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Review Article

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# A REVIEW OF AZITHROMYCIN USED IN COVID-19

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**ABSTRACT**

The Strategic Plan for Biodefense Research of the U.S. Department of Health and Human Services emphasizes the urgent need for medications that can efficiently target many pathogens as part of our readiness for infectious disease threats. Azithromycin is a notable broad-spectrum therapeutic highlighted in the University of Oxford's RECOVERY trial, yet it was notably absent from the World Health Organization's SOLIDARITY trial. This review explores the pharmacological versatility of azithromycin, including its antibiotic, antimalarial, and antiviral properties, and discusses its history as among the most frequently repurposed drugs within the macrolide class. Additionally, we assess the clinical and socio-economic significance of azithromycin in the context of respiratory pandemics, presenting a model that clarifies its combinatorial way of action against COVID-19 pneumonia.

## INTRODUCTION

The COVID-19 pandemic has highlighted drug repositioning as a quick way to find effective treatments. Comparing this approach to the conventional strategy of creating new medications from scratch reveals definite advantages. One major advantage is the lower risk of failure, as repurposed drugs have already proven their safety through extensive clinical trials for their existing uses. Additionally, the time to develop these drugs is shorter because the necessary safety checks, production capabilities, and distribution channels are already established. Overall, this approach also costs significantly less—bringing a new drug to market can cost between $2–3 billion, while repositioning an existing drug typically costs about $300 million. These benefits are especially important during global health crises like the current one, where there is no FDA-approved treatment specifically for COVID-19.

The FDA has approved the use of the macrolide antibiotic azithromycin in treating a variety of respiratory conditions, including pneumonia, chlamydia, and typhoid. Research has also been done on how well it works to prevent malaria. Azithromycin has a good absorption rate of around 35–42% in both healthy individuals and those with cystic fibrosis. After taking a single 500 mg dose, the concentration of the drug in body tissues exceeds what is needed to fight most pathogens effectively. It can also reach levels in immune cells that are more than 200 times greater than in the bloodstream, and its long half-life of 68 hours allows it to maintain effective concentrations for several days. Azithromycin has been incredibly effective against a variety of illnesses during the past 50 years due to its capacity to concentrate in immune cells and provide tailored treatment. There has been interest lately in investigating its possible antiviral properties.

Considering azithromycin as a therapy option during this pandemic is supported by the fact that patients with COVID-19 frequently have severe respiratory distress and pneumonia. Although the RECOVERY study from the University of Oxford decided to include it, its combination with hydroxychloroquine in some trials did not work out, hence it was removed from the World Health Organization's SOLIDARITY experiment. This review looks into how azithromycin may interact with SARS-CoV-2, the virus causing COVID-19, while also impacting the immune response in pneumonia cases associated with COVID-19. We also discuss possible global risks like antimicrobial resistance that could arise from the widespread use of azithromycin. Ultimately, we explore how a macrolide antibiotic first developed in the 1970s has become a viable treatment option during one of the biggest health and economic challenges of the 21st century.

### A Macrolide Antibiotic for a Respiratory Pandemic

Azithromycin is part of the macrolide class of antibiotics, which are natural compounds featuring a large ring structure. Macrolides work by stopping bacteria from producing proteins, which are necessary for their growth and replication. The first macrolide to be identified was erythromycin, which was widely used as a substitute for individuals who were allergic to or resistant to penicillin. Azithromycin is a derivative of erythromycin and was designed to be better absorbed by the body with fewer side effects. It effectively kills many types of bacteria,

including those causing whooping cough and Legionnaires' disease.

In the 1970s, macrolides became recognized as effective treatments for inflammatory illnesses. Since then, azithromycin has emerged as a key antibiotic for treating diseases like chlamydia, malaria, pneumonia, and trachoma. Numerous laboratory studies over the years show its broad effectiveness against various pathogens. These broad-spectrum drugs are relatively safe and have a history of being successfully repurposed for different illnesses, making them appropriate for emergencies. If azithromycin had been discovered earlier, it might have helped fight the Spanish Flu pandemic, especially given its ability to inhibit influenza virus replication in certain lung cells.

Azithromycin is among the safest medications for national health systems, according to the World Health Organization. It has a lengthy history of managing respiratory disorders with comparatively few short-term adverse effects.

**Spatiotemporal Modulation of Host Antiviral Responses**

In the fight against viral infections, type I interferons (IFNs) are crucial because they control autocrine and paracrine signaling via the IFN receptor (IFNAR), so preventing replication and spread. A dysregulated antiviral response has been directly associated with the increased death rates seen in COVID-19 patients in the context of SARS-CoV-2. This is an important chance for focused therapeutic action.

A complex and frequently compromised antiviral response occurs during coronavirus infections, according to research on SARS-CoV, MERS-CoV, and current results about COVID-19. It's interesting to note that lower IFN levels have been observed in the lungs of COVID-19 patients, suggesting a worrying trend. However, IFNs and IFN-stimulated genes (ISGs) are produced locally in bronchoalveolar lavage (BAL) samples from critically ill patients, and this is correlated with activated lung-resident dendritic cells (DCs). Sadly, this local IFN response usually occurs after viral replication peaks, which prevents efficient viral removal and exacerbates cytokine release syndrome (CRS). Activated monocyte-derived macrophages have been found to accumulate in lung tissue in MERS-CoV-infected animals due to similar delays in IFN responses. The presence of faulty CD4+ and CD8+ T cells as well as lymphopenia in individuals with severe COVID-19 is most likely due to insufficient IFN production. It has been shown that blocking IFNAR signaling during MERS-CoV infections prevents the development of virus-specific T cells, which are necessary for the survival and proper operation of T cells. Timely synthesis of IFN is essential for effective responses from T and natural killer (NK) cells. IFN response delays, such as those shown in COVID-19, have a detrimental impact on T cell migration and proliferation, which ultimately leads to cell death. Investigation into the dynamics of local and systemic IFN responses during COVID-19 and their contributions to the severity and progression of the disease is necessary. However, the innate and adaptive immune systems are connected by IFNs, which are crucial regulatory molecules.

