

Impact of COVID-19 pandemic on the pattern of azithromycin prescribing: a review

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Abstract

Objective: Emergence of COVID-19 infection and its persistence globally for three years in a row (2020-2022) entailed several modifications in healthcare services, among which drug prescribing was an important outcome. This review aims to highlight changing trends in azithromycin prescribing during pandemic years.

Methods: PubMed database was systematically searched for combinations of the following keywords: Antibiotics; Antimicrobial resistance; Azithromycin; COVID-19.

Results: A total of 12 articles were included in this review. All included studies demonstrated a notable increase in azithromycin consumption during COVID-19 pandemic in Spain, Brazil, USA, India, Croatia, and Jordan. Healthcare systems worldwide should be prepared to address anticipated outcomes of increased azithromycin use particularly possible changing trends in azithromycin resistance, and systemic side effects of the drug.

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Introduction

The emergence of the coronavirus disease-2019 (COVID-19 pandemic) at the end of 2019 has instigated adoption of many drastic measures and modifications in healthcare systems worldwide. This was notably associated with an increasing tendency in prescribing of several drugs such as those used for their anti-inflammatory, antiviral, and

Keywords

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immunomodulatory effects [1]. Likewise, many antimicrobials such as antibiotics and antifungals were increasingly prescribed to treat bacterial and fungal infections that developed secondary to the viral infection [2].

Of particular interest is the increased consumption of antimicrobials, a trend that has led to a growing concern over the potential increase of antimicrobial resistance and its adverse outcomes [3]. Among these antimicrobials azithromycin has been recommended and therefore used by many authorities heavily at the beginning of the pandemic because of its ability to counteract secondary bacterial infections in medically compromised COVID-19 patients. Prior to COVID-19 pandemic, azithromycin has been used as a broad-spectrum antibiotic indicated for bacterial respiratory infections. It is effective in the management of respiratory infections in young children, and in community-acquired pneumonia in hospitalized patients [4]. Furthermore, it is capable of preventing severe respiratory tract infections when administered to patients suffering viral infection [4]. Its anti-inflammatory and antiviral properties make it useful for some RNA viruses [5]. The antiviral activity of azithromycin against Zika and Ebola viruses has been reported by *in vitro* studies [6-8], though clinically not proven yet. Further, this antibiotic has a characteristic pharmacokinetic profile in the form of good oral bioavailability, efficient tissue penetration and persistence, which facilitate the once-daily or twice-daily dosing regimen particularly useful for pediatric patients, non-compliant patients or patients whom a once daily oral dose is recommended [9].

Although some authorities describe this drug as potentially effective in combating SARS-CoV-2 due to its antiviral and immunomodulatory effects [10], its effectiveness in the management of COVID-19 is still debatable due to doubts concerning the methodological limitations of the investigating studies being mainly retrospective and

observational in nature [11]. Additionally, it has mainly been investigated in a combined treatment protocol with hydroxychloroquine, which makes the analysis of only the effect of azithromycin difficult [11]. The controversy about azithromycin is also attributed to the potential side effects of this drug. Although this antibiotic is considered relatively safe in the adult, pediatric, and pregnant populations [12], a number of side effects have been identified especially with intravenous administration, including gastrointestinal disturbances, ototoxicity, and injection site complications [13]. Its use may also be associated with development of bacterial resistance [14], and proarrhythmic events [15], which could lead to a life-threatening arrhythmia particularly in the elderly and patients who have heart disease, or use other QT prolonging drugs [16].

Based on the above and considering the continuous debate on azithromycin use in COVID-19, it is expected that the healthcare system will be faced by a possible increased demand for prescribing azithromycin, which warrants assessment of the prescribed quantities, and trends in its use. This should be accompanied by evaluating the potential associated risks with the main aim to provide policy makers with the appropriate guidelines and improve antibiotic prescribing practices of healthcare professionals. Therefore, this study aimed to systematically review the literature to evaluate the changing trends in azithromycin prescribing during COVID-19 pandemic years 2020-2022.

Methods

Eligibility criteria

The following inclusion criteria were used:

1. Papers published in English
2. SARS-CoV-2 literature published from December 2019 until March 31, 2022
3. Case reports and series

4. Reviews
5. Expert opinions and letters to the editor
6. Patients: Adult patients affected by COVID-19 infection
7. Intervention: Azithromycin use in the treatment of COVID-19.

