*
PL (n = 12)	8 (67%)	4 (33%)		

Source: the authors.

Table 5. Comparison of dialysis use among SAM, AMR, PL and PLAM groups

	With dialysis	Without dialysis	X^2	p
SAM (n = 4)	0 (0%)	4 (100%)	10.068	0.018*
AMR (n = 6)	2 (33%)	4 (67%)		
PL (n = 4)	1 (25%)	3 (75%)		
PLAM (n = 8)	7 (88%)	1 (12%)		

Source: the authors.

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sed were hypertension (HT), type 2 diabetes mellitus, coronary artery disease, heart failure and chronic obstructive pulmonary disease (COPD). The chi-square test found no difference in the frequency of occurrence of any comorbidity both when comparing drug groups and outcome groups ($X^2 < 2.426$; $p > 0.119$). As a complementary analysis, patients were classified into those who had 3 comorbidities or more and 2 comorbidities or less. The chi-square test was used to investigate whether those with more than 3 comorbidities had a higher frequency of death in the sample. The results showed that 100% of patients with more than 3 comorbidities (n = 7) died, compared to 67% of patients with 2 comorbidities or less (n = 10). Despite the descriptive difference, the test did not find a significant difference ($X^2 = 3.020$; $p = 0.082$).

The drug and outcome groups were also compared in relation to the reason for hospital admission. It was analyzed whether patients who were admitted to hospital due to COVID-19 died more often than due to other causes (all others grouped into a single category), but there was no statistical difference. Descriptively, 30% (n = 3) of patients in the AM group were admitted to hospital due to COVID-19, and in the PL group, 58% (n = 7).

In the AM group, 70% (n = 7) used the antibiotic for ventilator-associated pneumonia (VAP), and 30% (n = 3) for urinary tract infection (UTI). In the PL group, 84% (n = 10) used it for VAP, 1% (n = 1) for UTI, and only 1% for other causes (1 patient with osteomyelitis). No differences were found in comparisons between groups in any of these variables either.

Finally, one of the secondary objectives of this study was to assess the recovery duration from the infectious condition for each of the antibiotics used through PCR analysis, in addition to the progression of renal dysfunction with urea and creatinine data on D0, D3, D7, D10 and D14. However, this analysis was hampered due to the low sample number, and it was not possible to obtain reliable data due to the high death rate within the first 5 days of hospital admission.

DISCUSSION

The work's main objective was to assess the primary outcome – death or discharge – of patients. The tests showed no difference in the frequency of death and discharge in either of the two analyses. In other words, polymyxin B use did not protect patients from the final negative outcome – death, even when only AM was used in organisms resistant to these. This result is consistent with the two studies that used AM to replace polymyxin B without an increase in mortality.[9-13] Once again, it is highlighted that the replacement of polymyxin B with gentamicin or amikacin was not a strategic option for antimicrobial control, but rather a necessity due to the current restriction and shortage of polymyxin B. However, in terms of public health, considering costs and antimicrobial resistance, this result is consistent with the possibility of strategies to restrict broad-spectrum antibiotic use.

However, the results showed that, contradictorily, the group of patients who had an infection with AM-resistant bacteria (and were treated with this drug due to the scarcity of polymyxin B) had lower mortality (33%) than the group who had an infection with AM-sensitive bacteria.

This contradiction allows us to raise two hypotheses for the results obtained. The first would be that replacing polymyxin B with AM did not impact death. The second would be that patients treated during the pandemic had a high risk of death, and this would occur regardless of the class of antimicrobial used.

Although polymyxin B is a broad-spectrum antibiotic for gram-negatives, especially for *Acinetobacter spp*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae carbapenemase* (KPC),[15,20] its use was not superior to AM use, as it did not lead to fewer infections and did not reduce the need to use other antibiotic cycles or total hospital stay. In other words, once again, in terms of public health, antimicrobial resistance and global development, using AM instead of polymyxin B would be justified.

The results shown in table 3 showed that patients who used polymyxin B remained admitted to hospital in a critical environment longer than the group that used AM. The attempt to justify these results was a complementary analysis to assess whether these patients remained alive longer because they had used the antibiotic. However, no statistical difference was observed between these variables, i.e., the hypothesis raised did not justify the difference in days of hospital admission in a critical environment. However, it is worth noting that, possibly, different and more enlightening results would be obtained with a larger sample, since the average number of days is descriptively longer in the PL group (AM = 8.5 ± 5.75 vs. PL = 15.2 ± 11.2 days). It is worth noting that, even though they remained in a critical environment for longer and used antibiotics for longer, this did not influence the primary outcome (death or discharge).

The secondary outcome assessed was in relation to progression to dialysis. The first result obtained showed that patients in the PL group needed dialysis more than those in the AM group. Although both classes of drugs are known to be nephrotoxic,[15,20] it was expected that the group that used AM would have a worse renal outcome. The complementary analysis carried out to clarify the result obtained demonstrated that, in reality, when two drugs were used in the same patient (i.e., the sum of two nephrotoxic drugs), there was a greater progression to dialysis.

Regarding comorbidities, there was no statistical difference between groups, i.e., having HT, type 2 diabetes mellitus, coronary artery disease, heart failure or COPD alone. did not cause more patients to die, even when assessing whether having 3 or more comorbidities (e.g., the impact of the sum of diseases) also did not demonstrate a worse outcome. However, the results showed that 100% of patients with more than 3 comorbidities died, demonstrating the need for a larger sample group (with a possible result different from that obtained). It is assumed that this result would be different due to the fact that the impact of comorbidities on the death outcome has already been analyzed in previous studies, in which

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it was seen that patients with comorbidities (mainly cardiovascular) had worse outcomes compared to patients without comorbidities.[21-23]

Regarding age or number of infections, there was no difference between groups. The reason that led to antibiotic use and hospital admission also did not impact the outcome.

Although, descriptively, more patients admitted to hospital due to COVID-19 died than due to other causes, there was no statistical difference in the tests performed. In other words, hospital admission for COVID-19 was not what impacted the death of patients.

The evolutionary comparison of PCR from treatment was hampered, as most patients died within the first 5 days after starting antibiotic therapy.

The study has restrictions, mainly due to the small sample size, which did not allow for a more meaningful analysis of the impact of some variables (such as age and comorbidities). The high number of patients who died within the first 5 days after identifying the infectious process was also a limiting factor (impairing the evolutionary comparison of laboratory tests, such as PCR, urea and creatinine). Despite the limitations, the study contributes to clinical practice by reinforcing the importance of carrying out more studies comparing broad-spectrum AMR use, helping the medical community when making decisions related to the prescription and rational use of these drugs. The study also helps professionals assess the results of drug substitution measures in scenarios of national shortages of these drugs.

CONCLUSION

The temporary shortage of polymyxin B led to its therapeutic replacement, with AM use. The results of this action showed that there are two viable hypotheses: that this replacement did not change the primary outcome (death); or regardless of the drug used, the outcome would be the same. No differences were observed between comorbidities and age between groups. Although both drugs are nephrotoxic, it was seen that the greatest need for dialysis occurred when there was concomitant use of the two classes of AMR. The study demonstrates the importance, in terms of public health, of using broad-spectrum AMR in a rational manner, aiming at the possibility of replacement by smaller-spectrum AMR. However, the work has limitations due to the low number of patients, and these data require further studies.

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AUTHORS' CONTRIBUTIONS:

Fernanda Piazza Fernandes contributed to data collection, analysis and interpretation manuscript writing. **Maria Claudia Hahn Ferrucio** contributed to research design and data interpretation and manuscript review.

All authors approved the final version to be published and are responsible for all aspects of the work, including ensuring its accuracy and integrity.

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ORIGINAL ARTICLE

Post-COVID conditions: construction of a manual for health professionals in user management

Condições pós-COVID: construção de um manual para profissionais de saúde na gestão de usuários

Condiciones post-COVID: construcción de un manual para profesionales de la salud en la gestión de usuarios

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ABSTRACT

Background and Objectives: in the course of care for users affected by COVID-19, there were persistent signs and symptoms or the development of late symptoms called post-COVID conditions. Thus, it is necessary to promote Continuing Education in Health practices to meet post-COVID conditions. Thus, the study aimed to construct a manual to assist Primary Health Care (PHC) professionals in managing post-COVID conditions. **Methods:** the method proposed by Echer was adopted for constructing the manual, which provides six steps for structuring a manual. Moreover, this study used only five of them, and the sixth step consists of manual validity. In addition, the following guiding axes were established: objectivity, self-explanatory formulation, problematizing pedagogical approach inspired by Bordenave and Pereira and the Brazilian National Policy for Continuing Education in Health. **Results:** the study resulted in the construction of a manual that comprises 25 post-COVID conditions, presented in a didactic way, with content selection and language adjustment considering the target audience, with illustrations and flowcharts that facilitate the conduct of the line of clinical reasoning as well as inclusion of clinical cases aiming at bringing them closer to clinical practice. **Conclusion:** the manual construction allows professionals to offer the affected users a quality and resolutive assistance, minimizing the damage to their quality of life. Furthermore, it is expected that the manual will reach a wide dissemination in the most distinct health spaces, providing subsidies to health professionals.

Keywords: *Post-COVID conditions. Educational Technology. Delivery of Health Care.*

RESUMO

Justificativa e Objetivos: no decorrer do atendimento aos usuários acometidos pela COVID-19, ocorreram sinais e sintomas persistentes ou desenvolvimento de sintomas tardios denominados quadros pós-COVID. Assim, é

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necessário promover práticas de Educação Permanente em Saúde para atender às condições pós-COVID. Assim, o estudo teve como objetivo construir um manual para auxiliar os profissionais da Atenção Primária à Saúde (APS) no manejo das condições pós-COVID. **Métodos:** para a construção do manual foi adotado o método proposto por Echer, que prevê seis etapas para estruturação de um manual. Além disso, este estudo utilizou apenas cinco deles, e a sexta etapa consiste na validação manual. Além disso, foram estabelecidos os seguintes eixos norteadores: objetividade, formulação autoexplicativa, abordagem pedagógica problematizadora inspirada em Bordenave e Pereira e na Política Nacional de Educação Continuada em Saúde. **Resultados:** o estudo resultou na construção de um manual que contempla 25 condições pós-COVID, apresentado de forma didática, com seleção de conteúdo e ajuste de linguagem considerando o público-alvo, com ilustrações e fluxogramas que facilitam a condução da linha de raciocínio clínico bem como inclusão de casos clínicos visando aproximá-los da prática clínica. **Conclusão:** a construção manual permite aos profissionais oferecer aos usuários acometidos uma assistência de qualidade e resolutiva, minimizando os prejuízos à sua qualidade de vida. Além disso, espera-se que o manual alcance ampla divulgação nos mais distintos espaços de saúde, proporcionando subsídios aos profissionais de saúde.

Palavras-chave: *Condições pós-COVID. Tecnologia Educacional. Prestação de cuidados de saúde.*

RESUMEN

Antecedentes y Objetivos: en el transcurso de la atención a usuarios afectados por COVID-19 se presentaron signos y síntomas persistentes o el desarrollo de síntomas tardíos denominados condiciones post-COVID. Así, es necesario promover prácticas de Educación Continua en Salud para afrontar las condiciones post-COVID. Así, el estudio tuvo como objetivo construir un manual para ayudar a los profesionales de la Atención Primaria de Salud (APS) en el manejo de las condiciones post-COVID. **Métodos:** para la construcción del manual se adoptó el método propuesto por Echer, el cual proporciona seis pasos para estructurar un manual. Además, este estudio utilizó sólo cinco de ellos, y el sexto paso consiste en la validez manual. Además, se establecieron los siguientes ejes rectores: objetividad, formulación autoexplicativa, enfoque pedagógico problematizador inspirado en Bordenave y Pereira y la Política Nacional Brasileña de Educación Continua en Salud. **Resultados:** el estudio resultó en la construcción de un manual que comprende 25 condiciones post-COVID, presentado de forma didáctica, con selección de contenidos y ajuste del lenguaje considerando el público objetivo, con ilustraciones y diagramas de flujo que facilitan la conducción de la línea de razonamiento clínico. así como la inclusión de casos clínicos con el objetivo de acercarlos a la práctica clínica. **Conclusión:** la construcción manual permite a los profesionales ofrecer a los usuarios afectados una asistencia resolutiva y de calidad, minimizando el daño a su calidad de vida. Además, se espera que el manual alcance una amplia difusión en los más distintos espacios de salud, brindando subsidios a los profesionales de la salud.

Palabras-clave: *Condiciones post-COVID. Tecnologia Educacional. Prestación de atención médica.*

INTRODUCTION

Coronavirus Disease 2019 (COVID-19), a disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), characterized as a pandemic and which caused numerous deaths and ostensible demand on health services for a period of at least three years from 2020, it was recently no longer considered a public health emergency by the World Health Organization.[1] However, health professionals and services still face challenges related to the late repercussions of the disease.

The clinical presentation of SARS-CoV-2 infection ranged from asymptomatic conditions to severe pneumonia, including Severe Acute Respiratory Syndrome (SARS).[2] Given the global vaccination program for COVID-19, these symptoms, classified as acute, are systematically attenuating in response to the immunization of populations. It is estimated that 70% of the world's population has received at least one dose of some type of vaccine against COVID-19, corresponding to 13.38 billion doses administered globally. In Brazil, from February 5, 2021 to March 22, 2023, 189.4 million people were immunized.[3]

In addition to the complications evidenced during the acute period of the disease, so-called post-COVID conditions are currently observed,[4] also known as persistent symptoms of COVID-19, post-COVID syndrome[5], or long COVID, by some scholars.[6-7] Furthermore, post-COVID conditions are defined as "a range of new, recurrent or persistent clinical manifestations present after acute SARS-CoV-2 infection, when these are not attributed to other causes".[4] Therefore, they require improvement from health professionals in managing post-COVID conditions.[7]

Although the pathological manifestations of acute infection have already been widely described in research, investments are needed to understand the causes that explain the prolongation of symptoms.[8] In this regard, studies have shown that post-COVID conditions are characterized by presenting some symptoms, such as fatigue, dyspnea, metabolic changes, elevations in protein substances and the presence of inflammatory markers, which indicate damage to the metabolism of affected individuals.[8,9]

Therefore, it is imperative to mobilize efforts in the pursuit of specific scientific development and provide

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appropriate clinical training for health professionals in an assertive manner, minimizing damage arising from post-COVID conditions through promotion, prevention, therapy and rehabilitation.

Therefore, this study aimed to construct a manual to assist Primary Health Care (PHC) professionals in managing post-COVID conditions.

METHODS

This is methodological research on the construction of an informative manual following the steps described by Echer (2005).[10] The first four steps were covered in this study, namely: research project preparation; content definition and selection; language adaptation; and illustration inclusion. Furthermore, the following guiding principles were established: objectivity; self-explanatory formulation; problematizing pedagogical approach inspired by Bordenave and Pereira (1991)[11] and the Brazilian National Policy for Continuing Education in Health (PNEPS - *Política Nacional de Educação Permanente em Saúde*).

Below, the steps of Echer's (2005)[10] methodology developed in this study is detailed:

1st step: research project preparation

Initially, the researchers developed a research project that included the steps of introduction, objective, literature review, method, schedule, budget and references. The project made it possible to organize the study development, thus guaranteeing the best results.

2nd step: content definition and selection

A search was carried out for studies, manuals, protocols, national and international guides regarding the management of post-COVID conditions. To achieve this, first, the researchers developed a search for studies in the Virtual Health Library, which encompasses several databases, thus making it possible to select original and review articles. Furthermore, due to the scarcity of articles published during the manual's construction period, it was necessary to deepen this search in documents published by national and international government bodies.

Additionally, information archived in researchers' own database was used, obtained from collections carried out in previous research with the responsible multidisciplinary team. for care at the Rehabilitation Center linked to PHC in the city that is the focus of the study, aiming to combine theory and practice in light of the local reality.

Furthermore, in this step, the team of researchers, after obtaining the subsidies they organized and structured, met in a total of twenty meetings, in person and online, in order to discuss how to approach and what to actually address in the instrument to be constructed. This dialogue process made it possible to jointly define which guiding axes would be suitable for use as well as suitable for the proposal intended to be constructed. Still in this process, the most relevant content was jointly discussed and defined based on published research and data previously collected from the multidisciplinary team. Furthermore, it should be noted that the dialogue between researchers made it possible to discuss the steps to follow in Echer's methodology.

3rd step: language adaptation

In this step, it was necessary to define the language structure to be included in the proposed manual, in order to serve the target audience. Thus, in the case of health professionals, for adaptation, scientific language was considered, characterized by easy-to-compress and summarized writing.

4th step: illustration inclusion

The inclusion of illustrations seeks to facilitate the understanding of information, as it helps to consolidate content and makes the material attractive.[10,12] Therefore, illustrative figures prepared by the authors are included in the manual. Thus, for each of the human body systems covered in the manual, to present the symptoms of post-COVID conditions, an image with the respective affected target organ (brain, heart, lungs, etc.) was created. In its surroundings, signs and symptoms were described, providing a didactic presentation to professionals.

The study was approved on June 23, 2022 by the Research Ethics Committee, under Opinion 5.485.653 and CAAE (*Certificado de Apresentação para Apreciação Ética* - Certificate of Presentation for Ethical Consideration) 55337722.0.0000.5564, as required by Resolutions 466/12 and 510/2016 of the Brazilian National Health Council, which deals with research involving human beings.

RESULTS

Considering the method used in the study proposal and the guiding principles, the result comprises a manual that deals with 25 post-COVID conditions, which were the most reported in the previous study carried out by the researchers together with the multidisciplinary team of the aforementioned service. Thus, Figure 1 summarizes the concepts and conceptions involved in this construction.

Figure 1. Founding theoretical bases in the manual construction.
Source: prepared by the authors (2023).

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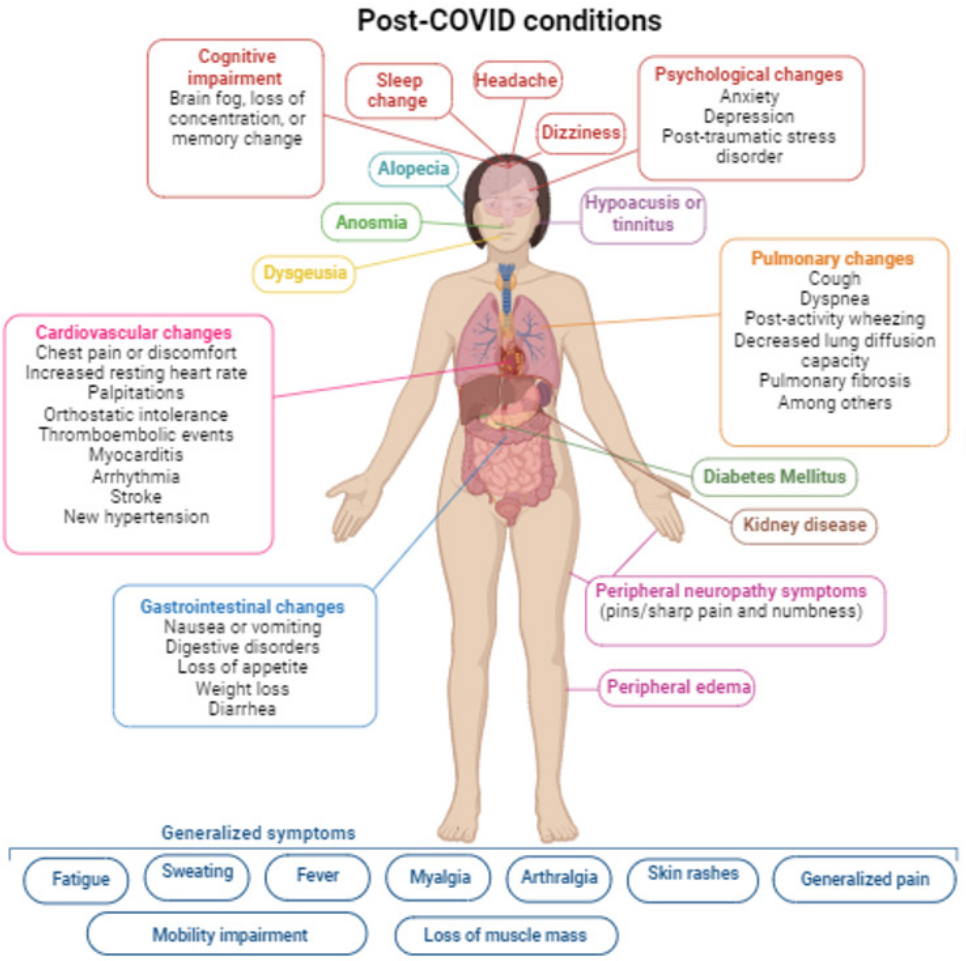

Figure 2. Signs and symptoms of post-COVID conditions.
Source: prepared by the authors (2023).