The potential of IFNs as a therapeutic strategy is further highlighted by their dysregulation in COVID-19. Preventive IFN treatment can effectively prevent viral infections; for example, IFNa nasal drops have been shown to protect healthcare workers against COVID-19 for 28 days with few side effects. Additionally, against a variety of viral strains, such as respiratory syncytial virus (RSV), Ebola, Zika, influenza H1N1, enterovirus, and rhinovirus, azithromycin has shown promising antiviral qualities in both laboratory and clinical settings. By boosting IFNb expression in primary bronchial epithelial cells, azithromycin considerably lessens respiratory problems in infants with RSV bronchiolitis and eases flare-ups of virus-induced asthma. Additionally, it upregulates genes including MDA5 and RIG-I that are crucial for viral detection. Interestingly, azithromycin has been shown to inversely correlate with viral load at clinically relevant concentrations without having a deleterious effect on healthy cells. Azithromycin is positioned as a viable remedy for the delayed local IFN responses due to its capacity to localize within macrophages while boosting type I IFN production. This can improve viral clearance and reduce the risk of CRS and macrophage activation syndrome (MAS).

IFNs and azithromycin can both boost the host's IFN response during viral infections, but when they are given is important. It has been shown that early IFN treatment, particularly before the peak of viral replication, effectively protects mice against MERS-CoV and SARS-CoV infections. On the other hand, delayed IFN therapy can impede virus clearance and exacerbate immunopathology. Similarly, while late-stage usage of azithromycin may result in negative consequences, early or prophylactic treatment can aid in blocking viral entrance. Important details regarding the best time and efficacy of IFN therapy for COVID-19 will be provided by ongoing clinical trials evaluating these treatments. Refining tactics that use both IFNs and azithromycin requires a better knowledge of IFN response kinetics in SARS-CoV-2 infections. Azithromycin’s well-documented prophylactic capabilities and emerging evidence of its capacity to strengthen the immune system and directly inhibit viral replication underscore the need for further exploration in therapeutic contexts.

**Spatiotemporal Modulation of Host Antiviral Responses**

To stop viral replication and spread following infection, type I interferons (IFNs) are crucial because they control autocrine and paracrine signaling via the IFN receptor (IFNAR). The dysregulated antiviral response to SARS-

CoV-2 infection is one of the most crucial targets for therapeutic intervention, as it has been linked to the significant death rates observed in COVID-19.

A complicated antiviral response occurs during coronavirus infections, according to research on SARS-CoV, MERS-CoV, and new findings in COVID-19 pathogenesis. The lungs of COVID-19 patients have been shown to contain low amounts of IFNs. Nevertheless, local synthesis of IFNs and IFN-stimulated genes (ISGs) has been seen in critically ill patients' bronchoalveolar lavage (BAL) despite systemic IFN insufficiency. This is linked to the activation of lung-resident dendritic cells (DCs). This local IFN response was delayed in comparison to viral replication peaks using animal models of SARS-CoV infection, which hindered viral clearance and exacerbated cytokine release syndrome (CRS). MERS-CoV-infected mice showed similar IFN response delays, which led to an accumulation of activated monocyte-derived macrophages in the lungs. A lack of IFN production is probably the cause of the defective CD4+ and CD8+ T cells and lymphopenia seen in severe COVID-19. Blocking IFNAR signaling during MERS-CoV infection decreases the formation of virus-specific CD4+ and CD8+ T cells, which are essential for T cell survival and function Early IFN production is necessary for effective T and natural killer (NK) cell responses; delayed IFN responses, such those shown in COVID-19, impede T cell migration and aid in cell death. Investigations on the precise timing of local and systemic IFN responses during COVID-19, as well as how they affect the course and intensity of the illness, are still ongoing. Nonetheless, IFNs are recognized as crucial modulators that link the adaptive and innate immune systems.

The potential for therapeutic intervention is highlighted by IFN dysregulation in COVID-19. Preventive IFN treatment can prevent viral infection; for instance, IFNa nasal drops have shielded medical staff from COVID-19 for 28 days without causing serious side effects. Azithromycin has also demonstrated antiviral effectiveness both in vitro and in vivo against a variety of viral strains, including rhinovirus, Ebola, Zika, influenza H1N1, respiratory syncytial virus (RSV), and enterovirus. Furthermore, in infants suffering from RSV bronchiolitis, azithromycin can dramatically lower respiratory morbidity. By increasing the expression of IFNb in primary bronchial epithelial cells, standard dosages of azithromycin (10 mg/ml in vivo) reduce virally caused asthma flare-ups. Additionally, azithromycin increases the expression of genes, including MDA5 and RIG-I, that are involved in viral detection. It has been demonstrated that azithromycin inversely correlates with viral load at clinically relevant concentrations without compromising healthy donor cells. Importantly, azithromycin’s ability to localize in macrophages while enhancing type I IFN production suggests its potential to correct delayed local IFN responses, thereby promoting viral clearance and reducing CRS and MAS development.