The study excluded articles that exclusively discussed the following:

1. In vitro and animal studies
2. Antibiotics other than azithromycin
3. Non-COVID-19 literature

Information sources

A literature search was conducted in MEDLINE/PubMed using the combinations of "COVID-19" and the following keywords: "Antibiotics", "Antimicrobial resistance", and "azithromycin", Reference lists of retrieved articles were also screened for the same keywords.

Selection process

The Mendeley Reference Manager was used to select studies. Two reviewers (N. D-O and O. A-H) independently selected the eligible studies. Any disagreement between reviewers was resolved by consensus or by a third reviewer (S. A-H).

Results

Study selection

A total of 12 articles were determined to be appropriate and were included in the review.

Study characteristics

COVID-19 associated trends in azithromycin prescribing are described in Table 1.

Table 1.

Country	Author	Study type	Location	Azithromycin	Period
USA	Buehrle et al. [17]	retrospective cohort study	Single center	monthly increase by 3.6 days of therapy/1,000 bed days of care	March to June 2020 compared to previous months
	Dieringer et al. [18]	Cross-sectional study	84 medical facilities	Increase in azithromycin use was among the greatest increases in the use of individual antibiotics (6.2 days of therapy per 1,000 days present).	January to May 2020 compared to corresponding periods in previous years
	Nestler et al. [19]	Retrospective observational study	Single center	in April 2020 (103-109 DOT per patient day) compared to 27-50 in mean DOT /1,000 PD in April 2019– March 2020	April and May of 2020 when compared to the preceding year
	Staub et al. [20]	Retrospective observational study	Single center	azithromycin use in the pre-COVID-19 period versus the first 3 weeks of admitting COVID-19 patients showed a significant weekly increase of 48.7 DOT per 1,000 days. In the second post-COVID-19 period, there was a significant decrease in azithromycin weekly antimicrobial use of 58.2 DOT per 1,000 days	The study period was separated into a pre-COVID-19 period (December 1 to February 29, 2020) and 2 post-COVID-19 periods (March 1–21 and March 22–May 15 (March 4, 2020).

Country	Author	Study type	Location	Azithromycin	Period
Spain	Garcia et al. [21]	Retrospective analysis	Regional health system in Spain	In March 2020 azithromycin prescriptions were higher for the middle-income group when compared to March 2019	March 2020 compared to March 2019
	Gonzalez et al. [22]	Letter to the editor	National	The use of azithromycin in March 2020 was 400% the use of the same molecule in February 2020, and more than 320% the consumption of azithromycin in January 2019	The period of January 2017 to February 2020 compared to March 2020
	Grau et al. [23]	A retrospective quasi-experimental before– after study	Single center	azithromycin, reached maximum consumption in March (defined daily doses (DDD)/100 bed-days B change of 19. 442	from January 2018 to February 2020 and from March to June 2020.
	Grauet al. [24]	Retrospective	66 acute care hospitals	Increased consumption 200. 01%(DDD/100 bed-days) and 275. 09%(DDD/100 discharges)	2019 compared to 2020
India	Suliset al. [25]	Retrospective analysis	National	38. 0 million excess doses of non-CAF azithromycin (equivalent to a minimum of 6. 2 million azithromycin treatment courses) between June and September 2020, After the end of lockdown, between June and September 2020, azithromycin sales were 34. 4% higher than observed in the corresponding months of the previous year, followed by a decline after the peak of the first epidemic wave	January 2018 to December 2020
Brazil	Silva et al. [26]	Retrospective observational	Single center	azithromycin consumption increased rapidly from January 2020 to April 2020, with a MPC of 5. 21. DDD from January 2019 to December 2020 also increased from 8. 1 (2019) to 9. 7 (2020)	January 2019 to December 2020
Croatia	Bogdanic et al. [27]	Retrospective analysis	National	azithromycin distribution increased in hospital (3. 62 and 3. 19 times, respectively) and non-hospital pharmacies (1. 93 and 1. 84 times, respectively) compared to the average consumption in the same months in 2017–2019	November and December 2020 compared to the same months in (2017–2019)
Jordan	Al-Azzamet al. [28]	Retrospective	National	Azithromycin consumption was increased 74% from 1. 54 DID (2019) to 2. 55 DID (2020)	2019 compared to 2020

DOT: Days of therapy; non-CAF: non-child-appropriate formulation; DID: DDD per 1000 inhabitants per day; MPC: Monthly percent change; DDD: Dose per Day.