As for the manual graphic assembly, the result comprised a division between pre-textual elements and textual elements, with pre-textual elements being any and all content developed to facilitate handling the manual by PHC professionals. Therefore, pre-textual elements are illustrative cover, manual presentation, list of abbreviations and manual organization description.

Regarding textual elements, the definition of the term post-COVID conditions was addressed, and how the pathology is codified in the International Classification of Diseases, followed by the presentation of a figure illustrating all of its signs and symptoms (Figure 2).

Subsequently, the post-COVID conditions selected for the manual were presented, separated by body systems or locations of the human body, with their respective illustrative images, such as neurological, psychological/psychiatric, audio vestibular, smell and taste, gastrointestinal, dermatological, respiratory, cardiovascular, endocrine, renal changes and generalized symptoms, followed by a pathophysiological explanation.

Afterwards, each post-COVID condition (sign or symptom) is explained, along with a clinical case, its assessment and management. Furthermore, different colors were used in the titles, present in the textual elements, thus making it possible to quickly find information and icons throughout the manual, with reading suggestions for delving deeper into the topic. Additionally, flowcharts adapted from other literature were used, as can be seen in figure 3.

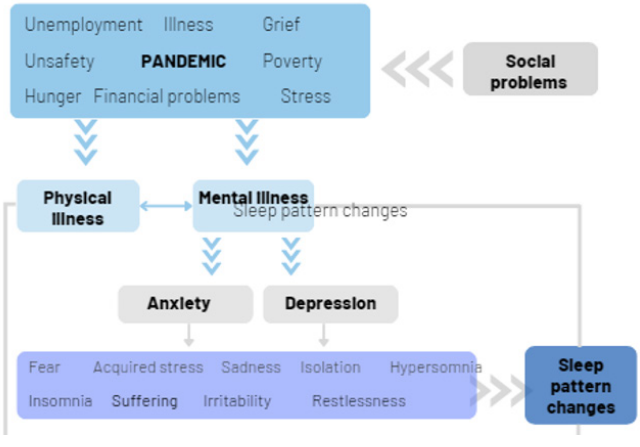

Figure 3. Example of a didactic flowchart of biopsychosocial factors associated with sleep disorders.
Source: prepared by the authors (2023).

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Finally, in certain situations that require specific professional development, materials with specific guidelines were inserted, as can be seen in the following example (Figure 4) by attaching a folder on olfactory training guidelines.

Figure 4. Example of inserting explanatory materials: smell training.
Source: prepared by the authors (2023).

DISCUSSION

The development of a manual for use within the scope of the Brazilian Health System (SUS – *Sistema Único de Saúde*) is a necessary and indispensable resource, characterized as a light technology to be used in the process of Continuing Education in Health (CEH) and/or Health Education.[13] To this end, the initiative and commitment spent on creating an educational manual are not only well received, but also encouraged in the SUS Health Care model.

When considering the relevance, for the health field, of a scientific construction with this educational character, choosing concepts and conceptions to guide its development, such as objectivity, self-explanatory formulation and problematization, combining them with the principles inscribed in PNEPS, there is the selection of information in a material with feasible and positive potential.

That said, Echer (2005)[10] highlights that manuals must contain clear and objective language so that individuals who use them understand what is written. Therefore, the author points out that it is necessary to select which information is really essential to be included in the manual, as it must be attractive and succinct, in addition to having a significant orientation to the proposed topic.

In the same vein as the construction of explanatory materials with clear and objective information, a study carried out in Australia on the development of a manual for people with heart failure points to the importance of using verbal and non-verbal language that facilitates understanding by those involved. Thus, the authors created a manual with a reading level equivalent to that of the 6th grade, also using pictorial visualizations. As a way of assessing the expected understanding, they approached manual users, asking them to present in their own words what they understood about the manual.[14]

By developing a self-explanatory presentation in a manual, as in the case of this study, professionals are able to handle it quickly with immediate responses, helping to understand the symptoms described by users, which assessment procedures should be performed as well as management given the clinical condition presented. This corroborates, therefore, a Cuban study that pointed out that constructing and using a practical guide is essential to provide accurate information and better care, in addition to facilitating clinical decision-making in a shorter time, considering it to be a synthesis tool.[15]

Using images in the constructed manual, in association with each post-COVID condition, provided a visually attractive structure. In line with findings in the literature, in addition to recommending using simple language, it is essential that manuals contain images, with the aim of facilitating communication with the reader and, in this way, making the material more attractive and inviting, since reading and understanding become more simplified and objective.[16]

Furthermore, considering that the proposal embedded in the construction of this educational technology is aimed at health professionals' improvement, production was guided by focusing on the problematizing conceptions of teaching and learning. Thus, from a pedagogical point of view, it is understood that using a proposal with a problematizing nature, which introduces a clinical case for each of the post-COVID conditions, leads professionals to compare the service situation with the situation problematized in the manual, providing greater security regarding the conduct to be agreed upon and greater learning, especially given the fact that the accumulated experience with post-COVID conditions is still incipient.

However, it is argued that using clinical cases for teaching is beneficial, as it arouses interest in learning and improves the capacity for self-learning, clinical thinking, analysis and problem-solving.[17] Still, another study points out that, in the academic scenario, it was observed that teaching approaches based on clinical cases ensure that students have greater self-perceived competence and confidence, compared to students subjected to a traditional teaching model without problematization.[18]

Furthermore, since the manual preparation also took PNEPS as a guiding reference, it is reinforced that health workers' education strategies involve the problematization of their work processes,[19] thus defining one of the methodological bases for learning, together with meaningful and reflective learning.[20]

Authors such as Bordenave and Pereira (1991)[11] discussed in the 20th century the importance of problematization as a teaching and learning strategy, concluding that learning consists of a naturalized human response to a problem situation. These conjectures are deepened by considering that, at the center of the teaching and

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learning process, is the social and individual reality of human life as a guiding axis and trigger for pedagogical practices, and, faced with this reality, there are problems that instigate resolution or improvement.[21]

Therefore, structuring the proposed manual based on real situations tends to assist in the learning process, since, in this way, the final product is not restricted to just a pragmatic listing of post-COVID conditions. Such care taken by researchers finds scientific support in a study where researchers clarify the importance of problematization as a resolving path for clinical training, pointing to the simulation scenario as a real user care environment, which favors and instigates clinical improvement.[22]

Subsequently, it is discussed that educational materials must be adequate in terms of the sequence of content and organization of ideas, prioritizing subjects, using brief, clear and objective writing. Therefore, it is essential that there is a presentation with attractive colors, spacing and choice of the ideal font, in order to allow a language that is accessible to the target audience and facilitates reading.[23] Furthermore, the importance of validating these materials is observed in the literature in order to make their scientificity and applicability legitimate through the reformulation of texts, readjustment of illustrations and adjustments regarding formatting, in order to qualify the constructed product.[24]

Therefore, the signs and symptoms covered in the manual, organized based on changes by systems or locations of the human body, allow professionals to search for the post-COVID condition of interest in a practical way, considering the clinical event that users manifest during care. Manual organization according to the main demands present in the service allows quick and objective access, which can also be facilitated with the use of colors; consequently, this agility will provide safer and more qualified assistance.[25]

Given the above, construction of educational technology became possible and involved the collective, valuing the reality of the service and following the methodological principles guided by Echer for the construction of manuals and PNEPS, in addition to having the ability to guarantee professional development, as it clarifies and updates health professionals on the assessment and management of post-COVID conditions.

Furthermore, the manual construction allows professionals to offer the affected user quality and resolute assistance, minimizing damage to their quality of life. Furthermore, it is expected that the manual will be widely disseminated in the most diverse health spaces, providing support to health professionals.

Finally, it is believed that the manual organization, based on established principles, guaranteed the construction of concise material capable of achieving the objective of professional development. However, as limitations of this study, it is necessary for the manual to go through the validity process, in order to guarantee your qualification; however, even though it is not validated, the manual was produced by experts on the subject who, prior to the manual preparation, made up the proposal construction team.

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Prevalence and factors associated with physical activity practice in people living with HIV/AIDS

Prevalência e fatores associados à prática de atividade física em pessoas vivendo com HIV/AIDS

Prevalence and factors associated with physical activity practice in people living with HIV/AIDS

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ABSTRACT

Background and Objectives: physical activity practice (PAP) by people living with HIV (PLHIV) has been recommended in medical literature. This measure is shown to be effective in managing PLHIV. However, it is estimated that only 50.7% of PLHIV comply with recommended physical exercise guidelines. This study aimed to analyze the prevalence and factors associated with PAP in PLHIV using antiretroviral therapy. **Methods**: a cross-sectional observational study composed of 276 PLHIV on antiretroviral therapy (ART), treated at the Specialized Outpatient Service of a municipality in the countryside of the Northeast in 2018. The variables analyzed included biochemical, anthropometric and blood pressure data as well as the Framingham Risk Score (FRS). They were divided into two groups: physical activity practitioners (PAp); and physical activity non-practitioners (PANp). Data were correlated using Pearson's chi-square test, with statistical significance if $p<0.05$, and through inferential statistics. **Results**: of the study participants, most were men, and of the total contingent, 67% (n=185) were PANp and of these, 8.6% had cardiovascular event moderate and high risks (CVER) according to FRS. The PAp group had a lower median for the age variable [37 (41-48) years, p=0.004] and a higher median for the weight variable [68 (60-77.5) kg, p=0.015]. Among the PAp, there was a high prevalence of low risk. **Conclusion**: lack of PAP is highly prevalent among PLHIV and these are more associated with moderate and high CVER, in addition to the metabolic and bodily consequences of the viral condition and antiretroviral therapy.

Keywords*: HIV. Exercise. Risk Factors. Cardiovascular Diseases.*

RESUMO

Justificativa e Objetivos: a prática de atividade física (PAF) por pessoas vivendo com HIV (PVHIV) tem sido recomendada na literatura médica. Tal medida mostra-se eficaz no manejo de PVHIV. Entretanto, estima-se que apenas 50,7% das PVHIV estão em conformidade com as diretrizes de exercício físico recomendadas. O objetivo

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deste estudo foi analisar a prevalência e os fatores associados à PAF em PVHIV em uso de terapia antirretroviral. **Métodos:** estudo transversal, formado por 276 PVHIV em terapia antirretroviral (TARV), atendidos no Serviço Ambulatorial Especializado (SAE) de um município do interior do Nordeste em 2018. As variáveis analisadas incluíram dados bioquímicos, antropométricos e pressóricos e também o Escore de Risco de Framingham (ERF). Dividiram-se em dois grupos: praticantes de atividade física (pAF); e não praticantes de atividade física (NpAF). Os dados foram correlacionados por meio de Teste Qui-Quadrado de Pearson, com significância estatística se p<0,05, e através da estatística inferencial. **Resultados:** dos participantes do estudo, a maioria era homem (55,4%). Do contingente total, 67% (n=185) eram NpAF e, desses, 8,6% possuíam risco moderado e alto de eventos cardiovasculares (RECV) segundo ERF. O grupo pAF apresentou menor mediana na variável idade [37 (41-48) anos, p=0,004] e maior na variável peso [68 (60-77,5) kg, p=0,015]. Entre os pAF, houve uma alta prevalência de risco baixo. **Conclusão:** a falta da PAF é altamente prevalente entre PVHIV, e esses estão mais associados ao moderado e alto RECV, além das consequências metabólicas e corporais da condição viral e da terapia antirretroviral.

***Descritores**: HIV. Exercício Físico. Fatores de Risco. Doenças Cardiovasculares.*

RESUMEN

Justificación y Objetivos: la práctica de actividades físicas (PAF) por parte de las personas que viven con el VIH (PVVIH) ha sido recomendada en la literatura médica. Esta medida ha demostrado ser efectiva en el manejo de las PVVIH. Sin embargo, se estima que solo el 50,7% de las PVVIH cumplen con las pautas recomendadas de ejercicio físico. El objetivo de este estudio fue analizar la prevalencia y los factores asociados a PAF en PVVIH usuarias de tratamiento antirretroviral. **Métodos**: estudio observacional transversal, conformado por 276 PVVIH en terapia antirretroviral (TARV), atendidas en el Servicio Ambulatorio Especializado (SAE) de un municipio del interior del Nordeste en 2018. Las variables analizadas incluyeron datos bioquímicos, antropométricos y de presión arterial, así como el Puntuación de Riesgo de Framingham (PRF). Se dividieron en dos grupos: practicantes (pAF) de actividad física; y no practicantes de actividad física (NpAF). Los datos se correlacionaron mediante la Prueba de Chi-Cuadrado de Pearson, con significancia estadística si p<0,05, y mediante estadística inferencial. **Resultados**: de los participantes del estudio, la mayoría eran hombres, y del total del contingente, el 67% (n=185) eran NpAF y, de estos, el 8,6% tenían riesgo moderado y alto de eventos cardiovasculares (RECV) según PRF. El grupo de pAF tuvo una mediana menor para la variable edad [37 (41-48) años, p=0,004] y una mediana mayor para la variable peso [68 (60-77,5) kg, p=0,015]. Entre las pAF, hubo alta prevalencia de bajo riesgo. **Conclusión**: la falta de PAF es altamente prevalente entre las PVVIH, y estas están más asociadas a RECV moderado y alto, además de las consecuencias metabólicas y corporales de la condición viral y la terapia antirretroviral.

***Palabras clave:** VIH. Ejercicio Físico. Factores de Riesgo. Enfermedades Cardiovasculares.*

INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS) is caused by the Human Immunodeficiency Virus (HIV). In addition to causing various damages to the human body, this etiological agent also has the potential to reduce immune function and increase vulnerability to opportunistic diseases. Therefore, continuous administration of antiretroviral therapy (ART) is of fundamental importance to reduce morbidity and mortality caused by this pathogen and significantly increase HIV-positive patients' life expectancy.[1]

According to the epidemiological overview (in Brazil, from 2007 to 2021, 381,793 cases of HIV were reported in the Notifiable Diseases Information System), the large number of people affected is evident, which makes the search for therapeutic improvements, both pharmacological and non-pharmacological, a relevant point in health sciences.[2]

However, the chronicity of both HIV infection and ART use in people living with HIV (PLHIV) often has negative effects on body composition and lipid and carbohydrate metabolism. Among these possible metabolic and bodily consequences, dyslipidemia, lipodystrophy syndrome, generalized obesity and insulin resistance can be mentioned. Therefore, there is an increased risk of cardiovascular events (CVER), such as myocardial infarction, elevated systemic blood pressure and stroke. [3, 4]

Given the higher cardiovascular risk in PLHIV, especially among ART users, physical activity practice (PAP) has been recommended. This non-pharmacological, effective, safe and relatively cheap measure is useful in the prevention and treatment of metabolic and bodily disorders resulting from HIV and ART activity in the human body.[5]

PAP has positive impacts on the physical health and well-being not only of the general population, but also of patients using ART. It is worth noting that physical exercise (PE) is conceptualized as an organized and planned bodily activity with the aim of strengthening physical conditioning or maintaining PAP musculoskeletal body homeostasis, different from physical activity, which does not have the same objective. It is possible to observe in physically active PLHIV undergoing antiretroviral (ARV) treatment the prevention of diseases and improvements

in glycemic regulation, control of systemic blood pressure, progress in the lipid profile, reduction of stress and improvement in quality of life. Therefore, patients who practice regular PE tend to have lower levels of triglycerides (TG), lipodystrophy and advanced glycation end product, in addition to smaller abdominal circumference when compared to sedentary PLHIV.[6]

Through aerobic physical activities, it was possible to notice a reduction in central and trunk fat as well as body perimetry, enabling a reduction in insulin resistance and an improvement in the lipid profile in PLHIV. Furthermore, strength exercises were responsible for increasing lean mass, weight gain and muscle strength.[3, 7]

Infection chronicity and bodily changes caused by ART often have an impact on the psychological aspects of this group. In view of this, regular physical activity plays an important role as it is closely associated with reducing levels of anxiety and depression in PLHIV. This effect is due to the release of endogenous and hypothalamic opioids that act on the emotional state, promoting physical and mental well-being. According to studies, a significant reduction in symptoms of moderate to severe depression was observed in PLHIV undergoing intervention through regular PE.[7, 8]

However, low adherence by PLHIV to interventions related to PAP still constitutes a challenge for improving physical health, mental health and well-being in this group of patients. It is estimated that 50.7% of HIV-positive individuals comply with the World Health Organization (WHO) recommendations, which indicates practicing at least 75 to 150 minutes of intense aerobic physical activity or 150-300 minutes of moderate physical activity.[9]

This data shows that, although PAP has beneficial potential for PLHIV and is indicated for reducing health problems, the percentage of physically active individuals in this group is still below what is desired.[8-10]

Therefore, the present study aims to analyze the prevalence and factors associated with PAP in PLHIV using ART.

METHODS

This is a cross-sectional observational study, in which data obtained from a structured questionnaire used in the umbrella project "Development of a classifier algorithm to predict cardiovascular disease in patients using antiretroviral drugs using a computational model" were analyzed.

Sample participants were recruited between January and November 2018, the period in which the main project mentioned above was carried out, at the Department of Sexually Transmitted Infections in Imperatriz-MA (reference point for service to southern Maranhão and other geographically close municipalities, including some cities in the states of Tocantins and Goiás), which was made up of 276 people, gathered for convenience, of which 91 were practitioners and 185 were not physical activity practitioners, according to anamnesis collected in conjunction with WHO recommendations.

These recommendations advise that any body movement produced by skeletal muscles that require energy expenditure should be considered as physical activity. This concept also includes physical activities carried out during work, games, household chores, travel and leisure activities.[11]

The inclusion criteria for this research were being PLHIV, aged between 20 and 55 years old and using ARV. At the same time, people with cognitive impairment, therapeutic failure or abandonment of ART were considered as exclusion criteria. Furthermore, the sample was divided into two groups: physical activity practitioner (PAp); and physical activity non-practitioner (PANp).