During viral infections, both azithromycin and IFNs can increase the host's IFN response, but timing is key: Prophylactic or early azithromycin treatment may help prevent viral entry, while late-stage administration may have adverse effects; IFN treatment before peak viral replication has been demonstrated to protect mice against SARS-CoV and MERS-CoV infections, whereas late IFN administration worsens immunopathology and hinders viral clearance; Important information regarding the timing and efficacy of IFN treatments for COVID-19 will be obtained from ongoing clinical studies; both IFN and azithromycin-based strategies will benefit from an understanding of the kinetics of IFN responses in SARS-CoV-2 infection.

**Limitations and Potential Adverse Effects of Azithromycin**

Even though azithromycin's pharmacological profile has been thoroughly characterized and it is used in many clinical settings, the medication has drawbacks and possible side effects, some of which have been well-documented since it was first used to treat bacterial pneumonia.

**Cardiovascular and Gastrointestinal Effects**

1-5% of patients administered azithromycin suffer from minor side effects like gastrointestinal upset, headache, and dizziness. However, more serious adverse effects, particularly connected to the cardiovascular system, have been a concern. The medication azithromycin has been linked to QT prolongation and torsades de pointes, potentially life-threatening arrhythmias. In 2012, when administering azithromycin to patients who have the following conditions, the FDA issued a warning to exercise caution:

- Prolonged QT interval
- Congenital long QT syndrome
- Hypokalemia
- Hypomagnesemia
- Bradycardia
- A history of torsades de pointes, arrhythmias, or uncompensated heart failure.

This caution was brought about by a large retrospective cohort study that revealed that patients receiving a 5-day treatment of azithromycin had a greater risk of cardiovascular death than those receiving amoxicillin, ciprofloxacin, or a placebo.[83]

However, some studies have reported contrasting results. For instance, dogs with chronic atrioventricular block did not experience QTc prolongation when given intravenous azithromycin.[84] Furthermore, there is no evidence that long-term azithromycin usage in patients with cystic fibrosis or chronic obstructive pulmonary disease (COPD) increases the risk of cardiovascular mortality. Furthermore, a study exploring azithromycin

monotherapy for COVID-19 reported a lower mortality rate compared to hydroxychloroquine monotherapy (10.9% vs. 18.9%, adjusted for comorbidities and demographics) at 21 days.[85]

Antimicrobial Resistance

The emergence of antibiotic resistance is one of the main issues with azithromycin. Macrolide-resistant strains of organisms such as Streptococcus pneumoniae, S. pyogenes, Staphylococcus aureus, and Haemophilus species have emerged following prolonged or frequent use of azithromycin.[86] Furthermore, long-term treatment of patients with chronic lung diseases has been associated with a 2.7-fold increase in macrolide-resistant bacteria, which poses a serious threat both to individual patients and to the broader community due to the potential for resistant infections to spread.

These resistance issues highlight the importance of using azithromycin primarily for short-term treatment and caution when considering its long-term use. Efforts are underway to develop novel non-antibiotic macrolides, which may offer a safer, long-term solution to managing chronic diseases without contributing to resistance.

## DISCUSSION

The ongoing global health crisis calls for effective and cost-efficient treatment strategies. Repositioning antibiotics, particularly those that are low-cost, historically safe, and widely available, is a pragmatic approach amidst the evolving pandemic and economic recession. By applying the pharmacological, historical, and socio-economic parameters used to evaluate azithromycin's repositioning for respiratory pandemics, similar broad-spectrum therapeutics could be identified and expanded upon to combat future infectious threats.

### Azithromycin's Mechanisms of Action in COVID-19

Azithromycin has shown promising in vivo properties that can be categorized into two main effects: local actions against the initial SARS-CoV-2 infection and systemic modulation of the host's immune response throughout COVID-19 progression.

### 1. Local Infection Control

Azithromycin rapidly concentrates in phagocytes and has a unique ability to repolarize macrophage subpopulations towards an activated M2 phenotype, strengthening the body's natural defenses against infection.

To reverse the delayed immune responses in COVID-19 patients, the drug raises type I interferon (IFNb). Additionally, it triggers the activation of MDA5 and RIG-I, two crucial sensors for the early detection of viral infections.

Additionally, two crucial processes in SARS-CoV-2 replication—endolysosomal processing and receptor-mediated endocytosis—are inhibited by azithromycin. In particular, it might inhibit CD147, a receptor linked to viral invasion and a possible COVID-19 treatment target.

### 2. Global Immune Modulation

As the illness worsens, the cytokine storm and hyperinflammation become important pathogenic indicators of severe COVID-19 pneumonia. Azithromycin can help reduce this excessive inflammation by modulating the immune system. Azithromycin is thought to have stronger immunomodulatory effects and fewer adverse effects than other macrolides, which makes it a better choice for lowering inflammation and enhancing therapeutic results.

### Challenges in Defining Optimal Dosage and Treatment Strategy

The potential of azithromycin as a COVID-19 treatment is encouraging; however, more information is needed on the dosage and time of administration. There is currently not enough clinical data to identify the best course of action for COVID-19 pneumonia. Randomized controlled trials (RCTs) are required to assess the optimal azithromycin monotherapy and combination with other medications, such as hydroxychloroquine.

