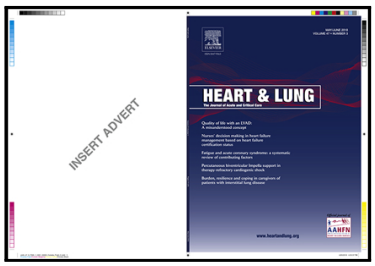

Clinical efficacy of Azithromycin for COVID-19 management: A systematic meta-analysis of meta-analyses

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Clinical efficacy of Azithromycin for COVID-19 management: A systematic meta-analysis of meta-analyses

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Abstract

Background: Azithromycin has been adopted as a component of the COVID-

Journal Pre-proof

19 management protocol throughout the global healthcare settings but with a questionable if not downright unsubstantiated evidence base.

Objectives: In order to amalgamate and critically appraise the conflicting evidence around the clinical efficacy of Azithromycin (AZO) vis a vis COVID-19 management outcomes, a meta-analysis of meta-analyses was carried out to establish an evidence-based holistic status of AZO vis a vis its efficacy as a component-in-use of the COVID-19 management protocol.

Methods: A comprehensive systematic search was carried out through PubMed/Medline, Cochrane and Epistemonikos with a subsequent appraisal of abstracts and full-texts, as required. The Quality of Reporting of Meta-analyses (QUOROM) checklist and the Assessment of Multiple Systematic Reviews (AMSTAR) methodology were adopted to assess the methodological quality of the included meta-analyses. Random-effects models were developed to calculate summarized pool Odds Ratios (with 95% confidence interval) for the afore determined primary and secondary outcomes.

Results: AZO, when compared with best available therapy (BAT) including or excluding Hydroxychloroquine, exhibited *statistically insignificant* reduction in mortality [(n= 27,204 patients) OR= 0.77 (95% CI: 0.51-1.16) (I2= 97%)], requirement of mechanical ventilation [(n= 14,908 patients) OR= 1.4 (95% CI:

0.58-3.35) (I^2= 98%)], induction of arrhythmia [(n= 9,723 patients) OR= 1.21 (95% CI: 0.63-2.32) (I^2= 92%)] and QTc prolongation (a surrogate for torsadogenic effect) [(n= 6,534 patients) OR= 0.62 (95% CI: 0.23-1.73) (I^2= 96%)].

Conclusion: The meta-analysis of meta-analyses portrays AZO as a pharmacological agent that does not appear to have a comparatively superior clinical efficacy than BAT when it comes to COVID-19 management. Secondary to a very real threat of anti-bacterial resistance, it is suggested that AZO be discontinued and removed from COVID-19 management protocols.

Keywords: COVID-19; Azithromycin; Arrhythmia; Mortality; Torsades de pointes

Introduction

The emergence of Coronavirus Disease 2019 (COVID-19) pandemic has led to several strategies adopted by the scientific community to contain the ŘŜØIꞏăűIꞏűłyƎ ŜŦŦŜŎű 2Ŧ űKłă yƵØŜf ØłℕdzăΣ 2yŜ 2Ŧ űKŜϒ ōŜłyƎ ΨŘℕdzƎ ℕŜLJdzℕLJ2ăłyƎΩ űKIꞏű essentially is exploring such medications that stood the test of time for non-COVID ailments to be incorporated into the COVID-19 management protocols secondary to the anti-viral, immunomodulatory and/or anti-inflammatory properties of such pharmacological agents. [1-3] One of them happens to be Azithromycin (AZO), a macrolide that disrupts the aminoacyl-tRNA transition primarily in gram-negative bacteria and is explored for its potential effect on containing suppurate secondary bacterial pneumonia in COVID-19 patients. [4] Several studies attempted to establish its effect on COVID-associated mortality as well as secondary in-patient outcomes including but not limited to arrhythmic induction and QTc prolongation providing a mixed cumulative inference with some pointing in favor whereas others pointing against its efficacy and adoption. [5-7] In order to counter and amalgamate the conflicting evidence, a meta-analysis of meta-analyses was conducted to explore the clinical efficacy of AZO for COVID-19.