Using a semi-structured questionnaire, originating from the umbrella project, to which this research is linked, the values of the aspects to be analyzed were obtained. This questionnaire was applied to patients who wished to participate in the research at the end of their medical appointments, in a separate environment, where anthropometric measurements were taken, notes of laboratory tests relevant to the research and explanations about the reasons for the research and how the data would be used. The variables analyzed included: clinical-laboratory factors, such as systolic blood pressure (<140mmHg), diastolic blood pressure (<90mmHg), total cholesterol (<200mg/dl), high-density lipoprotein (HDL) (>40mg/dl), TG (<175 mg/dl), fasting blood glucose (<100mg/dl), urea (<20mg/dl) and creatinine (<1.2mg/dl) (analyzed using the Mann-Whitney U test); anthropometric factors, such as waist circumference, abdominal circumference (<102cm for men and <88cm for women) and waist-to-height ratio (<0.5) (analyzed using Student's t test), weight, Body Mass Index (<24.9), hip circumference and waist-hip ratio (analyzed using the Mann-Whitney U test); and social factors, such as PAP, sex and age (using the chi-square test).

For statistical analysis of the data obtained, the Statistical Package for the Social Sciences (SPSS®) software version 19.0 was used. Data were analyzed using Pearson's Chi-Square Test, with statistical significance if $p<0.05$, and Mann-Whitney's U test, being a non-parametric test applied to two independent samples, and Student's t-test, which is a useful hypothesis test in statistics when it is necessary to compare means.

The Framingham Risk Score (FRS) is used as a calculation to predict the risk of cardiovascular diseases (CVD) of a given patient based on the analysis of gender, age, blood pressure, diabetes, smoking, LDL-cholesterol and HDL-cholesterol, classifying according to the score as low, moderate or high.[3]

The project that this study is part of was carried out in accordance with the required ethical standards (Resolutions 466/2012, 510/2016, 580/2018 of the Ministry of Health), and was approved by the *Universidade Federal do Maranhão* Research Ethics Committee, under Opinion 2,781,461on July 23, 2018 (Certificate of Presentation for Ethical Consideration (CAAE - *Certificado de Apresentação para Apreciação Ética*): 84787918.0.0000.5087). All participants signed the Informed Consent Form, and their data was tabulated in a protected Google spreadsheet, available for viewing only after request and acceptance.

RESULTS

Regarding the research sample space, a total of 276 participants were obtained, of which 55.4% (n=153) were male. Furthermore, it is also noteworthy that a large sample size of 185 (67%) individuals did not practice physical activity while only 91 (33%) practiced physical activity.

Furthermore, it was possible to observe a contrast in CVER according to FRS, given that, among those included in the PANp group, 91.4% (n=169) had low CVER and 8.6% (n=16) had moderate and high risk, whereas in the PAp group, there was a high prevalence of low risk, in which 98.9% (n=90) were included in this risk range and only 1.1% (n=1) were in the moderate and high risk range (p-value = 0.014).

Table 1 brings together the variables that were analyzed by the study, with only age and weight showing a statistically significant difference (p<0.05). Therefore, it was found that the PAp group had a lower median age [37 (31-45) years; p=0.004] and higher median weight [68 (60-77.5) kg; p=0.015] in relation to the PANp group, with a median age of 41 (34.5-48) years and weight of 63.00 (55.25-73.75) kg.

Other risk factors (RF) were also analyzed, however p>0.05 in all, not showing statistical significance, namely waist-hip ratio (WHR), waist-height ratio (WHtR), total cholesterol (TC), HDL, TG, fasting blood glucose (FBG), Body Mass Index (BMI), waist circumference (WC), abdominal circumference (Abdc), hip circumference (HC), urea and creatinine. The investigation of these data in the PANp group showed higher medians in WHR [0.88 (0.83-0.88)], WHtR [0.526±0.76], TC, [170 (142-192)], HDL [40.11 (33.90-47.00)], TG [147.5 (109 -190.3)] and FBG [94 (86-102)].

Furthermore, the PAp group had a higher prevalence of BMI [24.80 (22.71-28.11) kg/m^2], WC [85.45±9.59 cm], Abdc [89.91±9.61], HC [98 (94-102)], urea [25.64 (21.88-31)] and creatinine [0.82 (0.64-1.01)].

The data analyzed showed similar median systolic blood pressure (SBP) and diastolic blood pressure (DBP) between the PAp and PANp groups. For PAp, SBP [120 (113-130) mmHg] had a median equal to PANp [120 (110-133) mmHg]. Regarding DBP, the medians were 81 (71-90) mmHg for PANp and 80 (74.5-89.5) mmHg for PAp.

DISCUSSION

According to the analysis of study results, it was found that the number of PLHIV who practice physical activities is still lower than expected, given the beneficial potential that could be provided to them, such as reducing aggregate cardiovascular risk, reducing irregular fat deposits throughout the body (lipodystrophy) and reducing laboratory components that are harmful if in excess, such as TG.

This study consisted of 276 patients with HIV using ART. The majority were male (55.4%), which is similar to another study in which the predominant population with HIV were men (57.9%).[10]

This higher incidence can be explained by the fact that these individuals, when younger, have poor knowledge about the forms of HIV transmission and prevention, the large number of sexual partners, in the case of men who have sex with men, and conception misconception by heterosexual men that they have immunity to HIV. Furthermore, the latter are not highlighted in virus prevention policies or actions, which makes them vulnerable to infection.[11-13]

Not performing PE corresponded to 67% of the total individuals in the sample. A study in the United States on physical activity in PLHIV showed that the majority of patients (68%) had low adherence.[14] In agreement, research carried out in Malawi also reported that the majority (40%)

Table 1. Prevalence of risk factors associated with physical activity.

	PANp	PAp	p-value
Age*	41 (34.5-48)	37 (41-48)	0.004
Weight*	63.00 (55.25-73.75)	68 (60-77.5)	0.015
BMI*	24.38(21.40-27.38)	24.80 (22.71-28.11)	0.262
WC**	85.00±12.32	85.45±9.59	0.761
Abdc**	89.41±11.91	89.91±9.61	0.730
HC*	96 (91-102)	98 (94-102)	0.077
WHR*	0.88 (0.83-0.88)	0.86 (0.82-0.93)	0.293
WHtR**	0.526±0.76	0.522±0.71	0.674
SBP*	120 (110-133)	120 (113-130)	0.648
DBP*	81(71-90)	80 (74.5-89.5)	0.48
Total cholesterol*	170 (142-192)	166 (143-200)	0.832
HDL*	40.11 (33.90-47.00)	38.95 (31.70-47.82)	0.525
Triglycerides*	147.5 (109 -190.3)	131 (97-191)	0.224
Fasting blood glucose*	94 (86-102)	92 (84.93-99)	0.216
Urea*	25.23 (20.67-29.51)	25.64 (21.88-31)	0.404
Creatinine*	0.80 (0.66-0.95)	0.82(0.64-1.01)	0.58

*Abbreviations: BMI - Body Mass Index; WC - waist circumference; Abdc - abdominal circumference; HC - hip circumference; WHR - waist-hip ratio; WHtR - waist-to-height ratio; SBP - systolic blood pressure; DBP - diastolic blood pressure; HDL - high-density lipoproteins; *Mann-Whitney U test - values described as median and interquartile range; **Student's t test - values described as mean and standard deviation.*

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of PLHIV on ART had low levels of physical activity.[15]

To elucidate this behavior, according to the referenced literature, PLHIV reported barriers that made it difficult to perform physical activities, such as physical fatigue, gastric disorders, muscle pain, low weight, negative self-perception about lack of physical capacity, fear of contaminating training partners when injured, lack of social support and financial and time restrictions. [16]

PE is conceptualized as an organized and planned bodily activity with the aim of strengthening physical conditioning or maintaining musculoskeletal body homeostasis. However, evidence indicates that PAP has beneficial effects, such as improvements in balance and strength. In this context, the use of PAP as a non-pharmacological therapy in patients with the HIV virus was suggested, since the comorbidities caused by the virological condition are aggravated by a sedentary lifestyle.[17]

Furthermore, studies demonstrate that this portion of the population suffers accelerated aging in relation to the uninfected and, consequently, has an increased risk for age-dependent pathologies and, mainly, for CVD.[18-20]

As determined by the analysis of data from the sample space, it is clear that older individuals tend to practice less physical activity, which contrasts with the benefit exposed in the literature, given that the cardiovascular risk in PLHIV increases with aging and that moderate to vigorous physical activities would be indicated to reduce mortality in adults between 50-79 years old.[21]

Regarding the body changes provided by PAP for PLHIV, the literature shows that this intervention has the capacity to provide an increase in lean mass along with an increase in individuals' weight.[3] Therefore, the data obtained in the present study are consistent with those found by other authors, as a higher median was observed in the weight variable in the PAp group when compared to the PANp group.

At the same time, analyzes based on the FRS indicate that CVER is exponentially higher in PLHIV when compared to the public without the disease, possibly due to the effect of endothelial and inflammatory damage that the pathology and ART cause in the human body, such as accumulation of visceral fat.[22, 23]

Additionally, the relationship between physical activity and CVD risk is linked to the cardiorespiratory fitness of these patients. This physical aspect is considerably diminished in PLHIV and is associated with an increase in plasma inflammatory markers which, through PAP, can be reduced.[18, 20]

Therefore, scientific data confirms an improvement in cardiorespiratory capacity with high-intensity PAP as a therapeutic measure in female patients, with no improvements in males. This data is potentially explained by the imbalance and hormonal instability of women with HIV in periods adjacent to menopause, which leads to other cardiovascular RF, imposing the need for more intense training than traditional training.[24] Such perspectives were corroborated by the sample survey of the present study, since the PANp group has a greater number of individuals at moderate and high risk of CVD, according to FRS, and also a smaller number classified at low risk in relation to the PAp group.

Comparing the data from the study in question with others found in the literature, it is identified that, among individuals affected by the virus, males, in addition to being those with the highest prevalence of HIV, have a higher risk of CVD than women.[22-24]

Therefore, it appears that health actions and policies on HIV prevention must be developed for the general public, but with a focus on men, since this study and the literature prove that this portion of the population has organic responses, mainly cardiac, distinct to HIV.

Furthermore, physiotherapy and PAP, together with ART, obtained significant positive results, as the grouping of these interventions helped to reduce body fat and its harmful metabolic components, in addition to also reducing glucose values.[24]

Accordingly, it is pointed out that regular and active PAp individuals present, compared to the PANp group, a better distribution of body fat and, therefore, are less prone to lipodystrophy.[24]

Regarding glucose and body fat levels, there is literature with results similar to those of the present study, indicating that a planned and individualized physical intervention is capable of promoting changes in these variables. Furthermore, the findings regarding total cholesterol and TG were similar in both studies, with reduced values among the PAp group.[25]

However, there was contradiction in the literature regarding data relating to BMI and HC, given that, in the literature, a reduction in these variables is indicated among physically active patients, which was not corroborated by the data analysis of this study.[25]

According to data evidenced by the study and together with the referenced literature, it appears that there is the possibility of a metabolic benefit with PAP in the organic response of PLHIV to the misfortunes caused by the combination between the current pathology and ART and, mainly, improve the hemodynamic profile by reducing the risk of future CVD. But the lack of PAP is still highly prevalent in this population. In this sense, it is important that the Specialized Outpatient Service team prioritizes actions that influence PAP by PLHIV, thus strengthening healthy lifestyle habits, in order to avoid early death from CVD. It is also important that healthcare professionals are trained to understand and prescribe PAP appropriately for their patients, given the benefits that can be brought about in clinical practice.

As limitations of this study, it can be noted that chronic HIV infection and the use of ART associated with patients' individual characteristics make people living with HIV a heterogeneous population that is difficult to parameterize. Furthermore, the lack of some potentially important variables that could modify the parameters found was not included in the present analysis, such as time spent practicing physical activity, time since diagnosis, degree of intensity of physical activity, CD4+ cell count, chronic diseases, among others.

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All authors approved the final version to be published and are responsible for all aspects of the work, including ensuring its accuracy and integrity.

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Hospital Santa Cruz

ORIGINAL ARTICLE

Congenital syphilis in Roraima and Venezuelan migration: analysis of cases at the state maternity hospital in the 2017/2018 and 2020/2021 biennia

Sífilis congênita em Roraima e a migração venezuelana: análise de casos na maternidade estadual nos biênios 2017/2018 e 2020/2021

Sífilis congénita en Roraima y migración venezolana: análisis de casos en la maternidad estatal en los bienios 2017/2018 y 2020/2021

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ABSTRACT

Background and objectives: in 2017 and 2018, Roraima experienced the most significant increase in congenital syphilis incidence rates among all federal units. This phenomenon occurred in parallel with the significant Venezuelan migration to the region. The study aimed to analyze the relationship between the increase in cases of congenital syphilis registered at the *Hospital Materno Infantil Nossa Senhora de Nazareth* and the Venezuelan migratory crisis. **Methods**: this is a document-based, descriptive research, covering the 2017/2018 and 2020/2021 periods, developed from data collected in copies of congenital syphilis report/investigation forms from the hospital. **Results**: in the 2017/2018 biennium, the peak of Venezuelan migration in Roraima, fewer cases of syphilis occurred than when the migratory flow declined. In the 2020/2021 biennium, there was a decrease in the migratory flow due to the closing of the border and the acceleration of the interiorization process. Although it is the period with the highest number of reports of congenital syphilis among Venezuelan mothers, the percentage is considerably lower than that recorded among Brazilian women. The incidence rate was higher among the group of Brazilian mothers (7.5/1,000 live births, in the 2017/2018 period, and 11.5/1,000 live births, in the 2020/2021 period). **Conclusion**: Venezuelan migration, although it may have eventually exerted some influence on the total number of cases of congenital syphilis, cannot be considered the determining factor for the increase in cases of the disease in the hospital in the defined period, and other factors deserve to be assessed as decisive in this case.

Keywords*: Maternal and Child Health. Congenital Syphilis. Migration and Health. Epidemiological Monitoring.*

RESUMO

Justificativa e objetivos: em 2017 e 2018, Roraima apresentou o aumento mais significativo nas taxas de incidência de sífilis congênita entre todas as unidades federativas. Este fenômeno ocorreu paralelamente à significativa migração venezuelana para a região. O estudo teve como objetivo analisar a relação entre o aumento de casos de sífilis congênita registrados no Hospital Materno Infantil Nossa Senhora de Nazareth e a crise migratória venezuelana. **Métodos:** trata-se de uma pesquisa documental, descritiva, abrangendo os períodos 2017/2018 e 2020/2021, desenvolvida a partir de dados coletados em cópias de fichas de notificação/investigação de sífilis congênita do hospital. **Resultados:** no biênio 2017/2018, pico da migração venezuelana em Roraima, ocorreram menos casos de sífilis do que quando o fluxo migratório diminuiu. No biénio 2020/2021, registou-se uma diminuição do fluxo migratório devido ao encerramento da fronteira e à aceleração do processo de interiorização. Embora seja o período com maior número de notificações de sífilis congênita entre mães venezuelanas, o percentual é consideravelmente inferior ao registrado entre as brasileiras. A taxa de incidência foi maior entre o grupo de mães brasileiras (7,5/1.000 nascidos vivos, no período 2017/2018, e 11,5/1.000 nascidos vivos, no período 2020/2021). **Conclusão:** A migração venezuelana, embora possa eventualmente ter exercido alguma influência no total de casos de sífilis congênita, não pode ser considerada o fator determinante para o aumento de casos da doença no hospital no período definido, e outros fatores merecem ser destacados. ser considerada decisiva neste caso.

Palavras-chave: *Saúde Materno-Infantil. Sífilis Congênita. Migração e Saúde. Vigilância Epidemiológica.*

RESUMEN

Antecedentes y objetivos: en 2017 y 2018, Roraima experimentó el aumento más significativo en las tasas de incidencia de sífilis congénita entre todas las unidades federales. Este fenómeno se produjo en paralelo con la importante migración venezolana a la región. El estudio tuvo como objetivo analizar la relación entre el aumento de casos de sífilis congénita registrados en el Hospital Materno Infantil Nossa Senhora de Nazareth y la crisis migratoria venezolana. **Métodos:** se trata de una investigación descriptiva, documental, que abarca los períodos 2017/2018 y 2020/2021, desarrollada a partir de datos recolectados en copias de formularios de informe/investigación de sífilis congénita del hospital. **Resultados:** en el bienio 2017/2018, pico de migración venezolana en Roraima, ocurrieron menos casos de sífilis que cuando el flujo migratorio disminuyó. En el bienio 2020/2021 se produjo una disminución del flujo migratorio debido al cierre de fronteras y la aceleración del proceso de interiorización. Si bien es el período con mayor número de reportes de sífilis congénita entre madres venezolanas, el porcentaje es considerablemente menor que el registrado entre las mujeres brasileñas. La tasa de incidencia fue mayor entre el grupo de madres brasileñas (7,5/1.000 nacidos vivos, en el período 2017/2018, y 11,5/1.000 nacidos vivos, en el período 2020/2021). **Conclusión:** La migración venezolana, si bien eventualmente pudo haber ejercido alguna influencia en el número total de casos de sífilis congénita, no puede considerarse el factor determinante del aumento de casos de la enfermedad en el hospital en el período definido, y otros factores merecen ser considerados. considerarse decisivo en este caso.

Palabras clave: *Salud Materno Infantil. Sífilis congénita. Migración y Salud. Vigilancia Epidemiológica.*

INTRODUCTION

According to data from the Ministry of Health (MoH), released in the 2019 Epidemiological Bulletin, the state of Roraima presented, between 2017 and 2018, the most significant increase in the incidence rates of congenital syphilis (CS) among all federative units (132.0%). In addition to the worrying increase, the bulletin also recorded that the mortality rate due to CS in children under one year of age (per 100,000 live births) in Roraima, in 2018, was 8.5, i.e., above the national mortality coefficient of 8.2.[1] The 2020 Bulletin, in turn, revealed that Roraima is among the twelve states that, in 2019, had syphilis detection rates in pregnant women higher than those in Brazil.[2] These data, however, hide an important sociodemographic aspect that significantly affected the provision of public services, including in the health field, in the state of Roraima, from 2015 onwards: the migration of predominantly low-income people from Venezuela.[3]

Venezuelan migration in the second half of the 2010s can be considered a watershed in Roraima's history.[4] The state had never received such a significant population contingent in an international migration process that was beyond the Brazilian authorities' control. The state's geographic position, which is the main entry point for Venezuelans into Brazil, made migration an especially challenging process in terms of controlling demographic growth.

Among the socio-structural impacts caused by the massive Venezuelan migration, one of the most persistent for state public management was that related to migrants' demands for medical and hospital care.[5] According to Roraima's 2020 epidemiological report, 2,792 births to Venezuelan mothers were registered, equivalent to 20.9% of all births that occurred that year.[6]

Local health authorities were concerned about controlling the disease during neonatal care. As soon as it was realized that many Venezuelan pregnant women did

not receive prenatal care (mainly rapid screening tests for syphilis and/or VDRL) and did not receive adequate medical treatment in their country of origin, which increases the risk of vertical transmission of the disease.[7]

This study aimed to analyze the relationship between the increase in the number of cases of CS in Roraima, more specifically at *the Hospital Materno Infantil Nossa Senhora de Nazareth* (HMINSN), and the Venezuelan migration crisis.

METHODS

The study was descriptive in nature, supported by a documentary basis, with a quantitative approach and retrospective temporal directionality. It was developed from data collected in copies of CS report/investigation forms – which consist of forms standardized by the MoH and filled out by health professionals – collected in HMINSN archives: the largest maternity hospital in Roraima and which until May 2021 was the only public maternity hospital in the state.

The time frame of this study focuses on two specific biennia: 2017/2018 and 2020/2021. This choice of periods deserves clarification as to the underlying reasons. Initially, the proposal for the work was to cover from 2017 to 2020. However, the authors became aware that the file containing copies of report forms for 2019 was damaged by a fortuitous event, making them unavailable for consultation. It was then considered that the absence of case records from 2019 could be overcome by a methodological strategy that will be explained below.