In conclusion, azithromycin is a promising short-term therapeutic option for respiratory pandemics due to its twin potencies of modifying immune responses and preventing viral entrance. But additional research is needed to understand the long-term dangers and benefits and to optimize its use, particularly in combination medicines.

## CONCLUSION

From a well-known antibiotic to a highly adaptable pharmacological agent with a wide range of therapeutic effects, azithromycin has changed over the last half century. At first, its main use was to treat bacterial respiratory illnesses, where its capacity to prevent the formation of bacterial proteins was quite helpful. Nonetheless, it has gained more recognition for its anti-inflammatory qualities and capacity to regulate immunological responses as a result of ongoing clinical and in vitro studies. These discoveries have expanded its use to encompass viral and immune-mediated illnesses in addition to exclusively bacterial infections.

The distinct modes of action of azithromycin account for its pharmacological flexibility. Its concentration in macrophages, which enables it to directly affect immune cells at the infection site, is one of its major characteristics. Azithromycin can quickly activate the host's immune system thanks to this property, particularly when viral infections are involved. Crucially, it has been demonstrated that azithromycin recapitulates host type I interferon (IFN) kinetics, strengthening the body's defenses against viral threats, especially during the early stages of infection. Reinforcing the innate immune response also depends much on the drug's

capacity to upregulate MDA5 and RIG-I, which are essential for the viral recognition system.

The lysosomotropic characteristics of azithromycin are another important aspect of its therapeutic potential. Because they hinder endolysosomal processing and receptor-mediated endocytosis, these characteristics have been essential in the use of azithromycin to stop viral reproduction. Azithromycin can successfully prevent the viral entry mechanisms that many viruses, including SARS-CoV-2, rely on by interfering with these activities. In addition to being useful for treating viral infections, these qualities also act as a preventative strategy, which is particularly vital in the context of pandemics and other international health emergencies.

Azithromycin has been shown to reduce global inflammation in addition to its direct antiviral effects. This is important in diseases like COVID-19 pneumonia, where hyperinflammation is a defining characteristic of the disease's course. Azithromycin has been used extensively over the past 50 years to treat chronic lung conditions such as cystic fibrosis and COPD without the serious cardiovascular hazards that come with other therapies. Given its lengthy history of usage and strong immunomodulatory effects, azithromycin has the potential to be a safe and effective treatment option in a variety of clinical contexts.

**Future Vision**

Azithromycin has a bright future ahead of it, particularly as research keeps finding new uses for this medication that is already in widespread usage. Azithromycin may be a key component of new therapy for a variety of infectious diseases due to its diverse therapeutic qualities. Its broad-spectrum activity, which encompasses both bacterial and viral infections, alongside its ability to modulate immune responses, makes it a global health resource for pandemics in the future.

One of the most exciting aspects of azithromycin's future is the possibility of using it as a preventive drug in the early stages of viral outbreaks. It may have a significant role in stopping the transmission of viruses at the population level due to its capacity to quickly accumulate in immune cells and strengthen antiviral immunity. In a variety of viral infections, early preventive azithromycin therapies have demonstrated potential in lowering viral load and minimizing illness severity. Because azithromycin targets both viral replication and host immune response pathways, it will be a useful tool in the fight against future pandemics as the globe continues to struggle with the threat of new viral illnesses.

Furthermore, azithromycin's lysosomotropic qualities offer yet another opportunity for its ongoing application and advancement. Azithromycin may become even more useful in preventing viral entrance into a wide range of diseases as our knowledge of endocytosis and lysosomal activity in viral infections grows. To boost immunity and stop the spread of viruses during pandemics, the preventive use of azithromycin in combination with other antiviral medications may be investigated.

Current studies on macrolides, such as azithromycin, and their immune-modulatory properties could lead to new therapy combinations that fully use these medications. To manage viral infections, for instance, combination therapy combining azithromycin with other antiviral drugs such as interferons or hydroxychloroquine may have synergistic effects. Finding the best azithromycin dosage, timing, and combination methods will require randomized controlled studies, particularly when taking COVID-19 and other respiratory viral infections into account.

Azithromycin's long-term positioning in chronic infectious illnesses is also crucial to its future. Azithromycin may be useful in treating inflammatory disorders and persistent infections where conventional treatments might be less successful or have unfavorable side effects because of its well-established safety profile and affordable price. Azithromycin may be added to a larger treatment toolset in the upcoming years to treat a variety of infectious disorders, including influenza, malaria, and bacterial pneumonia.

Overall, azithromycin is a prime candidate for upcoming repositioning initiatives due to its wide range of action, capacity to target viral replication, and ability to modify host immune responses. Because of its affordability, safety, and effectiveness, azithromycin may become a key component of global health policies when new infectious risks arise, particularly in places with low resources where access to costly, specialist treatments may be restricted. The growing amount of data about azithromycin's complex interactions with infectious microorganisms and the immune system indicates that its prospective uses in modern medicine are still a ways off.