Methods

Search strategy

The systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines[8] with a prospective study protocol (PSP) guiding the objectives, search strategy and planned analyses developed and subsequently adopted rigorously. Being a systematic review of meta-analyses, ethics approval was exempted from being sought.

Three investigators (ADKY, AHB & SYA), independently, carried out the literature search through Cochrane Database of Systematic Reviews, PubMed/Medline and Epistemonikos in accordance with the said PSP specifically looking for such meta-analyses where researchers have tried to establish the efficacy of AZO vis a vis COVID-19 management τ by critically appraising and adding together the evidence from primary research studies including randomized controlled trials (RCTs) and prospective as well as retrospective cohort studies. The reference lists of the selected, eligible meta-analyses were searched for relevant publications followed by manual search of those

publications over Epistemonikos to identify if their evidence has been incorporated in such a meta-analysis that could not be identified during the primary search.

The primary outcome, as determined prior to implementing the search strategy, was reduction in mortality. Secondary outcomes included requirement of mechanical ventilation and torsadogenic effect.

The search strategy included MeSH terms "COVID-19", "Azithromycin", "Standard of Care" and "Respiration, Artificial" and is concisely summarized in the ΨƑdzLJLJƒŜϒŜƴůl·ǁè ǡl·ůŜǁǁl·ƒΩ.

Study selection

Three investigators (ADKY, SMMA & HFK) independently, reviewed the cohort of eligible articles with independent consideration of the abstracts and full-texts, as required, followed by undertaking discussions to reach a consensus in those cases where disagreements arose. The updated PRISMA flow diagram (Figure 1) represents the study selection process transparently.

Manual extraction of the required data, in accordance with the pre-deteǁϒǁƴŜŘ ά/Kl·ǁl·ǑůŜǁǁăůǁǑă ƻŦ ăůdzŘǁŜăέ ůl·ōƒŜΣ ǿl·ă Ǒl·ǁǁǁŜŘ ƻdzů ǁƴŘŜLJŜƴŘŜƴůƒè ōè

three investigators (AHB, SZ & AUK). The extracted variables included publication year with the range of years of included studies, number of primary studies with the number of Included RCTs and respective meta-analysis numerical results. Three investigators (SYA, MK & NA), independently, authenticated the developed ά/ƘI·ǊI·ŎűŜǊλăűλŎă ƻŦ ăűdzŘλŜăέ űI·ōfŜφ

Statistical analysis

Three investigators (ADKY, AHB & SYA), independently, adopted the Cochrane Review Manager (v. 5.4) to develop Mantel-Haenszel Random-effects models in order to calculate summarized pool Odds ratio (with 95% confidence intervals) for the primary (reduction in mortality) and secondary outcomes (requirement of mechanical ventilation, induction of arrhythmia & QTc prolongation).[11] I^2 statistic was interpreted to comment on the heterogeneity with the conduction of sensitivity analysis explored to inspect heterogeneity.

Quality assessment and risk of bias

Three investigators (ADKY, AKK & RM), independently, adopted the Quality of Reporting of Meta-analyses (QUOROM) checklist to establish the degree of

thorough reporting. [9] Moreover, three investigators (AHB, OA & AF), independently, adopted the Assessment of Multiple Systematic Reviews (AMSTAR) methodology to assess the methodological quality of the included meta-analyses.[10] Three investigators (SYA, AA & AUB), independently, assessed the primary study overlap by exploring the Corrected Covered Area (CCA) measurement.[12]

Results

A comprehensive search carried out through PubMed/Medline, Cochrane Database of Systematic Reviews and Epistemonikos yielded 80 publications with no publications identified via manual search. After removing duplicates, the abstracts and, where required, full-texts of 71 publications were considered in accordance with the aforementioned inclusion eligibility criteria. Only 2 meta-analyses satisfied the inclusion eligibility criteria and were, therefore, included in the review. The underlying causes of exclusion of publications are concisely indicated in the relevant component of the PRISMA flow diagram (Figure 1).