The two biennia were considered landmark moments in relation to the flow of Venezuelan migrants to Roraima. In 2017 and 2018, the flow reached its peak (with around 85 thousand Venezuelans settled in the state), and demands for health services by migrants reached records. In 2020 and 2021, the border was closed due to the COVID-19 pandemic, which caused the migration flow to significantly reduce.[8] The research hypothesis then focused on the comparison between the two periods: the first with high-intensity migratory flow and the second with medium-intensity flow.

Thus, if migration were at the center of the factors that could explain the changes in the number of cases of CS in recent years in Roraima, it would be expected that the report forms from the years prior to 2019 would present data on an increase in cases, or, at least, that they would be data pointing to more cases than those recorded in the years after 2019, when the migratory flow cooled down.

The study population was made up of all CS report/investigation records, including cases with an unfavorable outcome, such as cases of miscarriages and stillbirths, and incomplete records (only page 1 of 2) completed by the *Hospital Materno Infantil Nossa Senhora de Nazareth* (HMINSN/ESU) Epidemiological Surveillance Unit from 2017 to 2018 and from 2020 to 2021, totaling 459 copies of report forms.

Copies of report forms for indigenous patients were excluded from the study, in addition to four other original report/investigation forms with a case note of "DISCARDED" that remained in the HMINSN/ESU files but were not forwarded to the Municipal Health Department of Boa Vista, for report purposes (CS hypothesis ruled out by ESU employees themselves).

As one of the objectives of this research was to reach the total universe of report/investigation forms for CS at HMINSN, it was not necessary to carry out a sample calculation.[9]

Data collection consisted of two main steps. Firstly, the information provided in copies of report/investigation forms from 2017/2018 and 2020/2021, filed in the hospital's ESU database, was collected manually. A form adapted by the authors was used as a data collection instrument, prepared based on information present in the MoH report/investigation form, in order to delimit the variables of interest for the study.

The report forms for the condition under analysis are important sources of health research, as they contain social, epidemiological, clinical and laboratory data on pregnant women and their unborn children.[10] However, it is worth noting that they do not contain a specific field for determining the nationality of mothers of children diagnosed or investigated with CS.

There is a recommendation from the Health Surveillance Superintendence of the municipality of Boa Vista that, from November 29, 2017, information regarding the nationality of patients should be included in the forms of Compulsory Reportable Diseases and Immediate Compulsory Reportable Diseases. In 2022, this document was reiterated, however, despite this, at least at HMINSN, information regarding nationality began to be, eventually, noted additionally in the section dedicated to the mother's residential data. In most cases, this information was ignored in reports. In 81.2% (373 records), there was no information on nationality and only in 18.7% (86 records) this note was present.

Faced with this scenario, the second stage of collection dealt with the primary collection of data regarding mothers' nationalities, precisely because the majority of report forms did not consider such information. To this end, a spreadsheet was created with the names of mothers whose nationalities were unknown, and research was carried out with the HMINSN Medical Archiving and Statistics Service, which has a record of all patients admitted to the hospital.

After completing the data collection stage, the information obtained by consulting the 459 records was tabulated and organized in an Excel spreadsheet (version 2204, Microsoft®) by year of report. Data analysis was carried out using descriptive statistics procedures, with results presented in tables.

To calculate the CS incidence rate, the number of reported/investigated cases of CS at HMINSN was used, divided by the number of live newborns in Roraima[11] during the two years under study, multiplied by a thousand.

The research was approved by the Research Ethics Committee of the *Universidade Federal de Roraima*, with

registration on Platform Brazil, according to Process 51435021.6.0000.5302.

RESULTS

For the time frame of two biennia (2017/2018 and 2020/2021), records of 459 CS report/investigation forms were found at HMINSN, including incomplete copies (which only contained page 1 of 2), but with information on relevance to the research and which, therefore, could not be excluded.

Table 1 (below) provides the distribution of cases reported/investigated at HMINSN according to maternal nationality with the time frame of 2017/2018 and 2020/2021. The method of organizing the table – according to mothers' nationality and year of service – makes it possible to understand, at a comparative level, the quantitative impact of migration compared to registration of cases over two biennia.

The data present in the table demonstrate progressive increase, in absolute value, of reports in the maternity ward for the periods analyzed. Furthermore, 2017 had the lowest occurrence of CS reports among mothers of Venezuelan nationality, representing only 2.70% (n=02) of total cases for that year, as opposed to 97.30% (n=72) of case records among Brazilian mothers.

In turn, the year with the highest number of reports among children of Venezuelan migrants was 2020, with 25.71% (n=36) of total cases (i.e., 140), as opposed to 73.57% (n= 103) of children of Brazilian women. It is important to highlight that, in 2021, there has been a drop in the number of reports among Venezuelan migrants compared to the previous year, totaling 14.67% (n=22) or 150 cases registered that year.

When analyzing incidence rates of cases of reported/investigated CS at HMINSN (per 1,000 live births), according to maternal nationality, a notable increase was observed between both groups over the two years, but with a higher incidence recorded among Brazilian mothers (Figure 1).

In table 2, which concerns access to prenatal care, it can be seen that 72.55% of mothers underwent follow-up; 20.92% did not undergo follow-up; 1.31% had this information ignored; and 5.23% did not fill out the form. When comparing groups of mothers, it is observed that, among Brazilian mothers, 76.09% had access to prenatal care and 17.22% did not, while among Venezuelan mothers, 52.94% had access to prenatal care and 41.18% no.

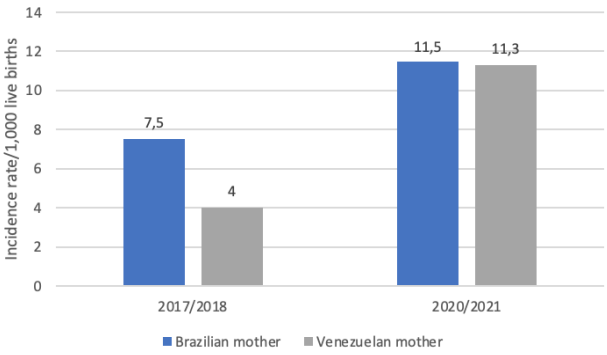

Figure 1. Incidence rates of reported/investigated cases of congenital syphilis (per 1,000 live births) according to mothers' nationality at Hospital Materno Infantil Nossa Senhora de Nazareth (2017/2018 and 2020/2021).

It is noted that, regarding the moment of maternal diagnosis, among Brazilian women, 68.38% were diagnosed with syphilis in a timely manner during prenatal care and 22.11% at childbirth/curettage. This percentage is different in the case of Venezuelans, since 55.88% received the diagnosis during prenatal care, and a higher percentage was diagnosed only during childbirth/curettage (35.29%) compared to Brazilian women.

During the period under study, the evolution of cases that resulted in a live newborn was recorded in 55.56% of records, as can be seen in Table 3 (below). Cases in which there was no information or incomplete copies corresponded to 30.07% of records; cases that resulted in miscarriage, 6.10%; cases that resulted in stillbirths, 2.40%; and those whose case evolution was categorized as ignored, 4.14%.

With regard specifically to cases that progressed to an unfavorable outcome, the data in Table 4 (below) indicate that the year with the highest proportion of this type of outcome was 2018, with 30.52% (n=29) of all cases report/investigation of CS registered that year.

Among the cases with an unfavorable outcome, in 2018, as can be seen, 16.84% (n=16) were miscarriages, 5.26% (n=05) were stillbirths and 4.21% (n= 4), with death annotation in a non-specific field of Brazilian women. Only 3.16% (n=03) and 1.05% (n=01) of cases of miscarriage and stillbirth, respectively, were related to Venezuelan mothers.

Table 1. Distribution of reported/investigated cases of congenital syphilis according to mothers' nationality at Hospital Materno Infantil Nossa Senhora de Nazareth (2017/2018 and 2020/2021).

Mothers' nationality	2017 (n= 74)		2018 (n= 95)		2020 (n= 140)		2021 (n= 150)		Total	
	n	%	n	%	n	%	n	%	n	%
Brazilian	72	97.30%	86	90.53%	103	73.57%	128	85.33%	389	84.75%
Venezuelan	2	2.70%	8	8.42%	36	25.71%	22	14.67%	68	14.81%
Guyanese	0	0.00%	1	1.05%	1	0.71%	0	0.00%	2	0.44%
									459	**100.00%**

Source: developed by the authors.

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Table 2. Distribution of reported/investigated cases of congenital syphilis according to information on mothers' epidemiological history (prenatal care and time of diagnosis) at no Hospital Materno Infantil Nossa Senhora de Nazareth (2017/2018 and 2020/2021).

Variables	Mothers' nationality							
	Brazilian		Venezuelan		Guyanese		Total	
	n	%	n	%	n	%	n	%
Prenatal care during this pregnancy								
Yes	296	76.09%	36	52.94%	1	50.00%	333	72.55%
No	67	17.22%	28	41.18%	1	50.00%	96	20.92%
Ignored	5	1.29%	1	1.47%	0	0.00%	6	1.31%
Not reported	21	5.40%	3	4.41%	0	0.00%	24	5.23%
Moment of diagnosis								
During prenatal care	266	68.38%	38	55.88%	1	50.00%	305	66.45%
At childbirth or curettage	86	22.11%	24	35.29%	1	50.00%	111	24.18%
After childbirth	16	4.11%	2	2.94%	0	0.00%	18	3.92%
Not performed	5	1.29%	1	1.47%	0	0.00%	6	1.31%
Ignored	1	0.26%	0	0.00%	0	0.00%	1	0.22%
Not reported	15	3.86%	3	4.41%	0	0.00%	18	3.92%

Source: developed by the authors.

Table 3. Distribution of cases of congenital syphilis according to the evolution of children's case at Hospital Materno Infantil Nossa Senhora de Nazareth (2017/2018 and 2020/2021).

Case evolurton	Mothers' nationality							
	Brazilian		Venezuelan		Guyanese		Total	
	n	%	n	%	n	%	n	%
Live	214	55.01%	40	58.82%	1	50%	255	55.56%
Death from congenital syphilis	0	0.00%	1	1.47%	0	0.00%	1	0.22%
Death from other causes	0	0.00%	1	1.47%	0	0.00%	1	0.22%
Miscarriage	22	5.66%	6	8.82%	0	0.00%	28	6.10%
Stillborn	9	2.31%	2	2.94%	0	0.00%	11	2.40%
Death annotation in non-specific field	6	1.54%	0	0.00%	0	0.00%	6	1.31%
Ignored	19	4.88%	0	0.00%	0	0.00%	19	4.14%
Not reported or unavailable due to lack of a copy of the back of the form	119	30.59%	18	26.47%	1	50%	138	30.07%

Source: developed by the authors.

Table 4. Percentage distribution of congenital syphilis cases by type of unfavorable outcome and year of report at Hospital Materno Infantil Nossa Senhora de Nazareth (2017/2018 and 2020/2021).

Type of unfavorable outcome	Mothers' nationality							
	2017		2018		2020		2021	
	Brazil	Venezuela	Brazil	Venezuela	Brazil	Venezuela	Brazil	Venezuela
Death from congenital syphilis	0.00%	0.00%	0.00%	0.00%	0.00%	0.71%	0.00%	0.00%
Death from other causes	0.00%	1.35%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Miscarriage	4.05%	0.00%	16.84%	3.16%	2.14%	0.71%	0.00%	1.33%
Stillborn	2.70%	0.00%	5.26%	1.05%	0.71%	0.00%	0.67%	0.67%
Death annotation in a non-specific field	0.00%	0.00%	4.21%	0.00%	1.43%	0.00%	0.00%	0.00%
Total	8.11%		30.52%		5.70%		2.67%	

Source: developed by the authors.

DISCUSSION

This research collected and organized information that could support debates within the scope of public health management and epidemiological surveillance regarding the effects of Venezuelan migration in Roraima, based on quantitative data obtained on cases of CS among patients (mothers and children) treated in the 2017/2018 and 2020/2021 biennia at HMINSN.

From what can be seen, 2017 was the year with the lowest record of CS reports among Venezuelan mothers. Interestingly, that same year, according to data from the Federal Police, more than 70 thousand Venezuelans

entered Roraima.[12] The year with the highest number of reports among children of migrants was 2020, when the Brazil-Venezuela border was closed due to the COVID-19 pandemic, and many Venezuelan migrants were being internalized to other states. By the way, that same year, there was an increase in cases of CS in federative units that, proportionally, received few internalized migrants, such as Bahia, Sergipe, Amapá and Alagoas.[13]

These data challenge the considerations made in a study that states that "the disorderly displacement of Venezuelans" would have caused an "increase in the incidence of sexually transmitted infections such as syphilis".[14] At least in the case of CS, this statement was not corroborated in the research. Even though the migratory process has influenced to some extent the increase in cases of CS, it is not possible to consider it as a determining factor.

The CS incidence rate varied between the groups analyzed. In 2017/2018, the incidence among Brazilian mothers was approximately twice as high as among Venezuelan mothers. However, in the 2020/2021 period, there was a minimal difference in the incidence rate between these two groups (Figure 1).

Attention is drawn to the low percentage of prenatal care among Venezuelan migrants: a phenomenon that deserves further investigation. On the one hand, it is possible that the difference in prenatal care quality between Brazilian and Venezuelan women arises from obstacles to access to pregnancy monitoring services by migrants in Brazil, but, on the other hand, this could arise from limited access to prenatal care in their country of origin. Consideration of testing these hypotheses could lead to a new study.

In this regard, it is worth mentioning research that sought to identify, in Ecuador, whether there was a difference in morbidity between children born to migrant mothers and local mothers.[15] Like Brazil, Ecuador has also received, in recent years, a large Venezuelan migratory contingent. The study by Ecuadorian researchers obtained a result similar to that found in this research: that Venezuelan mothers had a lower number of prenatal checks, when compared to local women. The research also demonstrated that, among migrant women who had undergone prenatal care, 71.90% did so with health services in Ecuador and 18.10% in their country of origin.

There is a correlation between the lack of prenatal care and stillbirth rates due to CS, which makes the scenario found in the research even more worrying.[16] Although, in recent years, Brazil has made progress in expanding access to prenatal care throughout the national territory, regional inequalities are still found, especially in the North. Barriers persist in this region that make it difficult for pregnant women to have timely access to prenatal care,[17] especially among the most vulnerable groups, such as indigenous people, black women and women with a low level of education.[18] As seen, in Roraima, migrant women are added to these groups.

Thus, 2018, the period with the highest occurrence of deaths, miscarriages and stillbirths related to CS at HMINSN, coincided with the moment of the intense flow of Venezuelan migrants to the state of Roraima. However, the research also indicated that the occurrence of these outcomes cannot be attributed to migrant women, considering that, of the 95 reports made that year, only eight were of children whose mother is Venezuelan (Table 1).

The unfavorable outcomes may be related to other factors, such as, probably, a global crisis in penicillin supply. A study that sought to analyze the shortage of benzathine penicillin in the city of Rio de Janeiro between 2013 and 2017 found that the lack of this antibiotic impacted CS control actions,[19] highlighting that pregnant women who are inadequately treated or who do not undergo treatment can transmit the infection to their babies, which could lead to fetal or neonatal death, in addition to other complications.

The study had limitations related to the fact that certain copies of CS report/investigation forms were incomplete. This occurred in 19 situations and, in all of them, it was not possible to identify the evolution of children's case. As a form of mitigation, these situations were grouped under the "not reported or unavailable due to lack of copy of the back of the form" item.

The research also presented some other limitations, such as the existence of two models of CS report/investigation forms used by the hospital, a standard MoH model and an unofficial one, in addition to the lack of data filling in some forms.

In the first case, there was a need to adapt the "prenatal care" variable content in the following terms: the official MoH form presents as possible answers "1 - Yes", "2 - No" and "9 - Ignored". The unofficial form presents as an option the number of consultations carried out by the pregnant woman, which varies from 0 to 6 or ignored. For this variable, when using the second form model, prenatal care was considered to have been carried out from one consultation, considering that, during the first consultation, it is already recommended by the MoH that pregnant women undergo a treponemal test, preferably the rapid test. In the second case, in relation to the forms with fields not filled in, missing information was inserted in the "not reported" field.

This study plays a significant role in understanding the challenges faced by public health in relation to Venezuelan migration in Roraima, particularly with regard to cases of CS. Data collected questions previous assumptions, and highlights the importance of prenatal care while challenging the direct correlation between disordered migration and the increase in cases of CS. Furthermore, the research highlights the need for policies and interventions that aim to improve access to prenatal care, especially among vulnerable groups, including Venezuelan migrants. The complexity of the factors involved in this scenario requires a multifaceted approach to improving maternal and child health in migration contexts, with special consideration for prenatal care quality.

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AUTHORS' CONTRIBUTIONS:

Natana Ferreira de Oliveira Xavier contributed to bibliographical research, writing summary, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Alexander Sibajev** contributed to writing the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics.

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ABSTRACT

Background and objectives: inanimate surfaces and equipment in the hospital environment are considered reservoirs of resistant and pathogenic microorganisms. In Pediatric Intensive Care Units, the risk of infection is also related to the severity of pathologies associated with the immaturity of the immune system of this population. This study aimed to investigate microbiological environmental contamination in a Pediatric Intensive Care Unit. **Method:** this is an exploratory cross-sectional study, carried out in a Pediatric Intensive Care Unit of a highly complex university hospital, located in southern Brazil. To assess environmental contamination, sterile swabs were rubbed on surfaces corresponding to the patient unit and in the common area. **Results:** twenty-eight surfaces were analyzed, 12 of which were located in units occupied by patients at the time of collection and 16 surfaces in the common use area. In the total number of surfaces analyzed by microbiological cultures, the patient unit showed 66.67% contamination by microorganisms, while surfaces in the common area showed 56.25%. Regarding the microbiological profile, all isolated microorganisms were Gram-positive and showed resistance, namely *Staphylococcus aureus* and coagulase-negative *Staphylococcus*. **Conclusion:** there was evidence of a high frequency of contamination on inanimate surfaces and equipment near and far from patients, essentially by pathogenic and multi-resistant microorganisms to antimicrobials.

Keywords: *Nosocomial Infection; Multiple Bacterial Pharmacoresistance; Pediatric Intensive Care Unit; Hospital Cleaning Service; Nursing.*

RESUMO

Justificativa e objetivos: superfícies e equipamentos inanimados no ambiente hospitalar são considerados reservatórios de microrganismos resistentes e patogênicos. Nas Unidades de Cuidados Intensivos Pediátricos, o risco de infeção também está relacionado com a gravidade das patologias associadas à imaturidade do sistema imunitário desta população. Este estudo teve como objetivo investigar a contaminação microbiológica ambiental

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em uma Unidade de Terapia Intensiva Pediátrica. **Método:** trata-se de um estudo exploratório transversal, realizado em uma Unidade de Terapia Intensiva Pediátrica de um hospital universitário de alta complexidade, localizado no Sul do Brasil. Para avaliar a contaminação ambiental, foram esfregados swabs estéreis nas superfícies correspondentes à unidade do paciente e na área comum. **Resultados:** foram analisadas vinte e oito superfícies, sendo 12 localizadas em unidades ocupadas por pacientes no momento da coleta e 16 superfícies em área de uso comum. No total de superfícies analisadas por culturas microbiológicas, a unidade paciente apresentou 66,67% de contaminação por microrganismos, enquanto as superfícies da área comum apresentaram 56,25%. Quanto ao perfil microbiológico, todos os microrganismos isolados eram Gram-positivos e apresentavam resistência, nomeadamente Staphylococcus aureus e Staphylococcus coagulase-negativa. **Conclusão:** houve evidência de elevada frequência de contaminação em superfícies inanimadas e equipamentos próximos e distantes dos pacientes, essencialmente por microrganismos patogênicos e multirresistentes aos antimicrobianos.

