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Highlights

- The aim of this study was to evaluate the correlation between antimicrobial consumption according to AWaRe classification and Carbapenem Resistant Gram-Negative Bacteria in a COVID-19 reference hospital.
- Access group accounted for 50% of all antimicrobial consumption, while Watch and Reserve groups accounted for 46% and 4%, respectively.
- Watch group had significant correlation with carbapenem resistant gram-negative bacteria density for both, clinical and total isolates, as well as for carbapenem resistant Klebsiella spp. and P. aeruginosa.
- Watch group was not correlated with carbapenem-resistant A. baumannii.

Impact of an antimicrobial stewardship program in a COVID-19 reference hospital according to the AWaRe classification

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Summary

This was a prospective observational study performed between January and October 2021. Antimicrobial consumption was classified according to AWaRe and expressed as daily defined doses (DDD/1000 patient-days). Watch group antibiotic consumption demonstrated a strong correlation with carbapenem resistance among both clinical and total isolates, but *A. baumannii* resistance did not correlate with antimicrobial consumption. Efforts to reduce antimicrobial consumption are needed; however, prevention and control guidelines are also a cornerstone to better results.

Background

Antimicrobial stewardship programs (ASP) have been associated with lower in-hospital antimicrobial consumption, earlier discharge when the oral switch protocol is implemented, and lower hospital costs. Nevertheless, their impact on antimicrobial resistance (AMR) remains an issue, and recent guidelines highlight the importance of reporting clinical and microbiological outcomes[1].

In order to homogenize antimicrobial usage reports, the World Health Organization (WHO) has classified antimicrobials into Access, Watch, and Reserve groups. One of its goals is to achieve 60% of all antimicrobial consumption from the Access group (https://www.who.int/publications/i/item/2021-aware-classification). However, achieving this target has been difficult due to the COVID-19 pandemic, and recent evidence has demonstrated that AMR increased after 2019–2020 (e.g., carbapenem and polymyxin resistance)[2,3].

Considering the lack of evidence on an association between ASP and lower AMR, the new WHO goal, and the COVID-19 pandemic, the aim of this study was to evaluate the correlation between antimicrobial consumption and AMR in a 515-bed COVID-19 reference hospital in South Brazil that has a structured infectious prevention and control department.

Material and Methods

This was a prospective observational study performed between January and October 2021. Antimicrobial consumption was classified according to AWaRe [i.e., Access, Watch, and Reserve groups (e.g., doxycycline, meropenem, and polymyxin, respectively)] (WHO 2021), and expressed as daily defined doses (DDD/1000 patient-days). Bacterial identification and susceptibility patterns were analyzed using a BD Phoenix ™ System (Mississauga, Canada). Carbapenem-resistant gram-negative bacteria (CR-GNB) were selected, and the culture results were classified as belonging to a clinical infection or colonization. The CR-GNB densities were expressed based on patient-day (PD) rates, (i.e., number of resistant unique isolates/PD × 1000). A Pearson's correlation analysis was performed. The ASP approach was followed as previously detailed[4].

Results

Antimicrobial consumption according to AWaRe and AMR is shown in Figure 1. During the study period, the median consumptions were 347.64 (IQR: 330.39–404.03) DDD/1000 patient-days for Access, 329.22 (IQR: 280.24–352.55) DDD/1000-patient-days for Watch, and 27.82 (20.35–31.81) DDD/1000 patient-days for Reserve antibiotics. The CR-GNB median densities for clinical and total isolates were 5.76 (IQR: 2.79–8.40)/1000-PD, and 15.70 (IQR: 9.83–19.53)/1000-PD, respectively.