**REFERENCE**

1. Pushpakom S, Iorio F, Eyers PA, et al. Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov., 2019; 18(1): 41-58. DOI: 10.1038/nrd.2018.168.
2. Nosengo N. Can you teach old drugs new tricks? Nature, 2016; 534(7607): 314-316. DOI: 10.1038/534314a.
3. Taylor W, Richie T, Fryauff D, Ohrt C, Picarima H, Tang D, et al. Tolerability of azithromycin as malaria prophylaxis in adults in northeast Papua, Indonesia. Antimicrob Agents Chemother., 2003; 47(7): 2199-2203.
4. Kong FY, Rupasinghe TW, Simpson JA, et al. Pharmacokinetics of a single 1g dose of azithromycin in rectal tissue in men. PLoS One., 2017 Mar 28; 12(3): e0174372. DOI: 10.1371/journal.pone.0174372.

5. Lode H, Borner K, Koeppe P, Schaberg T. Azithromycin: review of key chemical, pharmacokinetic and microbiological features. J Antimicrob Chemother, 1996; 37(suppl C): 1-8.
6. Massiot A, Tamalet A, Beydon N, Escudier E, Clement A, Corvol H, et al. Prophylactic azithromycin in patients with primary ciliary dyskinesia. Eur Respir J., 2018; PA798. DOI: 10.1183/13993003.congress2018.PA798.
7. Schögler A, Kopf BS, Edwards MR, et al. Novel antiviral properties of azithromycin in cystic fibrosis airway epithelial cells. Eur Respir J., 2015 Feb; 45(2): 428-439. DOI: 10.1183/09031936.00102014.
8. Gielen V, Johnston SL, Edwards MR. Azithromycin induces anti-viral responses in bronchial epithelial cells. Eur Respir J., 2010 Sep; 36(3): 646-654. DOI: 10.1183/09031936.00095809.
9. Murphy BS, Sundareshan V, Cory TJ, Hayes D Jr, Anstead MI, Feola DJ. Azithromycin alters macrophage phenotype. J Antimicrob Chemother, 2008 Mar; 61(3): 554-560. DOI: 10.1093/jac/dkn007.
10. Tyteca D, Van Der Smissen P, Mettlen M, et al. Azithromycin, a lysosomotropic antibiotic, has distinct effects on fluid-phase and receptor-mediated endocytosis, but does not impair phagocytosis in J774 macrophages. Exp Cell Res., 2002 Sep; 281(1): 86-100. DOI: 10.1006/excr.2002.5613.
11. West SK. Azithromycin for control of trachoma. Community Eye Health., 1999; 12(32): 55-6.
12. Andersen SL, Oloo AJ, Gordon DM, et al. Successful double-blinded, randomized, placebo-controlled field trial of azithromycin and doxycycline as prophylaxis for malaria in western Kenya. Clin Infect Dis., 1998; 26(1): 146-50. doi:10.1086/516281.
13. Stamm WE. Azithromycin in the treatment of uncomplicated genital chlamydial infections. Am J Med., 1991; 91(3A): 19S-22S. doi:10.1016/0002-9343(91)90396-F.
14. Itkin IH, Menzel ML. The use of macrolide antibiotic substances in the treatment of asthma. J Allergy., 1970; 45(3): 146-62. doi:10.1016/0021-8707(70)90124-3.
15. Girard AE, Girard D, English AR, Gootz TD, Cimochowski CR, Faiella JA, et al. Pharmacokinetic and in vivo studies with azithromycin (CP-62,993), a new macrolide with an extended half-life and excellent tissue distribution. Antimicrob Agents Chemother., 1987; 31: 1948-54.
16. Carlier MB, Scorneaux B, Tulkens PM. Accumulation, subcellular distribution, and activity of azithromycin (Az) compared to roxithromycin (Rx) and ciprofloxacin (Cp) in J774 macrophages. In: Program and Abstracts of the Thirty-First Interscience Conference on Antimicrobial Agents and Chemotherapy; 1991 Oct 28-Nov 1; Chicago, IL. Washington, DC: American Society for Microbiology; 1991; 184. Abstract 510.
17. Wildfeuer A, Laufen H, Muller-Wening D, Haferkamp O. Interaction of azithromycin and human phagocytic cells. Arzneim Forsch., 1989; 39: 755-8.
18. Saha D, Karim MM, Khan WA, Ahmed S, Salam MA, Bennish ML. Single-dose azithromycin for the treatment of cholera in adults. N Engl J Med., 2006; 354(23): 2452-62. doi:10.1056/NEJMoa054493.
19. Tran DH, Sugamata R, Hirose T, et al. Azithromycin, a 15-membered macrolide antibiotic, inhibits influenza A(H1N1)pdm09 virus infection by interfering with the virus internalization process. J Antibiot (Tokyo)., 2019; 72(10): 759-68. doi:10.1038/s41429-019-0204-x.
20. World Health Organization. World Health Organization Model List of Essential Medicines: 21st List. Geneva: World Health Organization, 2019. Available from: https://hdl.handle.net/10665/325771.
21. Socan M. Treatment of atypical pneumonia with azithromycin: comparison of a 5-day and a 3-day course. J Chemother, 1998; 10(1): 64-8.
22. Zarogoulidis P, Papanas N, Kioumis I, Chatzaki E, Maltezos E, Zarogoulidis K. Macrolides: from in vitro anti-inflammatory and immunomodulatory properties to clinical practice in respiratory diseases. Eur J Clin Pharmacol., 2011; 68(5): 479-503.
23. Li H, Liu D, Chen L, Zhao Q, Yu Y, Ding J, Miao L, Xiao Y, Cai H, Zhang D, Guo Y, Xie C. Meta-analysis of the adverse effects of long-term azithromycin use in patients with chronic lung diseases. Antimicrob Agents Chemother., 2013; 58(1): 511-7.
24. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents., 2020; 105949. doi:10.1016/j.ijantimicag.2020.105949 [published online ahead of print, 2020 Mar 20].
25. Hulme O, Wagenmakers E, Damkier P, Madelung C, Siebner H, Helig Larsen J, Gronau Q, Benfield T, Madsen K. A Bayesian reanalysis of the effects of hydroxychloroquine and azithromycin on viral carriage in patients with COVID-19: reply to Gautret et al. 2020. 2020.
26. Clincalc. Azithromycin [Internet]. 2020 Jul. Available from: https://clincalc.com/DrugStats/Drugs/Azithromycin
27. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. N Engl J Med., 2020; 382(19): 1787-99. doi:10.1056/NEJMoa2001282.
28. Holshue M, DeBolt C, Lindquist S, Lofy K, Wiesman J, Bruce H, Spitters C, Ericson K, Wilkerson S, Tural A, Diaz G, Cohn A, Fox L, Patel A, Gerber S, Kim L, Tong S, Lu X, Lindstrom S, Pallansch M, Ildon W, Biggs H, Uyeki T, Pillai S. First case of 2019 novel coronavirus in the United States. N Engl J Med., 2020; 382(10): 929-36.

29. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, Li Y, Hu Z, Zhong W, Wang M. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discovery, 2020; 6(1).
30. Kuper H, Wormald R. Topical azithromycin: new evidence? Br J Ophthalmol., 2007; 91(5): 566-7. doi:10.1136/bjo.2006.107102.
31. Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang Y, Wang Q, Miao H. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther., 2020; 5(1).
32. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol., 2020; 20(6): 355-62. doi:10.1038/s41577-020-0331-4.
33. Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D, Oltolini C, Castiglioni B, Din CT, Boffini N, Tomelleri A. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. Lancet Rheumatol., 2020 May 7.
34. Plewig G, Schopf E. Anti-inflammatory effects of antimicrobial agents: an in vivo study. J Invest Dermatol., 1975; 65(6): 532-6.
35. Zimmermann P, Ziesenitz V, Curtis N, Ritz N. The immunomodulatory effects of macrolides—a systematic review of the underlying mechanisms. Front Immunol., 2018; 9.
36. Aghai Z, Kode A, Saslow J, et al. Azithromycin suppresses activation of nuclear factor-kappa B and synthesis of pro-inflammatory cytokines in tracheal aspirate cells from premature infants. Pediatr Res., 2007; 62: 483-8.
37. Mehta P, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet., 2020; 395: 1033-4.
38. Qin C, et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis., 2020; 71(15): 762-8. doi:10.1093/cid/ciaa248.
39. Jang Y. Effect of clarithromycin on rhinovirus-16 infection in A549 cells. Eur Respir J., 2006; 27(1): 12-9.
40. Feldmann M, Maini RN, Woody JN, Holgate ST, Winter G, Rowland M, Richards D, Hussell T. Trials of anti-tumor necrosis factor therapy for COVID-19 are urgently needed. Lancet., 2020; 395(10234): 1407-9. doi:10.1016/S0140-6736(20)30858-8.
41. Xu X, Han M, Li T, Sun W, Wang D, Fu B, Zhou Y, Zheng X, Yang Y, Li X, Zhang X, Pan A, Wei H. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A., 2020; 117(20): 10970-5. doi:10.1073/pnas.2005615117.
42. Marsland BJ, Gollwitzer ES. Host–microorganism interactions in lung diseases. Nat Rev Immunol., 2014; 14: 827-35.
43. Mirkovic B, Murray MA, Lavelle GM, Molloy K, Azim AA, Gunaratnam C, et al. The role of short-chain fatty acids, produced by anaerobic bacteria, in the cystic fibrosis airway. Am J Respir Crit Care Med., 2015; 192: 1314-24.
44. Molyneaux PL, Cox MJ, Willis-Owen SAG, et al. The role of bacteria in the pathogenesis and progression of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med., 2014; 190: 906-13.
45. Chakrabort YS. Sequencing data (N = 3) shows Wuhan coronavirus integration in bacteria (Prevotella mostly), a Sequencing artifact, or is the virus infecting both bacterial and human cells? 2020. Available from: https://doi.org/10.31219/osf.io/ktngw. Accessed 20 Apr 2020.
46. Chakraborty S. The Wuhan coronavirus has integrated into Prevotella, which possibly causes the observed extreme virulence, as sequencing data from 2 different studies in China and Hong Kong show unequivocally. 2020. Available from: https://doi.org/10.31219/osf.io/ktngw. Accessed 20 Apr 2020.
47. Chakraborty S. The 2019 Wuhan Outbreak Could Be Caused by the Bacteria Prevotella, Which Is Aided by the Coronavirus—Prevotella Is Present (Sometimes in Huge Amounts) in Patients from Two Studies in China and One in Hong Kong. 2020. Available from: https://doi.org/10.31219/osf.io/usztn. Accessed 20 Apr 2020.
48. Mätto J, Asikainen S, Väisänen ML, Von Troil-Linden B, Könönen M, Saarela M, et al. Beta-lactamase production in Prevotella intermedia, Prevotella nigrescens, and Prevotella pallens genotypes and in vitro susceptibilities to selected antimicrobial agents. Antimicrob Agents Chemother., 1999; 43: 2383-8.
49. Choi EY, Jin JY, Choi JI, Choi IS, Kim SJ. Effect of azithromycin on Prevotella intermedia lipopolysaccharide-induced production of interleukin-6 in murine macrophages. Eur J Pharmacol., 2014; 729: 10-6.
50. Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Møller R, Jordan TX, Oishi K, Panis M, Sachs D, Wang TT, Schwartz RE, Lim JK, Albrecht RA, tenOever BR. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell., 2020; 181(5): 1036-45.e9. doi:10.1016/j.cell.2020.04.026.
51. Hadjadj J, et al. Impaired Type I Interferon Activity and Exacerbated Inflammatory Responses in Severe COVID-19 Patients. 2020. Available from: https://doi.org/10.1101/2020.04.19.20068015. Preprint at medRxiv.
52. Zhou Z, Ren L, Zhang L, Zhong J, Xiao Y, Jia Z, Guo L, Yang J, Wang C, Jiang S, Yang D, Zhang G, Li H, Chen F, Xu Y, Chen M, Gao Z, Yang J, Dong J, Liu B. Heightened innate immune responses in the respiratory tract of COVID-19 patients. Cell Host Microbe., 2020; 27(6): 883-90.e2. doi:10.1016/j.chom.2020.04.017.