Palavras-chave: *Infecção Hospitalar; Farmacoresistência Bacteriana Múltipla; Unidade de Terapia Intensiva Pediátrica; Serviço de Limpeza Hospitalar; Enfermagem.*

RESUMEN

Fundamento y objetivos: las superficies y equipos inanimados del ambiente hospitalario son considerados reservorios de microorganismos resistentes y patógenos. En las Unidades de Cuidados Intensivos Pediátricos el riesgo de infección también se relaciona con la gravedad de patologías asociadas a la inmadurez del sistema inmunológico de esta población. Este estudio tuvo como objetivo investigar la contaminación ambiental microbiológica en una Unidad de Cuidados Intensivos Pediátricos. **Método:** se trata de un estudio exploratorio transversal, realizado en una Unidad de Cuidados Intensivos Pediátricos de un hospital universitario de alta complejidad, ubicado en el sur de Brasil. Para evaluar la contaminación ambiental se frotaron hisopos estériles en las superficies correspondientes a la unidad de pacientes y en el área común. **Resultados:** se analizaron veintiocho superficies, 12 de las cuales estaban ubicadas en unidades ocupadas por los pacientes en el momento de la recogida y 16 superficies en el área de uso común. Del total de superficies analizadas por cultivos microbiológicos, la unidad de pacientes presentó un 66,67% de contaminación por microorganismos, mientras que las superficies del área común presentaron un 56,25%. En cuanto al perfil microbiológico, todos los microorganismos aislados fueron Gram positivos y presentaron resistencia, concretamente Staphylococcus aureus y Staphylococcus coagulasa negativo. **Conclusión:** se evidenció alta frecuencia de contaminación en superficies inanimadas y equipos cercanos y lejanos de los pacientes, esencialmente por microorganismos patógenos y multirresistentes a los antimicrobianos.

Palabras clave: *Infección Nosocomial; Farmacorresistencia Bacteriana Múltiple; Unidad de Cuidados Intensivos Pediátricos; Servicio de Limpieza Hospitalaria; Enfermería.*

INTRODUCTION

Inanimate surfaces and equipment in hospital environments are considered reservoirs of resistant and pathogenic microorganisms. Given this reality, environmental contamination constitutes an important source of dissemination of multidrug-resistant organisms (MDRO) in hospital environments.[1]

These pathogens are generally located on surfaces and equipment close to patients such as bed rails, bedside tables, cardiac monitors and infusion pumps and can be transmitted to patients through cross-contamination by the hands of healthcare professionals and companions.[1, 2]

In Pediatric Intensive Care Units (PICU), the risk of cross-contamination increases as these sectors accommodate critical patients who undergo various invasive procedures and require prolonged care due to their clinical condition. Therefore, they are more susceptible to acquiring healthcare-associated infections (HAIs) due to MDRO.[3] Furthermore, the risk of infection in the pediatric population is also related to the severity of underlying pathologies associated with the immaturity of the immune system in this population.[4, 5]

HAIs represent risks to patient safety, especially those involving microorganisms resistant to antimicrobials.[6] In this regard, surfaces and equipment in healthcare services are considered fomites of resistant and pathogenic microorganisms, and may represent risks to pediatric patients' clinical condition and survival.

Given the situation exposed, the question arises: what is the frequency of microbiological environmental contamination in a PICU? To answer this question, the present study aimed to investigate microbiological environmental contamination on inanimate surfaces and equipment in a PICU.

METHOD

Study design

This is an exploratory cross-sectional study that used data obtained from environmental microbiological samples from the aforementioned surfaces.

Study setting

The study was carried out in a non-profit tertiary

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university hospital in southern Brazil, which has 431 beds, being a municipal and state reference for highly complex care in the Brazilian Health System.

The institution has a PICU, with the availability of 7 patient units/beds for children aged between one month and 12 years. The study used microbiological samples collected from surfaces in the patient unit and the common area of PICU.

Study sample

Samples were included from surfaces in the patient unit and the common area of the PICU that were occupied, at the time of collection, by children hospitalized for a minimum period of 48 hours. Unoccupied units and units in which patients were hospitalized for less than the aforementioned minimum period were excluded from the sample.

To select the surfaces and equipment for the patient unit, the standardization of the Brazilian National Health Regulatory Agency (ANVISA (*Agência Nacional de Vigilância Sanitária*), 2012) was considered as well as selection based on proximity to patients and frequency of contact with the hands of professionals and companions.[7,8] In this way, the surfaces and equipment that made up the patient unit were divided into three groups: Group 1, composed of the patient unit fixed structures (gas panel, IV pole, shelf or bench, and side table); Group 2, consisting of equipment (mechanical ventilator, infusion pump and cardiac monitor); Group 3, consisting of bed rails and headboard, with the exception of mattress, as its disinfection occurs during patients' bath, in accordance with the standards of the study institution.

Surfaces and equipment in the area of common use between companions and professionals were selected according to the frequency of contact with the hands of professionals and companions.[7, 8] Therefore, alcohol gel dispensers, armchairs, administrative benches, door handles and drawers of nursing station furniture, emergency cart, scales for measuring children's weight, portable x-ray equipment, x-ray board, telephones, computer keyboards and mice were investigated.

Some of the equipment listed above was grouped when there was more than one unit in the sector. In these cases, the microbiological sample was collected using a single swab, applied to the surfaces of alcohol gel dispensers in patient units (2 units), alcohol gel dispensers in the common area (2 units), computer mice (4 units), computer keyboards (4 units), telephones (2 units) and scales (2 units), thus generating 6 grouped samples of surfaces.

Variables and data collection instrument

Data and microbiological sample collection took place on a single day, in September 2020, with data collected using an instrument including items identifying patients (name, medical record number, date of birth and hospitalization), unit (equipment and inanimate surfaces investigated) and results of the microbiological investigation of the surfaces.

Procedure for collecting microbiological cultures from environments

Environmental microbiological samples from the patient unit and common area were collected by a team of researchers previously trained to carry out this procedure. Collection was carried out in a single moment in the common area and at the pre-disinfection moment of the patient unit, which occurred in just one day.

Cultures were collected by rubbing sterile swabs (Olen Kasvi®) moistened with 0.9% saline solution on the surface, prioritizing the friction of the swab in areas of greatest contact with the hands, such as buttons, handles, touch screens of devices between others. After sample collection, the swabs were placed in Stuart medium and sent to the microbiology laboratory within a maximum period of 4 hours.

To identify the species and antimicrobial sensitivity profile, the swabs were inoculated into three tubes containing trypticase soy broth ((TSB), Kasvi®), the first with 6.5% NaCl, the second containing cefotaxime (8 µg/mL) and the third containing vancomycin. After incubation for 8 hours at 35 ºC, the vancomycin-resistant broth (VRE) was replicated on VRE agar (OXOID®, England), containing 6 µg/mL of vancomycin, 6 µg/mL of ciprofloxacin and colistin. TSB was replicated on Mac Conkey agar (Acumedia®) containing 8 µg/mL of cefotaxime, and the NaCl broth on salted mannitol agar. The identification of microorganisms was carried out using the manual methodology recommended by Jorgensen (2015). Antimicrobial susceptibility was determined by the disk diffusion method following recommendations from the Clinical and Laboratory Standards International (2019), including verification of disk test (D-test) among isolates. The D-test allows the detection of inducible resistance to clindamycin, as the resistance mechanism is not detected through the sensitivity test routinely used in laboratories, and the induction test, called the D-test, is recommended.[9]

Data analysis

The database was built in an electronic spreadsheet using MicrosoftExcel® and subsequently analyzed using Epi Info™ version 7.2.2.6 (Centers for Disease Control and Prevention, Atlanta, USA). Variables were described in measures of central tendency and frequency distribution, with the results presented in descriptive tables. A 95% confidence interval was considered when necessary. The results of microbiological mapping were presented in illustrations created in the softwares Paint.Net 2021 version 4.2.16 and Inkcape 2021 version 1.1.1.

Ethical considerations

This study is linked to the project entitled "*Investigação da contaminação ambiental em áreas críticas hospitalares e avaliação da efetividade da desinfecção*", and complied with the ethical precepts established by the Ministry of Health (Resolutions 466/2012, 510/2016 and 580/2018 of the Brazilian National Health Council), being approved by the institution's Research Ethics Committee on February 14, 2020, under Opinion 3.839.405

CAAE (*Certificado de Apresentação para Apreciação Ética* - Certificate of Presentation for Ethical Consideration) 28169520.0.0000.5231.

RESULTS

A total of 28 surfaces were analyzed, 12 of which were located in the units occupied by patients at the time of collection and 16 surfaces in the common area of the PICU.

Regarding the patient unit, four units were investigated, corresponding to 57.14% occupancy in the sector. Patients occupying the units analyzed had a mean hospitalization of 31.75 days (SD 15.54), with a minimum of 9 and a maximum of 44 days, with a median of 37 days.

In each patient unit, samples were collected from three groups of surfaces, totaling 12 groups of surfaces between the four units studied.

Of the total surfaces in the patient unit, 66.67% showed contamination by microorganisms, of which patient units B and C obtained contamination in all groups analyzed. As for the surface groups, Group 3 was contaminated in all patient units. Groups 1 and 2 showed the same frequency of contamination (50%) (Figure 1).

Regarding the surfaces in the common area, 16 surfaces were analyzed, of which 56.25% showed contamination by microorganisms, including companion seats, administrative counters, cabinet handles in the nursing station, emergency cart, scales, x-ray plate, phones and keyboards (Figure 2).

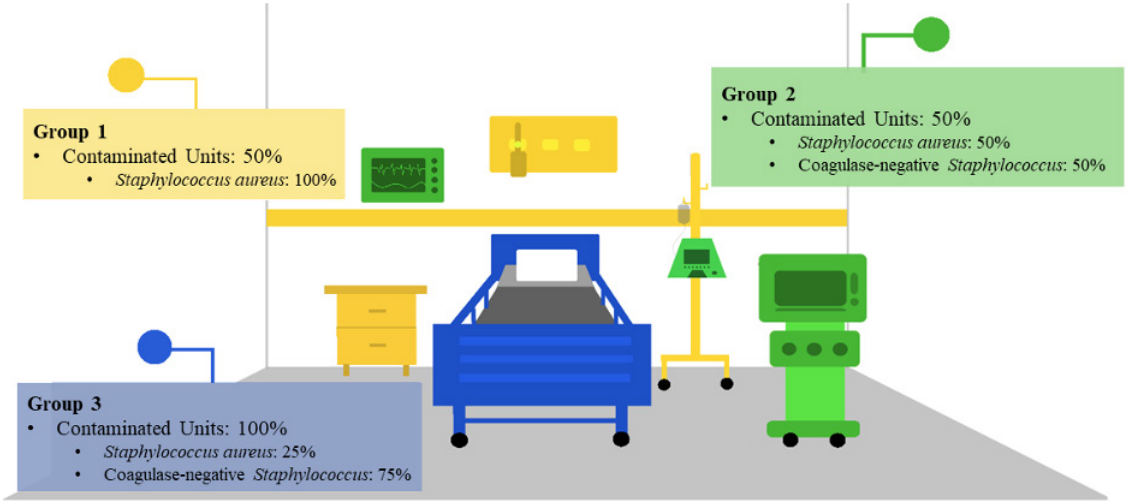

Figure 1. Distribution of environmental contamination by microorganisms in groups of surfaces in Pediatric Intensive Care Patient Units. Londrina, PR, Brazil, 2020.
Group 1 = gas panel, IV pole, benches/shelves and side table; Group 2 = mechanical ventilator, infusion pump and cardiac monitor; Group 3 = bed rails and headboard.
Source: the author (2021).

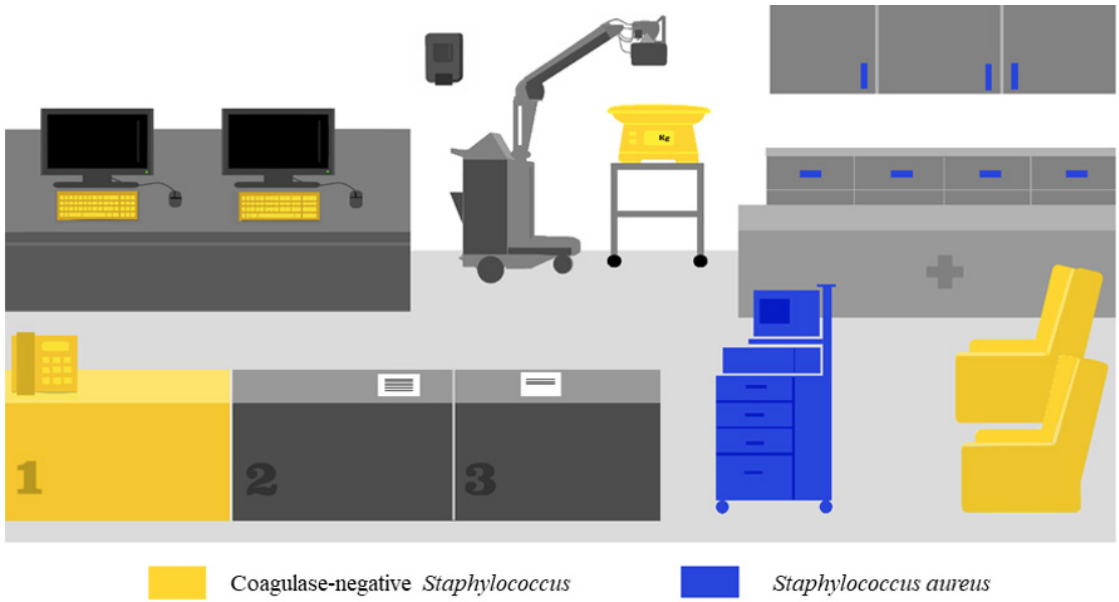

Figure 2. Distribution of environmental contamination of microorganisms isolated from cultures carried out on surfaces and equipment in the area of common use among companions and professionals in a Pediatric Intensive Care Unit. Londrina, PR, Brazil, 2020.
Source: the author (2021).

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Table 1. Distribution of the resistance profile of microorganisms isolated from surfaces in the patient unit at the pre-disinfection time (N=08) and on surfaces and equipment (N=09) in the common use area in a Pediatric Intensive Care Unit. Londrina, PR, Brazil, 2020.

	Resistance frequency			
	Patient unit		Common use area	
Antimicrobial agents	S. aureus (4) %	Coagulase-negative Staphylococcus (4) %	S. aureus (2) %	Coagulase-negative Staphylococcus (7) %
Clindamycin	25.0	100	100	71.4
Erythromycin	25.0	100	100	85.7
Penicillin	75.0	100	100	100
Oxacillin	50.0	100	100	100
Cefoxitin	50.0	100	100	100
Gentamicin	N	50.0	N	57.1
Ciprofloxacin	N	75.0	50.0	57.1
Teicoplanin	N	N	N	N
Tigecycline	N	N	N	N
Linezolid	N	N	N	N
Levofloxacin	N	50.0	N	42.8
Rifampicin	N	N	N	42.8
Sulfamethoxazole + Trimethoprim	50.0	50.0	50.0	46.8
Total microorganisms	4 (50.0%)	4 (50.0%)	2 (22.22%)	7 (77.78%)

N = negative culture.
Source: the author (2021).

Regarding the microbiological profile, all isolated microorganisms were Gram-positive. Coagulase-negative *Staphylococcus* (CNS) accounted for 50.0% of contamination in patient units and 77.8% on common area surfaces. *Staphylococcus aureus* was isolated in 50.0% of patient units and 22.2% of common area surfaces (Table 1).

Regarding the resistance profile of microorganisms isolated from surfaces in the patient unit, S. *aureus* isolates expressed 75.0% resistance to penicillin and 50.0% resistance to oxacillin, cefoxitin and sulfamethoxazole/trimethoprim. Among the CNS, all expressed resistance to clindamycin, erythromycin, penicillin, oxacillin and cefoxitin, followed by resistance to ciprofloxacin (75.0%). Among the microorganisms isolated from microbiological samples from the common use area, all S. *aureus* expressed resistance to clindamycin, erythromycin, penicillin, oxacillin and cefoxitin. Regarding CNS, all isolates were resistant to penicillin, oxacillin and cefoxitin, and 85.71% were resistant to erythromycin, and 71.43% were resistant to clindamycin, as shown in table 1. Among the CNS resistant to erythromycin and clindamycin, one isolate presented a positive D-test.

DISCUSSION

Contamination of inanimate surfaces and equipment in healthcare services contributes to the spread of pathogenic and resistant microorganisms, favoring cross-transmission and development of HAIs, especially among hospitalized patients in critical sectors.[3]

The present study showed the contamination of multiple inanimate surfaces and equipment by pathogenic and multi-resistant microorganisms in hospital environments, both in patient units and in the common use area of pediatric intensive care.

In patient units, more than half of bed rails and headboards were contaminated by microorganisms. Brazilian studies carried out in adult ICUs showed that the frequency of contamination on the guardrails of patients' beds was high, ranging from 45.5% to 81.8%.[10, 11] This high level of contamination may indicate that bed rails are considered a potential vehicle for microorganisms, mainly due to the high frequency of handling by healthcare professionals and family members.[2] However, another study with a similar methodology presented divergent results, which demonstrated that medication infusion pumps were the equipment most contaminated by microorganisms compared to bed rails.[12]

The surfaces analyzed in the common use area are not used in direct patient care, but they assist in the health team's work process, constituting an important source of dissemination of these microorganisms during healthcare. As in this study, in a university hospital in France, they observed the growth of Gram-positive bacteria on surfaces analyzed in the research, such as computer keyboards and mice.[13]

As these are surfaces used with high frequency and collectively, they pose a risk of transmitting pathogens to patients. Thus, protocols for hand hygiene for healthcare professionals and family members within healthcare services are recommended. The World Health Organization recommends hand hygiene in five moments as a strategy to prevent the spread of microorganisms.[1]

In addition to hand hygiene, it is necessary to disinfect these areas on a scheduled basis, following institutional protocols based on ANVISA recommendations, which recommends the use of 70% ethyl alcohol as the main disinfectant used to disinfect surfaces.[14]

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Regarding the species of microorganisms in this research, all isolates were Gram-positive, with a predominance of CNS, followed by S. *aureus*. A study in Eastern Ethiopia, which investigated contamination in stethoscopes and sphygmomanometers in some hospital units, indicated the Adult ICU as the sector with the highest prevalence of contamination by microorganisms in the objects analyzed. In relation to isolates, there was a higher frequency of Gram-positives, including S. *aureus* and multi-resistant CNS[15], corroborating data from the current research.

Regarding the resistance profile of microorganisms, it was possible to identify in patient units and in the area of common use CNS and S. *aureus* resistant to more than one class of antimicrobial agents, with a predominance of *Staphylococcus* spp. resistant to penicillin and oxacillin, while all CNS isolates also expressed resistance to clindamycin and erythromycin.

