

## Intervention

***Azithromycin 500mg every 24 hours for 10 days or until discharge.***

In the RECOVERY Trial we are testing azithromycin, a commonly-used macrolide antibiotic. It has immunomodulatory and also possible antiviral properties that suggest it may be beneficial.

## Summary of information on azithromycin in betacoronavirus infections.

The mechanism of immunomodulation includes decreased production of pro-inflammatory cytokines and inhibition of neutrophil activation.<sup>1-3</sup> Macrolides are widely used both in infectious pneumonia due to their antimicrobial activity and in chronic inflammatory lung disease due to the immunomodulatory effects.<sup>4</sup> Azithromycin is preferred over other macrolides because data suggest it has stronger immunomodulatory effects than other macrolides.<sup>3</sup>

The use of macrolides in influenza-associated pneumonia has been associated with a faster reduction in inflammatory cytokines and, in combination with naproxen, decreased mortality.<sup>5-7</sup> Observational studies in MERS-CoV have not demonstrated a mortality benefit of macrolide use.<sup>8</sup> Macrolides have not been evaluated in severe betacoronavirus infections in randomised controlled trials. The safety of macrolides is well established.

## Potential harm

Azithromycin (like all macrolides) can prolong the QT interval. It must be used with caution with other drugs that also prolong the QT interval (including hydroxychloroquine). It is also associated with worsening of myasthenia so should be used with caution in patients with myasthenia gravis.

## Frequently asked questions

1. Can someone already taking azithromycin (or another macrolide) be randomised into RECOVERY?  
Yes. If the macrolide can stop then all other suitable arms are available. If the macrolide is to continue the patient can still be randomised but will not be allocated azithromycin or hydroxychloroquine.
2. Can a participant already randomised in the trial (not to azithromycin) take a macrolide?  
Yes, if they are necessary for their care. If the participant is taking hydroxychloroquine the managing doctor should exercise caution because of their joint effects on the QT interval.

3. Is azithromycin safe when given during pregnancy?
4. Yes. The UK Teratology Information Service monograph concludes that there is no definitive evidence linking azithromycin with increased risk of miscarriage or congenital malformations (<https://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-MACROLIDES-IN-PREGNANCY/>). Azithromycin is detected in only low levels in breastmilk and is not expected to cause adverse events in breastfed infants.
5. Are the tablet and liquid preparations of azithromycin inter-changeable?  
Yes.
6. Can liquid azithromycin be administered down an NG tube?  
Yes.
7. Is there an IV formulation of azithromycin?  
We have not been able to source this through PHE.
8. In renal impairment, is any dose adjustment required?  
No.

## References

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4. Spagnolo P, Fabbri LM, Bush A. Long-term macrolide treatment for chronic respiratory disease. *Eur Respir J* 2013;42:239-51.
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