The characteristics of the included meta-analyses are demarcated accordingly. (Table 1 & Table S1)

Kamel AM et al. discouraged incorporation of AZO as a component of COVID-19 management protocol and recommended its discontinuation after undergoing a thorough meta-analysis by considering only RCTs to assess the efficacy of AZO against the best available therapy (BAT) vis a vis factors including but not limited to requirement for invasive mechanical ventilation and length of hospital stay.[13]

a l·yƎʅdzƭλƎdzyƖ· D Ŝű l·fɸ űŜǊϒŜŘ !½h άǿŜff-üƶfŜǊl·űŜŘɛ l·yŘ άăl·ŦŜ űƶ dzăŜɛ ōdzű reported them not having a better clinical outcome for COVID-19 patients when compared with BAT. Their conclusions were driven by the findings of an in-depth meta-analysis carried out by critically appreciating the findings from a group of studies including RCTs that compared AZO with BAT vis a vis ICU transfers and ECG changes.[14]

The QUOROM analysis, carried out to assess the degree of comprehensiveness of reporting in the included meta-analyses, and AMSTAR analysis, carried out to explore internal validity and methodological quality (Table S2), indicated Kamel AM et al. falling short of exploring the publication bias using standard

analysi(e)s. Mangkuliguna G et al. was found to have neither commented on the handling of missing data nor highlighted the data required to calculate effect sizes and confidence intervals in intention-to-treat analyses. Both of the included meta-analyses did not provide the list of excluded studies. That being indicated, both meta-analyses were mutually agreed to be of sufficiently high quality vis a vis the degree of comprehensiveness of reporting as well as internal validity and methodological quality. A substantial overlap at 20% between the primary studies considered in the included meta-analyses was recognized on CCA analysis. (Table S3) Since only 2 meta-analyses met the inclusion criteria and were subsequently incorporated in the meta-analysis of meta-analyses, sensitivity analysis was not carried out as the threshold for studies to carry out such an exploratory analysis was not met.

Our meta-analysis of meta-analyses reported statistically insignificant reduction in mortality [(n= 27,204 patients) OR= 0.77 (95% CI: 0.51-1.16) (I^2= 97%)], requirement of mechanical ventilation [(n= 14,908 patients) OR= 1.4 (95% CI: 0.58-3.35) (I^2= 98%)], induction of arrhythmia [(n= 9,723 patients) OR= 1.21 (95% CI: 0.63-2.32) (I^2= 92%)] and QTc prolongation (a surrogate for

torsadogenic effect) [(n= 6,534 patients) OR= 0.62 (95% CI: 0.23-1.73) (I^2= 96%)] upon comparing AZO against BAT. (Figure 2)

Discussion

Our research endeavor happens to be the very first attempt to undergo a comprehensive systematic review of meta-analyses that explores the clinical efficacy of AZO for COVID-19 considering the pertinent primary evidence in its totality, except for a recently published RCT. Oldenburg CE et al. concluded that AZO does not introduce a greater likelihood in an outpatient to become relieved of symptoms of COVID-19 at day 14 when compared with placebo.[15] It was not considered because of the fact that we included only meta-analyses and not individual RCTs.

A thorough meta-analysis of meta-analyses was carried out that assessed and amalgamated the relevant literature in its entirety. It would be correct to ascertain that AZO, when compared against BAT that may or may not contain Hydroxychloroquine, decreases neither the requirement of mechanical ventilation nor mortality among COVID-19 patients. That being affirmed, AZO was also found not to induce arrhythmia or torsadogenicity to a statistically

significant extent. Obliquely, similar findings pointing towards invalid adoption of such pharmacological agents that do not exhibit statistically significant betterment of patient outcomes when observed through the lens of robust RCTs further cement our data-driven deductions.[16]

No meta-analysis of meta-analyses has been undertaken before to explore the under-consideration research question which furthers the novelty of this systematic review as well as the universal implications, both explicitly and implicitly indicated, heralded by the findings.