CNS and S. *aureus* are microorganisms that colonize human skin and mucous membranes, and have a high potential to cause HAIs and bacteremia, especially in patients with immune system deficits or who use invasive devices, in addition to being related to formation of biofilms and broad spectrum of antimicrobial resistance.[1, 16, 17]

Research in Saudi Arabia analyzed frequently touched surfaces in PICU and Adult ICU, 65% of samples demonstrated growth of the ESKAPE group (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* species), including S. *aureus* and *Enterococcus* spp. Furthermore, there was environmental contamination in a PICU by Methicillin-resistant S. aureus on a chair, stethoscope, clipboard, keyboard and calculator.[18] A Brazilian study conducted in a PICU detected bacterial growth with a prevalence of S. *aureus* (51.9%) on stethoscopes, incubators, respirators, tables and monitors. Among all S. *aureus* isolates, the majority were resistant to oxacillin.[19]

Another study from southern Brazil analyzed environmental contamination by *Staphylococcus* spp. in an Adult ICU, which showed bacterial growth of CNS and S. *aureus* on surfaces close (infusion pump and side table) and distant (telephone and computer keyboards) to patients. Among the microorganisms, 85.7% were resistant to erythromycin, 71.4% resistant to penicillin and 57.1% resistant to clindamycin, while S. *aureus* isolates 83.3% were resistant to penicillin, 66.7% to erythromycin and 50% to oxacillin and clindamycin, respectively.[20]

Staphylococcus spp. is one of the main pathogens associated with hospital infections in ICUs.[21] Bacteria from the *Staphylococcaceae* family have the ability to survive on inanimate surfaces and equipment in healthcare services, generally close to patients, and despite being part of man's endogenous microbiota, they can contaminate surfaces, which makes cross-transmission possible.[22]

In Jeddah, Saudi Arabia, samples were collected in Adult ICUs and PICUs, in which Gram-positive isolates had a higher frequency of contamination compared to Gram-negative ones. The surfaces with the greatest contamination were nursing stations and patients' beds by S. *aureus*.[23]

Bacterial resistance represents a global challenge, which brings implications and concerns, mainly due to the high rate of development of HAIs due to MDRO.[6] Among the consequences of resistance, we can mention the prolongation of hospitalization time, therapeutic failure of antimicrobials due to resistance and financial impact on public healthcare services.[24]

Therefore, disinfection in healthcare services is a process that destroys microorganisms on surfaces and equipment, being essential to prevent and control the spread of MDRO, with ethyl alcohol at 70% and sodium hypochlorite at a concentration of 0.02% to 1% of the most used sanitizers in the disinfection of non-critical articles to eliminate MDRO.[1]

Considering the results found in this research, it was possible to observe the high potential for contamination of inanimate surfaces and equipment in hospital environments by both pathogenic microorganisms and those that are multi-resistant to antimicrobial agents. The evidence from this study can guide nursing actions, mainly by the Hospital Infection Control Committee to develop cleaning and disinfection protocols, in order to prevent and control hospital infections.

The reduced number of microbiological samples and collection in a single unit are limitations of this study. This situation is partly due to limited financial resources and beds in the pediatric unit at the hospital under study. The need for new studies with a larger number of samples is highlighted.

The results of this study demonstrate a high frequency of contamination on inanimate surfaces and equipment close and far from patients, essentially by pathogenic microorganisms that are multi-resistant to antimicrobials, which are mainly harmful to the health of patients with immaturity of the immune system, like the population of this research. Considering the above, it is necessary that hand hygiene and cleaning and disinfection protocols in healthcare institutions are standardized and rigorously assessed as a means of preventing and controlling MDRO infections.

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REVIEW ARTICLE

Scientific evidence on hepatitis B and SARS-CoV-2 infection: An integrative review

Evidências científicas sobre hepatite B e infecção por SARS-CoV-2: revisão integrativa

Evidencias científicas sobre la hepatitis B y la infección por SARS-CoV-2: revisión integradora

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ABSTRACT

Background and Objective: Hepatitis B is an infectious disease caused by a virus from the *hepadnaviridae* family, with worldwide distribution, and represents a serious global health problem. The pathology may have been affected by the COVID-19 pandemic, caused by the SARS-CoV-2 virus, making it possible for serious outcomes to occur when overlapping viral types. This study sought to describe the levels of scientific evidence of research carried out on the topic, establishing a relationship between hepatitis B virus infection and SARS-CoV-2 infection. **Content:** integrative literature review, with searches performed in the databases of the Medical Literature Analysis and Retrieval System Online, and Scientific Electronic Library Online, with analysis centered on the description of the methodological design, and on the classification of the level of evidence. **Conclusion**: the scientific production on hepatitis B associated with SARS-CoV-2 infection corresponds mostly to studies with a low level of evidence. The selected publications presented limitations such as the occurrence of studies with a small number of samples, lack of subsidiary data of patients in treatment, and occurrence of non-randomized selection. The results suggest the need for further investigations for the purpose of technological improvement, identification of risk factors, therapeutic intervention, and advanced clinical investigation, in order to encourage evidence-based healthcare practices.

Keywords*: Hepatitis B. SARS-CoV-2. COVID-19.*

RESUMO

Justificativa e Objetivos: a hepatite B é uma doença infectocontagiosa provocada por um vírus da família *hepadnaviridae*, com distribuição mundial, e representa um grave problema de saúde global. A patologia pode ter sido afetada pela pandemia de COVID-19, provocada pelo vírus SARS-CoV-2, sendo possível a ocorrência de desfechos graves na sobreposição entre os dos tipos virais. Este estudo buscou descrever os níveis de evidências científicas de pesquisas realizadas sobre o tema, estabelecendo relação entre a infecção por vírus da hepatite B e a infecção

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por SARS-CoV-2. **Conteúdo:** revisão integrativa da literatura, com buscas realizadas nas bases de dados do *Medical Literature Analysis and Retrieval System Online* e *Scientific Electronic Library Online*, com análise centrada na descrição do delineamento metodológico e na classificação do nível de evidência. **Conclusão:** a produção científica sobre hepatite B associada a infecção por SARS-CoV-2 corresponde majoritariamente a pesquisas com baixo nível de evidência. As publicações selecionadas apresentaram limitações, como a ocorrência de estudos com número reduzido de amostras, falta de dados subsidiários de pacientes em tratamento e ocorrência de seleção não randomizada. Os resultados sugerem a necessidade de novas investigações para fins de incrementos tecnológicos, identificação de fatores de risco, intervenção terapêutica e investigação clínica avançada, de forma a fomentar práticas assistenciais em saúde baseadas em evidências.

Descritores: *Hepatite B. SARS-CoV-2. COVID-19.*

RESUMEN

Justificación y Objetivo: la hepatitis B es una enfermedad infecciosa contagiosa causada por un virus de la familia *hepadnaviridae*, de distribución mundial, y representa un grave problema de salud mundial. Su patología puede haberse visto afectada por la pandemia de COVID-19, provocada por el virus SARS-CoV-2, y son posibles desenlaces graves cuando se superponen tipos virales. Este estudio buscó describir los niveles de evidencia científica de las investigaciones realizadas sobre el tema, estableciendo una relación entre la infección por el virus de la hepatitis B y la infección por el SARS-CoV-2. **Contenido:** revisión integradora de la literatura, con búsquedas realizadas en las bases de datos *Medical Literature Analysis and Retrieval System Online* y *Scientific Electronic Library Online*, con un análisis centrado en la descripción del diseño metodológico y en la clasificación del nivel de evidencia. **Conclusión:** la producción científica sobre la hepatitis B asociada a la infección por SARS-CoV-2 corresponde, en su mayoría, a investigaciones con bajo nivel de evidencia. Las publicaciones seleccionadas presentaron limitaciones como la ocurrencia de estudios con un número reducido de muestras, la falta de datos subsidiarios de los pacientes en tratamiento y la ocurrencia de selección no aleatoria. Los resultados sugieren la necesidad de seguir investigando para mejorar la tecnología, identificar los factores de riesgo, intervenir terapéuticamente y realizar investigación clínica avanzada, con el fin de promover prácticas sanitarias basadas en la evidencia.

Palabras llave: *Hepatitis B. SARS-CoV-2. COVID-19.*

INTRODUCTION

Hepatitis B is an infectious disease caused by a virus belonging to the hepadnaviridae family, described as the hepatitis B virus (HBV). This virus has tropism for human liver cells.[1] It is a globally distributed infection, with estimates pointing to a worldwide occurrence of around 300 million chronically infected people, with indicators of 1.5 million new cases per year.[2]

Hepatitis B is transmitted parenterally, percutaneously (by sharing needles and syringes and other contaminated sharps); invasive procedures that do not follow biosafety rules; sharing materials and personal objects with a solution that can come into contact with the infected individual's blood (toothbrushes, razors); sexually; and vertically, which can occur during childbirth or during the perinatal period in the mother-child relationship.[3-5]

The infection can develop into acute and chronic forms, both of which, in most cases, are asymptomatic or mildly symptomatic.[3,1] Progression to the chronic form of the disease, in addition to requiring ongoing health care, increases the risk of developing conditions such as cirrhosis of the liver and hepatocellular carcinoma.[1]

The hepatitis B virus has a direct relationship with physiological complications, including immunological ones, which makes those affected vulnerable to worsening liver conditions, among other alterations in the body.[1] Thus, in the context of the pandemic caused by the SARS-CoV-2 virus, which causes the coronavirus-19 (COVID-19) disease, generating a risk of harmful interaction,[6] the study of co-infections gains prominence, given the need for specific monitoring of SARS-CoV-2 cases in HBV patients.

SARS-CoV-2 is a ribonucleic acid (RNA) virus belonging to the Nidovirales family of viruses. SARS-CoV-2 has proteins called receptor binding-domain (RBD) that bind to angiotensin-converting enzyme 2 (ACE2) receptors, affecting cells in the respiratory system. The virus is transmitted through contact with respiratory droplets present in symptomatic or asymptomatic infected individuals. The main symptoms of COVID-19 are fever, cough, headache, loss of taste or smell, diarrhea, chest pain and severe dyspnea, with an incubation period ranging from 2 to 14 days.[6,7]

Epidemiological data show that the world has recorded around 760 million confirmed cases of COVID-19, with 6.8 million confirmed deaths from the infection. In Brazil, there have been 37 million cases and around 700,000 deaths from COVID-19.[8] Overall figures make the overlap between the SARS-CoV-2 and HBV viruses inevitable, in epidemiological terms.

The global emergency scenario caused by the SARS-CoV-2 pandemic and the occurrence of COVID-19, associated with other diseases, may be related to the in-

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creased risk of serious outcomes, especially for patients with chronic hepatitis B, due to the factors mentioned above. In this sense, surveying scientific studies and mapping levels of evidence is an important measure for updating clinical management and healthcare practices. That said, the present study sought to describe the levels of scientific evidence from research carried out on the subject, establishing a relationship between hepatitis B virus infection and SARS-CoV-2.

METHOD

This is an integrative review on the subject of the level of scientific evidence on hepatitis B and SARS-COV-2 infection. The integrative review is one of the methods of evidence-based healthcare practice, and consists of gathering and synthesizing scientific production on a given topic in a systematic way in order to deepen knowledge on the subject.[9]

The research was carried out from May to November 2022, following six methodological stages, established according to the literature,[9-11] as shown in figure 1.

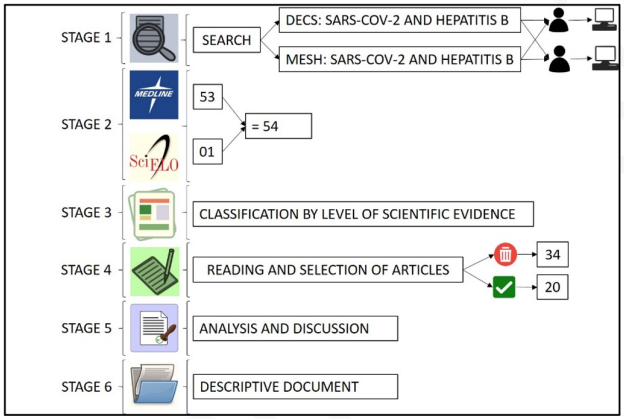

Figure 1. Flowchart of the research's methodological stages.

In the first stage, the guiding question was formulated: "What levels of scientific evidence are available in the studies produced on the relationship between chronic hepatitis B and SARS-CoV-2 infection?" This was an important question for selecting and analyzing the studies included in the research. The following keywords were then listed as primary inclusion criteria: Hepatitis B and SARS-CoV-2, according to the health sciences descriptors (DECS), and hepatitis B and SARS-CoV-2, according to the medical subject headings (Mesh).

In the second stage, the databases for the search and the eligibility criteria for the inclusion and exclusion of studies were defined, considering the analysis of the method and the observation of content pertinent to the relationship between hepatitis B and SARS-CoV-2 infection. The search was carried out in pairs using Boolean operators. Scientific articles found based on the descriptors defined in the first stage, published in English, Spanish and Portuguese, without restriction of territory, with a focus on hepatitis B and SARS-CoV-2 infection (COVID-19), with an abstract available in the databases: Medical Literature Analysis and Retrieval System Online (Medline) and Scientific Electronic Library Online (SciElo), published between 2020 and 2022, were considered eligible. At the time of the search, 53 articles were found in the Medline database and 1 article in SciElo, totaling 54 publications, with no exclusions, as all the studies found in the search strategy met the research eligibility criteria.

For the third stage, Table 1 proposed by Oliveira et al[11] was used to organize and present the results found, characterizing the studies according to the classification of levels of scientific evidence, according to the Melnyk and Fineout-Overholt model.[12] The classification being:

1. Evidence from a systematic review or meta-analysis of all relevant randomized controlled clinical trials or from clinical guidelines based on systematic reviews of randomized controlled clinical trials;
2. Evidence derived from at least one well-designed randomized controlled clinical trial;
3. Evidence obtained from well-designed clinical trials without randomization;
4. Evidence from well-designed cohort and case--control studies;
5. Evidence from systematic reviews of descriptive and qualitative studies;
6. Evidence derived from a single descriptive or qualitative study;
7. Evidence derived from the opinion of authorities and/or expert committee reports.

The fourth stage involved reading the abstracts of the scientific articles found and applying the eligibility criteria, as shown in Figure 1, as well as critically analyzing the articles found and applying and classifying the level of evidence of the studies. After reading the abstracts, 26 Medline articles were excluded because they did not fit the proposed theme, leaving a total of 28 articles. In the critical analysis of the articles found, 8 more articles were excluded as they also did not fit the proposed theme, resulting in 20 selected studies.

In the fifth stage, which corresponds to the interpretation of the results achieved, we discussed the data obtained from the results.

The sixth stage involved preparing the descriptive document for the study and presenting this review.

Regarding ethical aspects, the study does not involve human beings directly or indirectly, only published data, and there is no obligation to submit it to a research ethics committee. However, the authors declare that they have followed the ethical precepts described in Resolution No. 466 of 2012, as well as other guarantees of right.

RESULTS

The selected studies are listed in chart 1, considering information such as the titles of the papers, authors, journal of publication, thematic considerations, and the classification of the level of evidence.

Chart 1. Characterization of publications on the relationship between hepatitis B and SARS-CoV-2 infection, according to reference, thematic considerations, type of study, and level of evidence.

Reference	Thematic considerations	Type of study	Level of evidence
Jiménez-Mendoza J, Rivera-López F, González-Lara M, Valdez-Echeverría R, Castro-Narro G, Tore A, et al. Seroprevalence of hepatitis B and C viruses in moderate and severe COVID-19 inpatients: A cross-sectional study at a referral center in Mexico. Ann Hepatol. May 2022;27(3):100684.	Investigates the seroprevalence of hepatitis B and C viruses in patients hospitalized with COVID-19 in Mexico.[13]	Cross-sectional (retrospective) study	VI
Choe JW, Jung YK, Yim HJ, Seo GH. Clinical Effect of Hepatitis B Virus on COVID-19 Infected Patients: A Nationwide Population-Based Study Using the Health Insurance Review & Assessment Service Database. J Korean Med Sci. 2022;37(4):e 29.	Evaluates the effects of the hepatitis B virus on the body of patients infected with COVID-19.[14]	Cohort	IV
Librero Jiménez M, López Garrido MÁ, Fernández Cano MC. Letter to the editor: Reactivation of HBV triggered by SARS-CoV-2 in a patient with cirrhosis. Hepatology. March 2022;75(3):765–6.	Investigates possible reactivation of HBV triggered by SARS-CoV-2 infection.[15]	Case report	VI
Sagnelli C, Pisaturo M, Curatolo C, Codella AV, Coppola N, Sagnelli E. Hepatitis B virus/hepatitis D virus epidemiology: Changes over time and possible future influence of the SARS-CoV-2 pandemic. World J Gastroenterol. November 14, 2021;27(42):7271–84.	Describes the epidemiology of hepatitis B and D, and possible changes resulting from the SARS-CoV-2 pandemic.[16]	Literature review	V
Gómez Camarero J, Badia Aranda E, Quiñones Castro R, Saiz Chumillas RM, Alcoba Vega L, Díez Ruiz S, et al. Hepatitis B and C screening in hospitalized patients with SARS-CoV-2 infection. Gastroenterol Hepatol. April 2022;45(4):256–64. Doi: 10.1016/j.gastrohep.2021.09.002	Evaluates the results of a screening program for hepatitis B and C in hospitalized patients with COVID-19.[17]	Cross-sectional (prospective)	VI
Kazmi SK, Khan FMA, Natoli V, Hunain R, Islam Z, Costa AC dos S, et al. Viral hepatitis amidst COVID-19 in Africa: Implications and recommendations. J Med Virol. January 2022;94(1):7–10.	Scenario of viral hepatitis in the COVID-19 pandemic in Africa, consequences and recommendations.18	Literature review	V
Jindal A. Letter to the Editor: Outcomes in chronic hepatitis B infection and COVID-19 Not always benign! Hepatology. January 2022;75(1):230–230.	The author's opinion on the outcomes of hepatitis B and COVID-19 infections.[19]	Letter to the editor	VII
Lv X, Yang J, Deng K. Letter to the Editor: Unanswered questions about hepatitis B virus infection in patients with COVID-19. Hepatology. January 2022;75(1):229–229.	The author's opinion on unanswered questions regarding hepatitis B patients infected with COVID-19.[20]	Letter to the editor	VII
Alqahtani SA, Buti M. COVID-19 and Hepatitis B Infection. Antivir Ther. November 2020;25(8):389–97.	Presents the clinical relationship of patients with hepatitis B infected with COVID-19.[21]	Literature review	V
Pley CM, McNaughton AL, Matthews PC, Lourenço J. The global impact of the COVID-19 pandemic on the prevention, diagnosis and treatment of hepatitis B virus (HBV) infection. BMJ Glob Health. January 2021;6(1):e004275.	Provides an overview of the impact of the COVID-19 pandemic on the progress of hepatitis B virus programs around the world with a focus on the possible consequences for prevention, diagnosis, and treatment.[22]	Literature review	V
Liu R, Zhao L, Cheng X, Han H, Li C, Li D, et al. Clinical characteristics of COVID-19 patients with hepatitis B virus infection — a retrospective study. Liver Int. April 2021;41(4):720–30.	Study of the impact of co-infection with SARS-CoV-2 and chronic hepatitis B.[23]	Cohort study	IV
Ding Z yang, Li G xun, Chen L, Shu C, Song J, Wang W, et al. Association of liver abnormalities with in-hospital mortality in patients with COVID-19. J Hepatol. June 2021;74(6):1295–302.	Study of the association between liver abnormalities and hospital mortality in COVID-19 patients.[24]	Retrospective cohort study	IV
Yu R, Tan S, Dan Y, Lu Y, Zhang J, Tan Z, et al. Effect of SARS-CoV-2 coinfection was not apparent on the dynamics of chronic hepatitis B infection. Virology. January 2021;553:131–4.	Claims that the effects of SARS-CoV-2 co-infection were not apparent in the dynamics of chronic Hepatitis B infection.[25]	Cohort study	IV