53. Channappanavar R, et al. Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell Host Microbe., 2016; 19: 181-93.
54. Acharya D, Liu G, Gack MU. Dysregulation of type I interferon responses in COVID-19. Nat Rev Immunol., 2020; 20(7): 397-8. doi:10.1038/s41577-020-0346-x.
55. Zheng M, et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cell Mol Immunol. 2020; 17: 533-5.
56. Channappanavar R, et al. IFN-I response timing relative to virus replication determines MERS coronavirus infection outcomes. J Clin Invest., 2019; 130: 3625-39.
57. Du X, Zuo X, Meng F, Wu F, Zhao X, Li C, et al. Combinatorial screening of a panel of FDA-approved drugs identifies several candidates with anti-Ebola activities. Biochem Biophys Res Commun., 2020; 522: 862-8.
58. Wu YH, Tseng CK, Lin CK, Wei CK, Lee JC, Young KC. ICR suckling mouse model of Zika virus infection for disease modeling and drug validation. PLoS Negl Trop Dis., 2018; 12: e0006848.
59. Tran DH, Sugamata R, Hirose T, Suzuki S, Noguchi Y, Sugawara A, et al. Azithromycin, a 15-membered macrolide antibiotic, inhibits influenza (H1N1)pdm09 virus infection by interfering with the virus internalization process. J Antibiot (Tokyo). 2019; 72: 759-68.
60. Mosquera RA, De Jesus-Rojas W, Stark JM, Yadav A, Jon CK, Atkins CL, et al. Role of prophylactic azithromycin to reduce airway inflammation and mortality in an RSV mouse infection model. Pediatr Pulmonol., 2018; 53: 567-74.
61. Zeng S, Meng X, Huang Q, Lei N, Zeng L, Jiang X, et al. Spiramycin and azithromycin, safe for administration to children, exert antiviral activity against enterovirus A71 in vitro and in vivo. Int J Antimicrob Agents., 2019; 53: 362-9.
62. Touret F, Gilles M, Barral K, et al. In vitro screening of an FDA-approved chemical library reveals potential inhibitors of SARS-CoV-2 replication. Sci Rep., 2020; 10: 13093. doi:10.1038/s41598-020-70143-6.
63. Li C, et al. Azithromycin protects against Zika virus infection by upregulating virus-induced type I and III interferon responses. Antimicrob Agents Chemother, 2019; 63(12): e00394-19. doi:10.1128/AAC.00394-19.
64. Madrid PB, et al. Evaluation of Ebola virus inhibitors for drug repurposing. ACS Infect Dis., 2015; 1: 317-26.
65. Beigelman A, Isaacson-Schmid M, Sajol G, Baty J, Rodriguez OM, Leege E, et al. Randomized trial to evaluate azithromycin's effects on serum and upper airway IL-8 levels and recurrent wheezing in infants with respiratory syncytial virus bronchiolitis. J Allergy Clin Immunol., 2015; 135: 1171-8.
66. Di Paolo A, Barbara C, Chella A, Angeletti CA, Del Tacca M. Pharmacokinetics of azithromycin in lung tissue, bronchial washing, and plasma in patients given multiple oral doses of 500 and 1000 mg daily. Pharmacol Res., 2002; 46: 545-50.
67. Menzel M, Akbarshahi H, Tufvesson E, Persson C, Bjermer L, Uller L. Azithromycin augments rhinovirus-induced IFNb via cytosolic MDA5 in experimental models of asthma exacerbation. Oncotarget., 2017; 8(19): 31601-11. doi:10.18632/oncotarget.16364.
68. Li C, Zu S, Deng YQ, Li D, Parvatiyar K, Quanquin N, Shang J, Sun N, Su J, Liu Z, Wang M, Aliyari SR, Li XF, Wu A, Ma F, Shi Y, Nielsevn-Saines K, Jung JU, Qin FX, Qin CF. Azithromycin protects against Zika virus infection by upregulating virus-induced type I and III interferon responses. Antimicrob Agents Chemother., 2019; 63(12): e00394-19. doi:10.1128/AAC.00394-19. Advance online publication.
69. Muramatsu T. Basigin (CD147), a multifunctional transmembrane glycoprotein with various binding partners. J Biochem., 2016; 159(5): 481-90. doi:10.1093/jb/mvv127.
70. Crosnier C, Bustamante L, Bartholdson S, Bei A, Theron M, Uchikawa M, Mboup S, Ndir O, Kwiatkowski D, Duraisingh M, Rayner J, Wright G. Basigin is a receptor essential for erythrocyte invasion by Plasmodium falciparum. Nature, 2011; 480(7378): 534-7.
71. Wang K, Chen W, Zhou Y, Lian J, Zhang Z, Du P, Gong L, Zhang Y, Cui H, Geng J, Wang B, Sun X, Wang C, Yang X, Lin P, Deng Y, Ii D, Yang X, Zhu Y, Zhang K, Zheng Z, Miao J, Guo T, Shi Y, Zhang J, Fu L, Wang Q, Bian H, Zhu P, Chen Z. SARS-CoV-2 Invades Host Cells via a Novel Route: CD147 Spike Protein. 2020.
72. Pistol G, Matache C, Calugaru A, Stavaru C, Tanaseanu S, Ionescu R, Dumitrache S, Stefanescu M. Roles of CD147 on T lymphocytes activation and MMP-9 secretion in systemic lupus erythematosus. J Cell Mol Med., 2007; 11(2): 339-48.
73. Bian H, Zheng Z, Ii D, Zhang Z, Kang W, Hao C, Dong K, Kang W, Xia J, Miao J, Xie R, Wang B, Sun X, Yang X, Lin P, Geng J, Wang K, Cui H, Zhang K, Chen X, Tang H, Du H, Yao N, Liu S, Liu L, Zhang Z, Gao Z, Nan G, Wang Q, Lian J, Chen Z, Zhu P. Meplazumab Treats COVID-19 Pneumonia: an Open-Labelled, Concurrent Controlled Add-On Clinical Trial, 2020.
74. Wilson D, Goodman C, Sleebs B, Iiss G, de Jong N, Angrisano F, Langer C, Baum J, Crabb B, Gilson P, McFadden G, Beeson J. Macrolides rapidly inhibit red blood cell invasion by the human malaria parasite, Plasmodium falciparum. BMC Biol., 2015; 13(1): 19.
75. Ulrich H, Pillat MM. CD147 as a target for COVID-19 treatment: suggested effects of azithromycin and stem cell engagement. Stem Cell Rev Rep., 2020; 16(3): 434-40. doi:10.1007/s12015-020-09976-7.