That being indicated, one of the limitations of our study lies in a considerably high heterogeneity. After recognizing that for all of the analyzed outcomes, the majority of heterogeneity τ the *observed* variance in the effect size τ arises from true variance in the effect size secondary to inter-population variabilities that can be attributed to several underlying factors and is conceded as a limitation, those currently unknown factors are suggested as a direction of future research. Such suggested endeavors shall allow us to identify those specific predictors which portend a patient to relatively negative outcomes of COVID-19 τ a step towards optimized, individualized medicine.

Moreover, our systematic review could not consider literature disseminated in

languages other than English as well as that dispersed via those scientific journals that are not indexed in the searched databases upon which we implemented the search strategy. However, we aNŜ Ŏ2yŦƛŘŜyű ŭKI·ŭ ǎdzŎK ά∃NŜè fƛŭŜNI·ŭdzNŜέ ǎKI·ft ōŜ constituting no more than a minuscule proportion of the text that considers the under-consideration research question. In addition to that, as recognized in the supplementary material, there happens to be a significant overlap of primary studies considered by the included meta-analyses that might have introduced a confounding effect. We recognize that as an inherent limitation to the study design adopted and suggest that exploration be undertaken to develop such methodological adjuncts that would minimize the ramifications of this limitation.

The meta-analysis of meta-analyses portrays AZO as such a pharmacological agent that does not appear to have a comparatively superior clinical efficacy when it comes to COVID-19 management upon it being compared with BAT. On the flip side, it was not found to be causing arrhythmic induction or instituting a torsadogenic effect by prolonging QTc, either. However, secondary to a very real threat of anti-bacterial resistance [17], it is suggested that AZO be discontinued and removed from COVID-19 management protocols.

Supplementary data

The study protocol along with tables S1 to S3 constitute the Ψ{dzLJLJfŜY'ŜyűI·ℕë a I·üŜℕƗI·fΩ.

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Figure legends

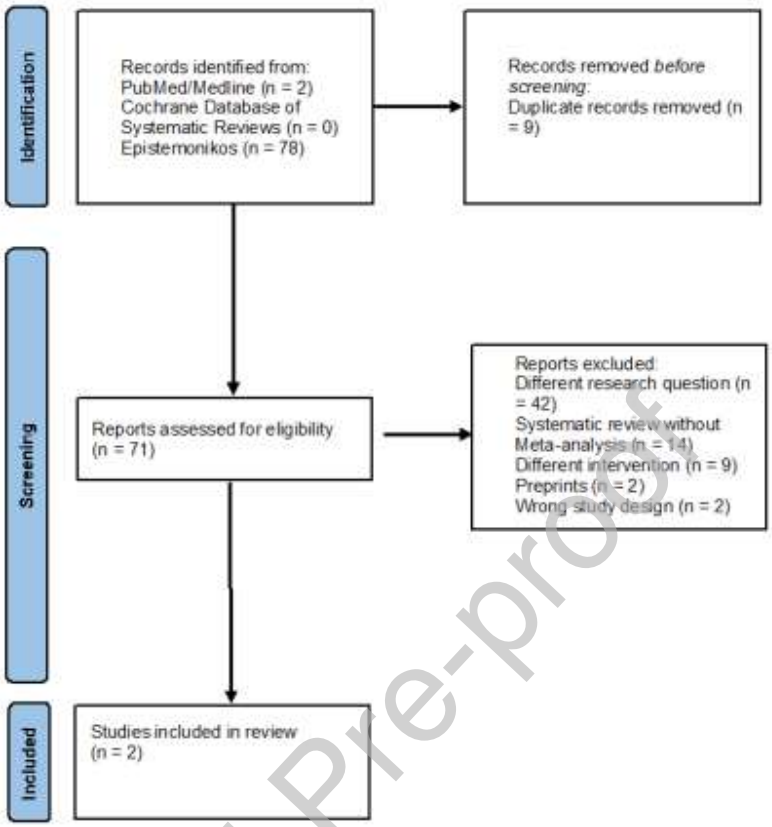

Figure 1. PRISMA flow-chart illustrating search, selection and inclusion of meta-analyses.