Discussion

Since the emergence of COVID-19 pandemic, the use of azithromycin in treatment protocols has generated an ongoing debate. A rapid review conducted by Gbinigie and Frie (2020) in 2020, that is

the first months of the pandemic, concluded that azithromycin can be used for treatment of secondary bacterial infection, otherwise there is no evidence to support its use in the treatment of COVID-19 [29]. Approximately one year later, during

the successive waves of the pandemic, another review was conducted by Echeverría-Esnal et al (2021) who recommended the use of azithromycin either alone or in combination with hydroxychloroquine in the early COVID-19 infection to reduce the potential for adverse disease outcomes such as duration of infection or need for hospitalization [11]. They also recommended its use in the COVID-19 advanced stage to reduce more severe adverse disease outcomes such as the time to successful ventilation discontinuation and mortality [11]. Therefore, considering the ongoing controversy related to azithromycin use in treatment protocols of COVID-19, we may witness an ongoing increased consumption of this drug on a global level.

This is evident when reviewing the studies included in this study, which were conducted in the Americas, Europe, and Asia. All of which clearly highlight the trending increased consumption of azithromycin which should warrant attention to the anticipated rise in the associated side effects.

The substantial increase in azithromycin use raises several serious concerns. The increased chronic use of azithromycin in COVID-19 has led to a rise in bacterial resistance [30]. This was shown by studies done in China where Zhu et al (2022) analyzed the distribution of drug resistance of specific common bacteria in the past three years as compared to drug resistance in the past decade and showed that *Streptococcus pneumoniae* and *Staphylococcus aureus* are highly resistant to macrolides [31]. Another study conducted in Mexico by López-Jácome et al (2022) has confirmed an increase in erythromycin resistance in *Staphylococcus aureus*, and they attributed this finding to the high azithromycin use [32]. A recent randomized controlled study revealed an increase in resistance to macrolide and non-macrolide antibiotics in the gut flora [49]. Multi-drug-resistant bacteria including extended spectrum beta-lactamase-producing strains, are highly prevalent among healthy adults in the community which could be further increased with the anticipated in-

crease in azithromycin use [50]. The growing use of azithromycin could further jeopardize the available therapeutic choices for certain infections such as travelers' diarrhea [25].

After the implementation of the COVID-19 huddle (March 24, 2020), which universally discouraged azithromycin use for COVID-19 treatment alone and encouraged antibiotic cessation in patients whose symptoms could be attributed to COVID-19, there was a significant decrease in azithromycin use for COVID-19 compared to pre-COVID-19 use [20]. However, there seems to be a trending increase in azithromycin use as shown by the studies reviewed here.

The increased use of azithromycin was paralleled by reduction in the consumption of other broad-spectrum antibiotics. Al-Azzam et al (2021) reported that in 2020, Jordan witnessed a marked reduction in amoxicillin use by 53%, while the use of azithromycin increased by 74% [28]. Moreover, Sulis et al (2021) found that COVID-19 likely contributed to about 38.0 million excess doses of azithromycin in India between June and September 2020 (i. e., after the lockdown and until the epidemic peak) [25]. Bogdanic et al (2022) estimated that the amount of extra azithromycin distributed in 2020 compared to previous years is equivalent to almost 38,000 extra 5-day courses with no obvious other reasons but COVID-19 [27]. The increased consumption of azithromycin is also reflected on the relatively high cost particularly in industrialized countries. Prices for the 14-day course of azithromycin are estimated to range between \$63 in the USA, to \$5 in India and Bangladesh [33].

As the current restrictions related to COVID-19 are easing worldwide it is recommended that more studies are conducted globally to estimate the most recent trends in patterns of azithromycin use, and to evaluate any changes in the reported side effects and antimicrobial resistance. This is particularly warranted for the large non-COVID-19 patient population for whom azithromycin is indicated for

its antimicrobial and immunomodulatory effects. Furthermore, more cross-sectional studies should be conducted among populations that consume self-prescribed azithromycin during COVID-19 and other infections.

Conclusions

The trending increase in azithromycin use globally associated with COVID-19 pandemic is likely to generate certain side effects associated with this antibiotic. Healthcare systems should be prepared to manage these side effects by educating and training the concerned healthcare professionals.

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Competing interests

Authors declare no competing interests

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