Ali E, Ziglam H, Kohla S, Ahmed M, Yassin M. A Case of Fulminant Liver Failure in a 24-Year-Old Man with Coinfection with Hepatitis B Virus and SARS-CoV-2. Am J Case Rep. September 3, 2020.	Presents the case of fulminant liver failure in a 24-year-old man with co-infection with hepatitis B virus and SARS-CoV-2.[26]	Case report	VI
Rodríguez Tajes S, Miralpeix A, Costa J, López Suñé E, Laguno M, Pocurull A, et al. Low risk of hepatitis B reactivation in patients with severe COVID-19 who receive immunosuppressive therapy. J Viral Hepat. January 2021;28(1):89–94.	Analyzes the risk of HBV reactivation in patients with severe COVID-19 and resolved HBV infection under immunosuppressive therapy.[27]	Prospective cohort study	IV
Wu J, Yu J, Shi X, Li W, Song S, Zhao L, et al. Epidemiological and clinical characteristics of 70 cases of coronavirus disease and concomitant hepatitis B virus infection: A multicentre descriptive study. J Viral Hepat. January 2021;28(1):80–8.	Analysis of 70 cases of co-infection by SARS-CoV-2 and hepatitis B to determine epidemiological, clinical, treatment, and outcome characteristics.[28]	Multicenter descriptive study	VI
Lv XH, Yang JL, Deng K. Clinical Outcomes of COVID-19 Patients with Chronic Hepatitis B Virus Infection Still Need to Be Explored. Clin Gastroenterol Hepatol. December 2020;18(13):3055–6.	Presents the authors' analysis of the results of a cohort study, determining that the clinical outcomes of COVID-19 patients with chronic hepatitis B virus infection still need to be explored.[29]	Letter to the editor	VII
Zhang B, Huang W, Zhang S. Clinical Features and Outcomes of Coronavirus Disease 2019 (COVID-19) Patients with Chronic Hepatitis B Virus Infection. Clin Gastroenterol Hepatol. October 2020;18(11):2633–7.	Reports the clinical evolution of COVID-19 patients with chronic hepatitis B virus infection and provides a reference for the clinical management of patients.[30]	Descriptive study/ Letter to the editor	VI
Anugwom CM, Aby ES, Debes JD. Inverse Association Between Chronic Hepatitis B Infection and Coronavirus Disease 2019 (COVID-19): Immune Exhaustion or Coincidence? Clin Infect Dis. June 5, 2020;ciaa592.	Authors' analysis of a study that showed an inverse association between chronic hepatitis B infection and coronavirus 2019 disease (COVID-19).[31]	Letter to the editor	VII
Lv XH, Yang JL, Deng K. COVID-19 Patients with Hepatitis B Virus Infection. Am J Gastroenterol. June 2021;116(6):1357–8.	Author's response to an article published on COVID-19 patients with hepatitis B virus infection.[32]	Letter to the editor	VII

The publications selected took place between 2020 and 2022. The studies were published in seven categories of journals: 30% in the field of hepatology, 15% in the field of gastroenterology and hepatology, 15% in the field of medical sciences, 15% in the field of virology, 10% in the field of gastroenterology, 10% in the field of viral hepatitis and 5% in the field of clinical infectious diseases. In terms of research design, most of the studies were observational, followed by literature reviews and expert opinions.

Regarding classification of the level of evidence according to the method adopted: 30% are level VI studies, those derived from a single descriptive or qualitative study; 25% level IV studies, i.e. evidence from well-designed cohort and case-control studies; 25% level VII, evidence derived from the opinion of authorities and/or expert committee reports; 20% level V studies, evidence originating from a systematic review of descriptive and qualitative studies.

DISCUSSION

The result of this integrative review outlines the scientific production on the relationship between hepatitis B and SARS-CoV-2 infection, from 2020 to 2022, the period corresponding to the duration of the pandemic by the new coronavirus. Although hepatitis B is a disease with important liver complications, such as cirrhosis and hepatocellular carcinoma, and which presents a global distribution and high morbidity and mortality,[2,1] the scientific production selected on the relationship between HBV infection and SARS-CoV-2 infection was discreet.

Of the studies found in this review, 30% corresponded to evidence level VI, i.e. evidence derived from a descriptive or qualitative study, considered to be of a low level.[9] When it comes to evidence-based health practices, descriptive studies and the personal experience of professionals are important, but the production of research considered to be of high scientific evidence, as in the case of a review with meta-analysis and randomized clinical trials, provides a better basis for making clinical and care decisions.[33]

Based on the research design, the results showed a significant number of letters to the editor (25%). The articles that were answered, despite fitting the theme proposed by this study, were not found at the time of the peer review, possibly due to the incompatibility of descriptors[34] or because they addressed subjects that indirectly raised questions about the relationship between HBV and SARS-CoV-2.

Among the findings of relevance, it was observed

that some studies indicate that there are two main routes of liver damage caused by SARS-CoV-2, the first can be explained by the binding of the virus to ACE2 receptors, which is found in abundance in the respiratory tract, but can also be found in liver cells, involved in functions related to the immune system.[21,28] The second route is related to drug-induced liver damage through the use of potentially hepatotoxic drugs used in the treatment of SARS-CoV-2 infection, especially the prolonged use of immunosuppressants.[21,28]

It was also observed that patients co-infected with HBV and SARS-CoV-2 showed a higher frequency of gastrointestinal symptoms. The laboratory abnormalities are similar to other studies found in this review, which indicate high levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), as well as levels of white blood cells, lymphocytes and platelet counts below normal. According to the authors, there were no differences between length of stay and poor prognosis in the two groups.[21,24,27,28]

One of the studies found in this review presents a case report of fulminant liver failure in a patient with HBV co-infected with SARS-CoV-2. In this case, the patient presented a rapid evolution of the condition, suggestive of the result of co-infection by SARS-CoV-2, in view of the mechanism known as the "cytokine storm" caused by the virus.[26] The finding of this report corroborates the hypothesis that SARS-CoV-2 can affect the host's immune response and increase HBV viral replication or its pathophysiological damage, both in acute and chronic infections.

It is important to note that studies suggest that HBV can cause a phenomenon known as "immune exhaustion", resulting from a reduction in the reactivity of T lymphocytes, disabling the production of cytokines and response to HBV and other viruses. In this sense, publications indicate that this phenomenon may reduce the cytokine storm common in patients with the COVID-19 condition.[21,31]

One of the cohorts included in this review points out in its results that in the group of patients co-infected with HBV and SARS-CoV-2, a series of systemic deregulations occurred, such as a decrease in immune cells, mainly lymphocytes; increased levels of TCD8 cells; thrombocytopenia; disorganized lipid metabolism; and elevated creatine kinase levels. This could be indicative of a worsening of the disease in this group of patients. Even so, the results of the study showed no significant differences in severity between cases of co-infection with SARS-CoV-2 and those with HBV monoinfection.[23]

When studying the clinical effect of hepatitis B in patients infected with COVID-19, another cohort study pointed out in its results that among HBV-infected patients the mortality rate was 13.5%, while among uninfected patients the rate was 8.2%. However, it should be noted that those affected by HBV also had other types of comorbidities. Furthermore, when adjusting for age, gender, cirrhosis, and comorbidities, no significant differences were observed between the two groups in terms of clinical outcomes. The results of this study indicate that HBV infection itself did not seem to affect the outcome of SARS-CoV-2 infection in these patients, nor did the antiviral therapy used for HBV reduce mortality, suggesting that there is no direct relationship of severity between hepatitis B and SARS-CoV-2 infection.[14]

A published case report presents the case of a patient infected with SARS-CoV-2, who presented HBV reactivation. According to the authors, the reason for the reactivation and multiplication of HBV may be due to co-infection with SARS-CoV-2, given that other causes were ruled out.[15] However, studies suggest that factors associated with the treatment of COVID-19 can trigger consequences in HBV infection.

Regarding the treatment of choice for SARS-CoV-2 infection, the immunosuppressants and corticosteroids used to treat the infection are considered to be at high risk of HBV reactivation, which highlights the importance of screening for the disease at the time of hospitalization of patients infected with SARS-CoV-2.[13] A study carried out in Spain points out that screening for hepatitis B in patients hospitalized with COVID-19 was necessary, given the risk of drug reactivation. The results of this cross-sectional study showed HBV reactivation in 14.2% of patients who did not use entecavir prophylaxis during treatment with immunosuppressants.[17]

A prospective cohort, with the aim of establishing the risk of hepatitis B virus reactivation in COVID-19 patients, showed in its results that 87% of co-infected patients had high ALT levels. Most of the patients who required immunomodulatory therapy, tocilizumab being the main medication, received prophylaxis with entecavir. Among the sample, none of the patients who received prophylaxis showed HBV seroconversion. Two patients who did not receive prophylaxis had a quantifiable viral load (HBV-DNA), but at low levels. Therefore, the data from this study indicate that immunomodulatory therapy over a short period of time may not be directly related to HBV reactivation in patients infected with SARS-CoV-2.[27]

A retrospective cohort study carried out in three centers of a hospital designated for the treatment of COVID-19 in Wuhan, China, highlights that there were no significant differences in the chemical levels of liver function between the groups of HBV patients co-infected with SARS-CoV-2 and those monoinfected with SARS-CoV-2. The mortality rate was 6% in the co-infected group, which also showed no difference between the groups.[24] The findings of another publication corroborate these results, stating that there were no significant changes in clinical characteristics or in liver function and enzyme tests. Another important finding was that co-infection with SARS--CoV-2 did not trigger seroconversion of chronic hepatitis B. Co-infection also did not cause changes in COVID-19 severity or an increase in length of hospital stay.[25]

However, a Chinese study found predictive evidence that a large proportion of HBV carriers, when infected with SARS-CoV-2, will not have severe disease outcomes. According to the authors' study, 26% of patients presented dysfunctions in liver function tests on admission, of which 19% progressed to severe disease, but this finding

was not related to the HBV infection status. In view of this, the authors recommend that liver function be constantly evaluated in COVID-19 patients who are hospitalized.[30]

A large part of the outpatient care sectors for viral hepatitis has been discontinued during the pandemic, corresponding to around 90%. In Italy, 26% of the beds made available for liver conditions have been converted into COVID-19 beds. Reduced access to these health services, including testing and screening programs, equipment, and human resources, may be a determining factor in the reduction of early detection of HBV, and the continuity of treatment of chronic carriers of the infection.[16,18,22]

Although HBV can be prevented through immunization, vaccination coverage has dropped significantly in the pandemic period. Global HBV vaccination levels have increased since the 1990s, but in 2020, the year the COVID-19 pandemic began, vaccination rates fell to the same levels as in 1990. In the first year of the pandemic, SARS-CoV-2 infection drastically impacted 25 years of progress in global hepatitis B vaccination, and this reduction in vaccination coverage may increase the incidence of HBV infection in early childhood and consequently increase the risk of chronic hepatitis B.[22,16] The effects of the COVID-19 pandemic on HBV vaccination and control may even outweigh the number of direct deaths from SARS-CoV-2 infection in the long term.[22]

The data reveal observational estimates whose parameters are often linked to government indicators or scientific opinions, and are subject to variations resulting from delays in feeding the systems, underreporting, and estimation errors. In addition, the scarcity of epidemiological data on the association between HBV infections and SARS-CoV-2 imposes limitations on the analyses, requiring studies which can test the various hypotheses raised through descriptive data, especially on a clinical basis.

The circulation and contact restrictions imposed worldwide to control COVID-19 may have interfered with the HBV transmission chain. The compulsory rules of controlled circulation may have impacted the disease through other risk factors, such as alcohol and drug use, unprotected sex, and an increase in home births without adequate prophylaxis.[22,16] The synergy between pre-existing risk factors and the SARS-CoV-2 pandemic suggests a critical scenario, negatively affecting the WHO strategy to eliminate hepatitis B as a public health threat by 2030.[2]

Mapping levels of evidence for the purposes of health care practices is an important measure, but integrative review studies have limitations in terms of their use in day-to-day health actions, since they produce an extract, i.e. a snapshot of the health situation investigated in a given time and space, requiring the production of studies with a higher level of evidence, such as meta-analyses or randomized clinical trials.

However, by describing the levels of scientific evidence of research associating SARS-CoV-2 infection with chronic HBV infection, this study has produced a critical description of the real potential of the studies listed, showing a high number of observational studies, which add little to care practices, and consequently highlighting and indicating the need for new research on the subject, with higher levels of evidence.

CONCLUSION

In view of the above, it can be concluded that the scientific production on hepatitis B associated with SARS-CoV-2 infection corresponds mostly to research with a low level of evidence, revealing incipient findings that may guide clinical and healthcare practices.

The publications selected for this review had some limitations which may impact on the validation of the results observed and described. In general, there were studies with small sample sizes, a lack of subsidiary data on patients undergoing treatment and non-randomized selection. In addition, the research method for integrative reviews produces a thematic snapshot, according to the position of the researchers at the time of the research, a reality that can change over time, especially considering a topic with recent facts, thus requiring a subsidiary analysis of other studies with methodological variety and checking for updates on the problem studied.

However, although the relationship between SARS-CoV-2 infection and HBV has not been fully clarified, it is clear that the pandemic caused by the SARS-CoV-2 virus had a negative impact on the process of prevention, diagnosis and management of hepatitis B in the world, the impacts of which need time, technological improvements, and new research focused on the evaluation of pharmacological therapies, the identification of risk factors, and advanced clinical research to promote innovations in public policies and evidence-based care practices.

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Elissandra Pinheiro da Costa contributed to all stages of the research, including: project design, bibliographic research, scientific writing, data collection, data analysis, and preparation of the scientific manuscript.

José André Pinho da Silva contributed to all stages of the research, including: drawing up the project, bibliographical research, scientific writing, data collection, data analysis, and preparation of the scientific manuscript.

Marcelo Siqueira de Oliveira contributed to and guided all stages of the research, including: drawing up the project, indicating and implementing the method, searching the literature, scientific writing, supervising data collection, analyzing the data collected, and preparing the scientific manuscript.

All the authors have approved the final version to be published and are responsible for all aspects of the study, including ensuring its accuracy and integrity.

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Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

REVIEW ARTICLE

Clinical-epidemiological characteristics of pregnant women with HIV/syphilis coinfection: an integrative review

Características clínico-epidemiológicas de gestantes com coinfecção HIV/sífilis: revisão integrativa

Características clínico-epidemiológicas de gestantes con coinfección VIH/sífilis: revisión integrativa

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ABSTRACT

Background and Objectives: HIV/syphilis coinfection is an important problem to be considered during pregnancy due to the various negative outcomes such as abortion, stillbirth, prematurity and congenital infections. The study is justified by the need to identify scientific evidence of clinical-epidemiological characteristics and vulnerabilities related to infections, factors that influence the prevalence, and if there are related health problems. The objective was to synthesize scientific evidence about sociodemographic characteristics and clinical manifestations of associated cases of syphilis and HIV. **Content:** this is an integrative literature review, searching the PubMed, MEDLINE, CINAHL, LILACS, BDENF and MedCarib databases, using the descriptors "HIV", "Syphilis", "Epidemiology", "Coinfection" and "Pregnant woman", combined by Boolean operators "AND" and "OR", guided by the question: what is the scientific evidence related to the clinical-epidemiological characteristics of pregnant women co-infected with HIV/syphilis? It was held from June to September 2022, including articles published in the last eight years. Nine primary articles published between 2015 and 2020 were selected. The association of infections was present in pregnant women of young adult age, non-white race/color, married, low level of education, housewives, residents of urban areas and belonging to more economically disadvantaged social classes. **Conclusion:** the study highlighted the importance of improving prenatal care, with the aim of reducing the risks of vertical transmission of these diseases, especially with the implementation of public policies aimed at the clinical management of co-infected pregnant women, the allocation of resources and the development of specific intervention protocols.

Keywords: *HIV. Syphilis. Pregnant Women. Coinfection. Health Profile.*

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RESUMO

Justificativa e Objetivos: A coinfecção HIV/sífilis é um problema importante a ser considerado durante a gravidez devido aos diversos desfechos negativos como aborto, natimorto, prematuridade e infecções congênitas. O estudo justifica-se pela necessidade de identificar evidências científicas de características clínico-epidemiológicas e vulnerabilidades relacionadas às infecções, fatores que influenciam a prevalência e se há problemas de saúde relacionados. O objetivo foi sintetizar evidências científicas sobre características sociodemográficas e manifestações clínicas de casos associados de sífilis e HIV. **Conteúdo:** trata-se de uma revisão integrativa da literatura, com busca nas bases de dados PubMed, MEDLINE, CINAHL, LILACS, BDENF e MedCarib, utilizando os descritores "HIV", "Syphilis", "Epidemiology", "Coinfection" e "Pregnant woman", combinados por Operadores booleanos "AND" e "OR", norteados pela questão: quais as evidências científicas relacionadas às características clínico-epidemiológicas de gestantes coinfectadas com HIV/sífilis? Foi realizado de junho a setembro de 2022, incluindo artigos publicados nos últimos oito anos. Foram selecionados nove artigos primários publicados entre 2015 e 2020. A associação das infecções esteve presente em gestantes em idade adulta jovem, raça/cor não branca, casadas, baixa escolaridade, donas de casa, residentes em zona urbana e pertencentes a classes sociais mais desfavorecidas economicamente. **Conclusão:** o estudo destacou a importância da melhoria da assistência pré-natal, com o objetivo de reduzir os riscos de transmissão vertical dessas doenças, especialmente com a implementação de políticas públicas voltadas ao manejo clínico das gestantes coinfectadas, à alocação de recursos e o desenvolvimento de protocolos de intervenção específicos.

Palavras-chave: *HIV. Sífilis. Gestantes. Coinfecção. Perfil de Saúde.*

RESUMEN

Antecedentes y objetivos: La coinfección VIH/sífilis es un problema importante a considerar durante el embarazo debido a los diversos resultados negativos como aborto, muerte fetal, prematuridad e infecciones congénitas. El estudio se justifica por la necesidad de identificar evidencia científica de características clínico-epidemiológicas y vulnerabilidades relacionadas con las infecciones, factores que influyen en la prevalencia y si existen problemas de salud relacionados. El objetivo fue sintetizar evidencia científica sobre las características sociodemográficas y manifestaciones clínicas de los casos asociados de sífilis y VIH. **Contenido:** se trata de una revisión integradora de la literatura, buscando en las bases de datos PubMed, MEDLINE, CINAHL, LILACS, BDENF y MedCarib, utilizando los descriptores "VIH", "Sífilis", "Epidemiología", "Coinfección" y "Mujer embarazada", combinados por Operadores booleanos "Y" y "O", guiados por la pregunta: ¿cuál es la evidencia científica relacionada con las características clínico-epidemiológicas de las gestantes coinfectadas con VIH/sífilis? Se realizó de junio a septiembre de 2022, incluyendo artículos publicados en los últimos ocho años. Se seleccionaron nueve artículos primarios publicados entre 2015 y 2020. La asociación de infecciones estuvo presente en mujeres embarazadas de edad adulta joven, de raza/color no blanca, casadas, de bajo nivel educativo, amas de casa, residentes de áreas urbanas y pertenecientes a clases sociales más desfavorecidas económicamente. **Conclusión:** el estudio destacó la importancia de mejorar la atención prenatal, con el objetivo de reducir los riesgos de transmisión vertical de estas enfermedades, especialmente con la implementación de políticas públicas orientadas al manejo clínico de las gestantes coinfectadas, la asignación de recursos y el desarrollo de protocolos de intervención específicos.