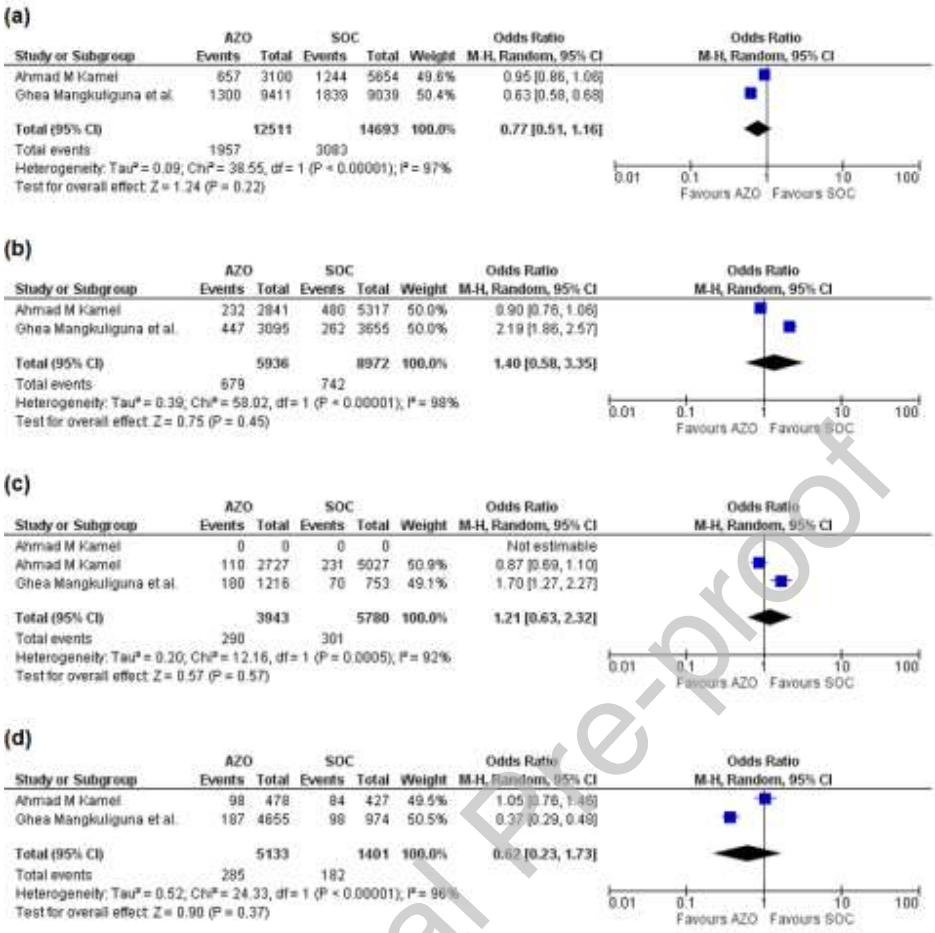

Figure 2. Pooled Odds ratio (with 95% Confidence Interval) for (a) mortality (b) requirement of mechanical ventilation (c) arrhythmic induction and (d) torsadogenic effect comparing Azithromycin to the Standard of Care.

Quick Look

Current Knowledge

Azithromycin (AZO) is adopted as a component of COVID-19 medical management protocol but its clinical efficacy is equivocal for COVID-19 management with several reported adverse events including QT_c prolongation.

What This Paper Contributes To Our Knowledge

This study is a comprehensive systematic review of meta-analyses that assess the current literature around the clinical efficacy of AZO for COVID-19 management exploring its effectiveness on containing COVID-19 associated mortality and requirement of mechanical ventilation. AZO-associated adverse events such as QTc prolongation have also been assessed to critically appraise its rationale for being a component of COVID-19 management protocols and conclusively suggests dropping AZO for COVID-19 management protocols on the grounds of no added benefit when compared against the best available therapy and incurred undeniable threat of antibiotic resistance.