Clinical isolates were all considered hospital-acquired infections, while only 7% of total isolates were on hospital admission. Among the clinical and total isolates, the *Acinetobacter baumannii* densities were 3.94 (IQR: 1.85–5.59)/1000-PD and 10.03 (IQR: 4.89–12.00) /1000-PD, respectively. Additionally, there were lower densities of clinical and total isolates from *Klebsiella* spp. and *Pseudomonas aeruginosa*, reaching 1.18 (IQR 0.77–1.70) /1000-PD and 5.07 (IQR: 4.24–6.17) /1000-PD in *Klebsiella* spp., and 0.29 (IQR: 0.24-0.7) /1000-PD and 0.34 (0.24-0.7) /1000-PD in *P. aeruginosa*, respectively.

The consumption of antibiotics of the Watch group had significant Pearson's correlations with CR-GNB density (clinical isolates P = 0.027, R = 0.691; total isolates P = 0.018, R = 0.724), carbapenem-resistant *Klebsiella* spp. (clinical isolates, P = 0.020, R = 0.714; total isolates, P = 0.034 R = 0.670), and carbapenem-resistant *P. aeruginosa* (clinical isolates, P = 0.017, R = 0.727; total isolates, P = 0.018, R = 0.723). However, it was not correlated with carbapenem-resistant *A. baumannii* (clinical isolates, P = 0.106, R = 0.542; total isolates, P = 0.065, R = 0.603).

Discussion

According to our results, 50% of all antimicrobial consumption belonged to the Access group, while 46% and 4% were from the Watch and Reserve groups, respectively. The correlation between the CR-GNB and Watch group was strong for both clinical and total isolates (clinical isolates, P = 0.027, R = 0.691; total isolates, P = 0.018, R = 0.724). Similar results were observed for *K. pneumoniae* and *P. aeruginosa*. However, *A. baumannii* did not correlate with antimicrobial consumption. Unfortunately, *A. baumannii* accounted for more than 50% of the CR-GNB. Our hospital during the

COVID-19 pandemic had suffered with lack of qualified human resources. Additionally, during the pandemic period we had faced a CRAB outbreak in COVID-19 ICUs, which was only settled when ICUs were entirely closed for environmental cleaning. Therefore, once an outbreak is not controlled only by ASP, infection control measures may have influenced on the statistical results of *A. baumannii* and its correlation to Watch group consumption. Indeed, systematic reviews that included both tools, i.e., culture results from the site of infection and colonization, have shown that the ASP results were inconclusive in almost 30% of studies, while another 20% demonstrated a negative impact[5]. Furthermore, it is important to highlight that better outcomes occurred in hospitals with a structured and present infection prevention and control department[5]. Therefore, our results highlight that ASP indeed impact on bacterial resistance from both, clinical and total isolates, however, it's important to define goals and measurements, and work together with infection control and hospital epidemiology department.

The COVID-19 pandemic has deeply affected bacterial resistance and has had a direct impact on antimicrobial consumption rates[2,3]. Furthermore, human resources have been affected in multiple ways, e.g., suffering from a lack of preparation and information, and burnout syndrome[6]. Additionally, the general perception is that patient safety and quality care have also been impaired[7]. The combination of these factors (i.e., higher antimicrobial consumption and compromised human resources) constitute the so-called "*perfect storm"* that has led to an increase in AMR and lower ASP efficiency when considering microbiological outcomes. Last but not least, environmental cleaning is also highly important, especially when considering pathogens such as *A. baumannii*[8].

Conclusion

In conclusion, Watch group antibiotic consumption demonstrated a strong correlation with carbapenem resistance among both clinical and total isolates, but *A. baumannii* resistance did not correlate with antimicrobial consumption. Efforts to reduce antimicrobial consumption are needed; however, prevention and control guidelines are also a cornerstone to better results.

Conflict of interests:

Authors declare no conflict of interests.

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Figure 1. Antimicrobial consumption according with AWaRe groups and carbapenem resistance densities, Jan–Oct, 2021. A, Access; B, Watch; C, Reserve; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CR, carbapenem-resistant; CR-GNB, carbapenem-resistant gram-negative bacilli.