Palabras clave: *VIH. Sífilis. Mujeres embarazadas. Coinfección. Perfil de Salud.*

INTRODUCTION

Sexually Transmitted Infections (STIs) are considered a public health problem and are part of the most common communicable pathologies, directly influencing the epidemiological scenario due to the negative consequences for individuals' health and lives o worldwide.[1]

Syphilis is an infectious, systemic disease, exclusive to humans, and transmitted mainly through sexual and vertical routes. Its association with the Human Immunodeficiency Virus (HIV) occurs frequently, since both are influenced synergistically: increased HIV transmissibility, transient increase in viral load, decreased number of TCD4+ lymphocytes, or even changes in the natural evolution of treponemal infection, with exacerbation of clinical manifestations, in addition to changes in diagnosis and decreased response to treatment.[2-3] Furthermore, both STIs affect similar vulnerable groups, such as homeless people, low education, multiple sexual partners and the young-adult age group.[1,2,3]

HIV and syphilis are diseases that must be notified to the Epidemiological Surveillance. However, many professionals do not include it in their routines, which can harm the planning of actions to prevent and control these infections and vertical transmission. From this perspective, HIV notification has occurred more effectively than syphilis.[4]

In Brazil, in 2020, 61,441 cases of syphilis in pregnant women were reported in the Notifiable Diseases Information System (SINAN - *Sistema de Informação de Agravos de Notificação*), with a detection rate of 21.6/1,000 live births. Between 2017 and 2019, there was an increase of 25.7%. In part, this increase can be attributed to the

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change in the criterion for defining cases for surveillance purposes, which made it more sensitive.[5]

In the period from 2000 to June 2021, 141,025 pregnant women with HIV were reported, with the highest prevalence in the Southeast. The detection rate of HIV infection has shown a slight upward trend in recent years, mainly due to the increase in rapid tests distributed by Stork Network.[6]

Regarding simultaneous HIV/syphilis infection, both are transmitted mainly through unprotected sex and vertically.[1] These are important problems during pregnancy, due to several negative outcomes, such as spontaneous abortion, fetal or neonatal death, prematurity and congenital infections.[7]

There is difficulty for SINAN in crossing information about HIV/syphilis co-infection, making it impossible to know the prevalence of these diseases in an associated way, as there are no co-infection data in the notification and investigation forms.[8] Therefore, to obtain this information, it would be necessary to cross-reference databases relating to each problem, using nominal data.

In this way, in isolation, the clinical-epidemiological characteristics of the diseases[8] of interest for this work are known. However, identifying scientific evidence that reports pregnant women who acquired HIV/syphilis co-infection is necessary to understand the factors, whether clinical, social and/or epidemiological, that can influence the prevalence of these STIs.

From this perspective, the objective was to synthesize scientific evidence about the clinical-epidemiological characteristics of pregnant women with HIV/syphilis co-infection globally.

METHOD

This is an integrative review, organized in the following stages: guiding question elaboration, literature search, data collection or extraction, study critical analysis, interpretation and presentation of results.[9]

The research question was prepared using the PICo strategy,[10] in which P (Population): pregnant women, I (Phenomenon of interest): clinical-epidemiological characteristics and Co (Context): HIV/syphilis co-infection, resulting in the following question: What is the scientific evidence related to the clinical-epidemiological characteristics of pregnant women with HIV/syphilis co-infection?

The survey of studies was carried out from June to September 2022 in the U.S. National Library of Medicine (PubMed), Cumulative Index to Nursing and Allied Health Literature (CINAHL Latin American Literature in Health Sciences (LILACS), Medical Literature and Retrieval System Online (MEDLINE) and Nursing Database (BDENF) databases. The controlled terms in Portuguese and their respective English counterparts were used, such as "HIV", "Syphilis", "Epidemiology", "Coinfection" and "Pregnant", with the help of the Boolean operators "AND" and "OR".

Full articles on the topic, available online and free of charge, published in Portuguese, English and/or Spanish and published between 2012 and 2022, were included. Duplicate articles and articles that did not answer the guiding question were excluded.

As for the time frame of the study, it is justified by the establishment of Ordinance 77 of January 12, 2012, which provided for rapid tests to be carried out in Primary Care to detect HIV and syphilis.[11]

To report the process of identification, screening, eligibility and inclusion of studies, the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) was used.[12] Duplication detection and article selection were carried out by two independent reviewers, using the Rayyan Systems Inc and EndNote (TM) platforms.

Data extraction and analysis were carried out using an adapted instrument, but validated by Ursi (2005), using the variables on identification, country and/or institution hosting the study, publication journal and methodological characteristics.[13] The interpretative analysis of included references was presented and organized in a descriptive way.

The methodological quality of studies was assessed in accordance with a tool modified by Machotka *et al*., (2009), consisting of 12 criteria that represent key elements to assess the methodological quality of the studies. Each item marked affirmatively was assigned a score=1, with the total score on this scale (maximum 12 points) being converted into a percentage (0-100%). The higher this result, the better the methodological quality of the study, with a score of 8.0 being considered acceptable.[14]

As this is an integrative literature review, this work did not require authorization from the Research Ethics Committee, in accordance with Resolutions 466/2012 and 510/2016, which deal with research carried out exclusively with scientific texts to review scientific literature.

RESULTS AND DISCUSSION

Based on the criteria established for the integrative review, 8 studies were selected, published between 2015 and 2020. The results found in the search are displayed in the flowchart (Figure 1) adapted from PRISMA.[12]

The articles were published between 2015 and 2020. The majority were in English, and one of them was in Portuguese. The methodological quality assessment scale[14] found that the majority of studies (87.5%) reached an acceptable score.

In Chart 1, the studies, authors and year of publication, country of publication, study design and a summary of the content of studies are presented, focusing on the main results, clinical-epidemiological characteristics and conclusions.

Regarding study setting, it was observed that the studies were carried out in America, Asia and Africa. Regarding the research design, there was a predominance of cross-sectional studies, and two used secondary analysis of data from randomized clinical trials (Chart 1).

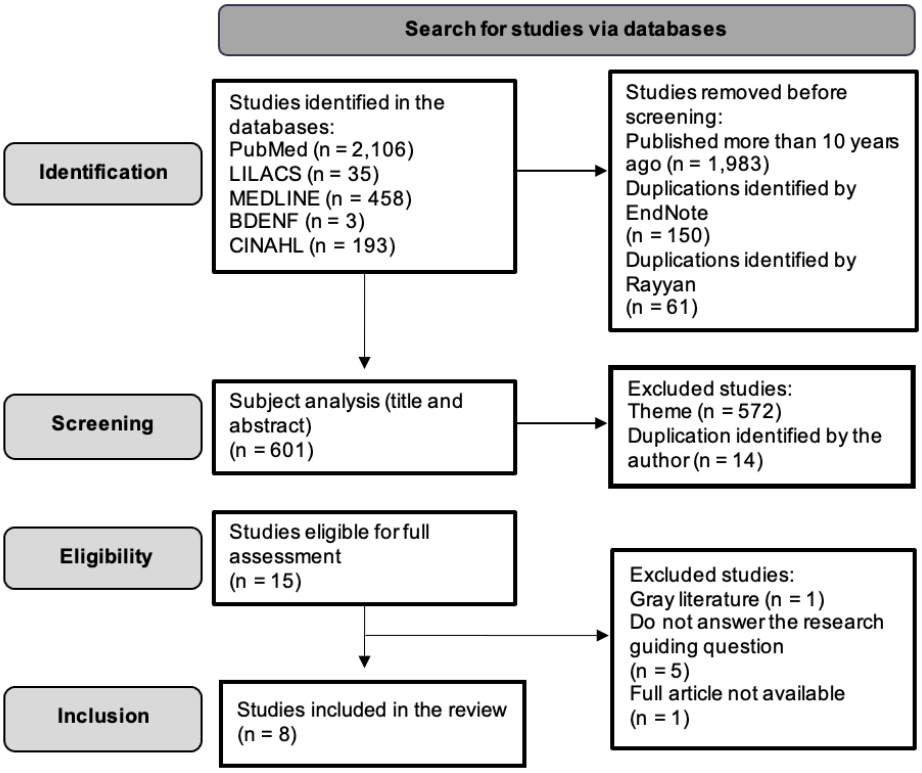

Figure 1. Study selection flowchart adapted from the PRISMA methodology (2021).

The pregnant women who were part of the study sample had similar sociodemographic characteristics that place them in a situation of greater vulnerability to contracting STIs, such as age range between 20 and 49 years old, black race/color, single, low level of education, housewives and early late prenatal care.

The diversity in the epidemiological scenario of HIV/syphilis co-infection indicated prevalence rates that varied from 0.05% to 10.2%.[15-17] The different prevalence shows the heterogeneous distribution of syphilis, and may also be related to the diagnostic criteria adopted by services.[17,18]

Other factors attributed to variation in prevalence may be related to the laboratory diagnosis method used, sociocultural diversity, socioeconomic status, prevention and control strategies, social risk factors, level of knowledge about prevention and, finally, access to health units to carry out prenatal care.[19]

In general, younger women are at greater risk of acquiring an STI.[20-21] However, in the case of pregnant women with HIV/syphilis co-infection, the prevalence was higher among those aged 25 or older, increasing with each change in age group, a finding also observed among the selected studies.[16-18,23-24] The finding may be attributed to the increased risk of exposure to STIs over time, making women more vulnerable to engaging in sexual activities without using barrier methods.[25]

Regarding the race/color variable, co-infection was more common in non-white women, and they are twice as affected as white women.[15,17,24] However, two studies, one in the city of Salvador (BA) and another carried out in 17 locations in Brazil, South Africa, Argentina and the USA, found different results, in which 89% of pregnant women with HIV/syphilis co-infection were white.[24,26]

Regarding marital status, four studies considered this variable.[16,23,27,28] Studies on HIV infection have shown that married pregnant women are the most exposed to the HIV virus, with a 3.29 greater chance of being infected with HIV when compared to single women, especially when partners have multiple partnerships.[17,20,23,29,30]

Considering that pregnant women and partners who participated in the studies had fewer years of study, it is possible to infer that formal education can be decisive in accessing health information and, consequently, in understanding the importance of prenatal care and adherence to treatment.[17,27-30]

The occurrence of STIs may be associated with income, as the most economically disadvantaged social stratum results in less access to preventive information and health care, greater use of sex for economic purposes and as a psychosocial coping mechanism, and housing in rural areas, characterized by compromised socioeconomic indicators, which impose difficulties in accessing specialized care.[15-18]

Two of the studies reported a higher prevalence of HIV/syphilis coinfection in pregnant women living in urban areas. Possible reasons are the presence of sex workers and the high prevalence of HIV in the urbanized population.[23,28]

It is also important to highlight the vulnerable situ-

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Chart 1. General characterization of included studies, authors and year, countries, study design, in addition to a summary of the content of studies focusing on the main results, clinical-epidemiological characteristics and conclusions of selected studies.

Author / Year	Country	Study design	Results	Main clinical-epidemiological characteristics	Conclusions
Endris et al., 2015	Ethiopia	Cross-sectional	Of 385 pregnant women, reactive syphilis was observed in 2.9%, and HIV seroprevalence was 11.2%. The prevalence of syphilis and HIV co-infection was 0.5%.	A high rate of syphilis was observed among women over 30 years of age, housewives, with a history of miscarriage and stillbirth. As for HIV, there were women between 21-29 years old, married and traders.	Syphilis and HIV are still important public health problems. Screening during prenatal care and strengthening health education was recommended.
Moura et al., 2015	Brazil	Cross-sectional	Of the total of 54,813 pregnant women, the prevalence of syphilis and HIV infections were 2.8% and 0.3%, respectively. Coinfection occurred in 0.05%, with a potential risk of HIV-infected pregnant women being coinfected by T. pallidum (5.71 times).	The average age was 23.3 years old, with 31.5% being adolescents; and 68.3% declared themselves to be of non-white race/color/ethnicity.	Syphilis was twice as prevalent among pregnant women in Maceió, compared to the national average, and coinfections with syphilis/HIV and HTLV/HBV were significantly associated.
Acosta et al., 2016	Brazil	Analytical retrospective cross-sectional	Of 1,500 positive pregnant women, the HIV/syphilis co--infection rate was 10.2%. The greatest vulnerability factors were late HIV diagnosis and lack of prenatal care. An association between vertical transmission of HIV and the presence of HIV/syphilis co-infection was identified.	The majority were young adults (25-34 years old), of black race/color/ethnicity and with less than eight years of education.	The group of pregnant women with HIV/syphilis was more vulnerable. Improving access to qualified health care will have a positive impact on reducing congenital syphilis and eliminating vertical transmission of HIV.
Yeganeh et al., 2016	Brazil, South Africa, Argentine and USA	Secondary analysis of randomized controlled clinical trial	Approximately 10% of 1,664 pregnant women enrolled had serological evidence of syphilis without documented adequate treatment, and 1.4% of infants were dually infected with HIV and syphilis.	Women with co-infection were significantly more likely to self-identify as non-white and consume alcohol, with 88% of HIV infections being acquired in utero.	Syphilis remains a common co-infection in HIV-infected women, and can facilitate intrauterine transmission. Most babies were asymptomatic at birth, but those with symptoms have high mortality rates.
Kinikar et al., 2017	India	Secondary analysis of randomized controlled clinical trial	Of the total of 658 HIV-infected mothers, 5% of mothers were also infected with T. pallidum, and 100% received penicillin. Syphilis diagnosis occurred a median of 29 days before birth.	Mothers with co-infection were more likely to have a low level of education, be housewives and less likely to have received antibiotic therapy.	The analysis showed a high rate of maternal syphilis associated with a greater risk of vertical transmission of HIV.
Mutagoma et al., 2017	Africa	Cross-sectional	Of the 55,432 pregnant women analyzed, HIV/syphilis co-infection was present in rural and urban areas. However, it was more likely in women living in urban areas, but less frequent in women with secondary education.	They occurred in pregnant women aged between 25 and 49 years who lived in urban areas and women with secondary education or higher, being less likely to be screened positive for syphilis.	Syphilis increased in HIV-positive pregnant women and decreased in HIV-negative women. HIV seropositivity and young age were associated risks for syphilis. HIV/syphilis co-infection was associated with a lower level of education and urban residence.
Biadgo et al., 2019	Ethiopia	Retrospective	Of the total of 3,504 pregnant women analyzed, the seroprevalence of HIV and syphilis was 4.1% and 1.9%, respectively. And 0.66% women had co-infection.	Age group 20–29 years and age group ≥30 years, compared with age <20 years and HIV infection, were significantly associated with syphilis infection.	Syphilis and HIV remain critical public health concerns among pregnant women. Screening for all pregnant women and studies on risk factors are recommended.
Kengne-Nde et al., 2020	Cameroon	Cross-sectional	Of the total of 3,901 pregnant women tested for syphilis, almost half (47.9%) were from urban areas and were under 25 years old. While the HIV epidemic was declining, a significant increase in the prevalence of syphilis was observed. Pregnant women residing in rural areas were more likely to be infected with syphilis than those in urban areas.	Single pregnant women were three times more likely to have HIV/syphilis co-infection than those who were married, in a stable relationship, widowed or divorced.	The epidemiological dynamics of syphilis suggest an increasing burden of infection among the general population of Cameroon. In addition to strategies to combat HIV, great efforts must also be made to prevent and combat syphilis, especially among HIV-positive women.

ation in which these pregnant women find themselves, as most of them were housewives, financially dependent on their partners, financially fragile and unable to negotiate the use of condoms.[17, 23,28]

Pregnant women with HIV are more susceptible to developing other STIs, and syphilis is one of the most common co-infections.[21] When they occur in association, one can affect the natural evolution of the other.[2,3] Syphilis can increase HIV viral load and decrease CD4 T lymphocyte cells.[21] HIV, on the other hand, influences the worsening of syphilis symptoms.[2,3] Furthermore, ulcerative genital lesions caused by syphilis have been associated with increased HIV acquisition and transmission. [24,27]

In this context, studies show that the prevalence of vertical transmission of HIV is substantially higher among pregnant women with co-infection,[17,24,27] presenting odds that vary from two to 3.71 times,[17,24] being explained by placental inflammation caused by *T. pallidum*, which compromises the structural and functional integrity of cells.[18,27]

It was found that pregnant women with HIV/syphilis co-infection do not adequately adhere to the recommended treatment.[17,24,27] At the same time, a reduced percentage of partners is treated, which contributes to maintaining prevalence and vertical transmission rates, due to ineffectiveness of treatment and, in the case of syphilis, reinfection.[17,24,27,32]

Regarding perinatal outcomes, syphilis causes high rates of negative pregnancy outcomes, especially among pregnant women who are not adequately treated.[17] Abortions and perinatal or neonatal deaths occur in 40% of children infected by untreated mothers or those who started prenatal care late, making timely treatment impossible.[1,15]

Another variable associated with HIV/syphilis co-infection was the consumption of alcohol and illicit drugs during pregnancy.[17,24] This association occurred with greater prevalence in single pregnant women and is linked to other risk factors, such as low education, low socioeconomic level, unwanted pregnancy, adoption of risky sexual behaviors, in addition to inadequate adherence to prenatal care and treatment.[32-34]

The fragility of the care provided was pointed out, as the lack of focus on prevention increases the risk of mother-to-child transmission of HIV by up to 30%, and non-adherence to antiretroviral therapy (ART) during pregnancy increases this risk.[31]

Based on the principle of equity of the Brazilian Health System (SUS - *Sistema Único de Saúde*), pregnant women with HIV/syphilis co-infection should be a priority in health care, however indicators of prenatal care quality indicate otherwise.[17]

In this sense, the importance of Primary Health Care and its integration with Specialized Care Services (SCS), maternity hospitals and Epidemiological Surveillance stands out, aimed at improving pregnant women's adherence to prenatal care, considering that this is an opportune moment for STI diagnosis, in order to reduce the risk of intrauterine infection.[17] Another issue would be to strengthen the actions that permeate the notification and monitoring system for mothers and newborns so that, like other countries, syphilis notification is based on data relating to the stage of the disease and monitoring of the main exposures and of HIV co-infection.[17,31,35-37]

Furthermore, the adoption of records in pregnant women's booklet about the actions adopted and referral to reference services are of great value. In regions that are difficult to access, there is a need to implement an outpatient clinic to monitor infectious diseases instead of adopting separate and disjointed services, especially in areas where the prevalence of diseases remains high. This location will support comprehensive health care, which includes health care, human rights and social participation. It will develop promotion, prevention, diagnosis, treatment and guarantee of clinical and laboratory follow-up of STIs.[1]

As limitations of this integrative review, the possibility of underreporting of cases of HIV/syphilis co-infection is cited, as most studies used secondary data, and, in the case of studies carried out in Brazil, notification forms do not have a field to fill in a form. comorbidities. It is also worth highlighting the difficulty in accessing some restricted publications, with only free access texts being included in the study, made available in full.

CONCLUSION

It was found that HIV/syphilis co-infection is more prevalent in pregnant women in the young-adult age group, of non-white race/color, married, with a low level of education, housewives as their occupation, residents of urban areas and belonging to classes most economically disadvantaged social groups.

Additionally, an association was observed between syphilis and the late start of prenatal care with an increased rate of unfavorable pregnancy outcomes, such as miscarriage, stillbirth and prematurity. It has been shown that the natural evolution of diseases can be affected when diseases are associated.

The studies analyzed showed the need to improve prenatal care, in order to ensure assistance, especially in medication administration and diagnostic test provision, with the aim of reducing the risks of vertical transmission by monitoring pregnant women with co-infection, partners and newborns.

Studies of this nature are important so that more effective strategies can be redirected in the implementation of public policies aimed at clinical management of pregnant women with HIV/syphilis co-infection, allocation of resources and development of specific intervention protocols.

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