Table 1: Characteristics of included meta-analyses

Meta-analysis	Population	No. Treatment Group	No. Control Group	Meta-Analysis Results	Direction of Findings
Kamel AM et al.	Suspected or confirmed Covid-19 patients	3,917	6,829	-28-day all-cause mortality [(n= 5,965 patients) OR= 0.96 (95% CI: 0.88-1.05) (I^2= 0%)] -Need for invasive mechanical ventilation [(n= 8,158 patients) OR= 0.96 (95% CI: 0.49-1.87) (I^2= 15%)] -Discharge within the study period [(n= 8,491 patients) OR= 0.93 (95% CI:	Discourages incorporation of AZO as a component of COVID-19 management protocol and recommends its discontinuation

				0.51-1.70) (I^2= 55%)] -Length of stay [1.11 (95% CI: -2.08 ï 4.31) (I^2= 88%)] -Incidence of arrhythmia [(n= 7,754 patients) OR= 0.91 (95% CI: 0.67-1.25) (I^2= 0%)] -Incidence of QTc interval prolongation [(n= 905 patients) OR= 1.06 (95% CI: 0.65-1.72) (I^2= 0%)]	

Mangkuligun a G et al.	Patients diagnosed with COVID-19 and admitted to the hospital	10,184	9,304	-Mortality [(n= 18,450 patients) OR= 0.95 (95% CI: 0.76-1.19) (I^2= 67%)] -Respiratory support [(n= 15,124 patients) OR= 1.30 (95% CI: 0.98-1.73) (I^2= 73%)] --Oxygen supplementation [(n= 3,466 patients) OR= 1.77 (95% CI: 1.13-2.77) (I^2= 56%)] --Non-invasive ventilation/High-flow nasal cannula [(n= 4,908 patients) OR= 0.90 (95% CI: 0.76-1.06) (I^2= 0%)] --Mechanical ventilation/Extracorpore	AZO is termed ñwell-toleratedò and ñsafe to useò but is reported not to have a better clinical outcome for COVID-19 patients when compared with the best available therapy.

				al membrane oxygenation [(n= 6,750 patients) OR= 1.22 (95% CI: 0.99-1.49) (I^2= 11%)] -Hospitalization period [(n= 18,389 patients) Std. Mean Difference= 0.12 (95% CI: -0.02-0.27) (I^2= 92%)] -ICU transfer [(n= 9,477 patients) OR= 1.21 (95% CI: 0.79-1.86) (I^2= 83%)] -Secondary infection [(n= 4,577 patients) OR= 1.23 (95% CI: 0.83-1.82) (I^2= 20%)] -Hypoglycemia [(n=	

				1,876 patients) OR= 0.73 (95% CI: 0.38-1.40) (I^2= 28%)] -Gastrointestinal symptoms [(n= 13,226 patients) OR= 1.03 (95% CI: 0.73-1.45) (I^2= 0%)] --Diarrhea [(n= 5,175 patients) OR= 1.31 (95% CI: 0.89-1.95) (I^2= 0%)] --Nausea/vomiting [(n= 3,876 patients) OR= 0.56 (95% CI: 0.24-1.30) (I^2= 0%)] --Others [(n= 4,175 patients) OR= 0.36 (95% CI: 0.11-1.23) (I^2= 0%)]	

				-Changes in Electrocardiogram [(n= 11,874 patients) OR= 1.16 (95% CI: 0.94-1.42) (I^2= 34%)] --Arrhythmia [(n= 1,969 patients) OR= 1.28 (95% CI: 0.94-1.74) (I^2= 0%)] --Tachycardia/Bradycardia [(n= 4,276 patients) OR= 1.18 (95% CI: 0.42-3.29) (I^2= 0%)] --QT prolongation [(n= 5,629 patients) OR= 1.06 (95% CI: 0.80-1.40) (I^2= 62%)]	

Conflict of Interest

The authors have no conflict of interest.