76. Tyteca D, Schanck A, Dufrêne YF, et al. The macrolide antibiotic azithromycin interacts with lipids and affects membrane organization and fluidity: studies on Langmuir-Blodgett monolayers, liposomes, and J774 macrophages. J Membr Biol., 2003; 192(3): 203-15.
77. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens T, Herrler G, Wu N, Nitsche A, Müller M, Drosten C, Pöhlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell., 2020; 181(2): 271-80.e8.
78. Yang N, Shen HM. Targeting the endocytic pathway and autophagy process as a novel therapeutic strategy in COVID-19. Int J Biol Sci., 2020; 16(10): 1724-31. doi:10.7150/ijbs.45498. Published 2020 Mar 15.
79. Hu TY, Frieman M, Wolfram J. Insights from nanomedicine into chloroquine efficacy against COVID-19. Nat Nanotechnol., 2020; 15(4): 247-9. doi:10.1038/s41565-020-0674-9.
80. Carlier MB, Garcia-Luque I, Montenez JP, Tulkens PM, Piret J. Accumulation, release and subcellular localization of azithromycin in phagocytic and non-phagocytic cells in culture. Int J Tissue React., 1994; 16: 211-20.
81. Yamaya M, et al. Clarithromycin inhibits type A seasonal influenza virus infection in human airway epithelial cells. J Pharmacol Exp Ther., 2010; 333(1): 81-90.
82. Yeganeh B, et al. Suppression of influenza A virus replication in human lung epithelial cells by noncytotoxic concentrations of bafilomycin A1. Am J Physiol Lung Cell Mol Physiol., 2015; 300(2): L270-86.
83. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. N Engl J Med., 2012; 366(19): 1881-90.
84. Thomsen MB, Beekman JD, Attevelt NJ, Takahara A, Sugiyama A, Chiba K, Vos MA. No proarrhythmic properties of the antibiotics Moxifloxacin or Azithromycin in anaesthetized dogs with chronic-AV block. Br J Pharmacol., 2006; 149(8): 1039-48.
85. Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero JM, Weinberg P, Kirkwood J, Muse A, DeHovitz J, Blog DS, Hutton B, Holtgrave DR, Zucker HA. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA., 2020; 323(24): 2493-502. doi:10.1001/jama.2020.8630. Advance online publication.
86. Serisier DJ. Risks of population antimicrobial resistance associated with chronic macrolide use for inflammatory airway diseases. Lancet Respir Med., 2013; 1(4): 262-74.
87. Li H, Liu DH, Chen LL, Zhao Q, Yu ZZ, Ding JJ, et al. Meta-analysis of the adverse effects of long-term azithromycin use in patients with chronic lung diseases. Antimicrob Agents Chemother, 2014; 58(1): 511-7.