South African National Department of Health
Evidence summary
Component: COVID-19

EVIDENCE SUMMARY: DOXYCYCLINE FOR THE TREATMENT OF COVID-19

Date: 15 October 2021

Research question: Should doxycycline be used in the treatment of ambulant patients with COVID-19?

Key findings

- This summary evaluated the evidence base for the use of doxycycline for treatment of COVID-19 in adults.
- One randomised controlled trial, comparing the use of doxycycline and usual care (n=780) to usual care alone (n=948), was identified. This RCT was conducted in the United Kingdom, as part of the PRINCIPLE platform study, and enrolled people aged 65 years or older, or 50 years or older with comorbidities.
- Doxycycline treatment was not associated with clinically meaningful reductions in time to recovery, hospital admissions or mortality, in patients treated for COVID-19 in the community. The doxycycline arm was stopped prematurely as the prespecified futility criterion was met.
- The currently available evidence does not support the routine use of doxycycline in the treatment of COVID-19, unless indicated for other reasons.

NEML MAC ON COVID-19 THERAPEUTICS RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
	X				

Recommendation: The Committee recommends that doxycycline not be used for the treatment of adults with COVID-19, unless indicated for other reasons.

Rationale: The available evidence does not support the routine use of doxycycline for the treatment of COVID-19. However, this is based on one large, multicentre, randomised controlled trial conducted in adults at increased risk of poor outcomes. Although clinically-relevant endpoints were reported, time to recovery was based on self-assessment in an open label study. A large proportion of enrolled participants (42.0%) were suspected to have COVID-19, but tested negative for SARS-CoV-2, and no results were available for some participants (12.9%). Minimal data were presented on adverse events, with serious adverse events only reported in the usual care arm. The doxycycline arm of this platform, adaptive study was stopped prematurely as the prespecified futility criterion was met.

Level of Evidence: Moderate certainty evidence
Review indicator: Evidence of safety and/or efficacy that is sufficient to change the recommendation.

NEML MAC on COVID-19 Therapeutics: Andy Parrish (chair), Gary Reubenson (vice-chair), Marc Blockman, Karen Cohen, Andy Gray, Tamara Kredo, Renee De Waal, Jeremy Nel, Helen Rees.

Note: Due to the continuous emergence of new evidence, this evidence summary will be updated when more relevant evidence becomes available.

Background: The preparation of was evidence summary was triggered by the publication of a randomised control trial, part of the UK PRINCIPLE trial,[1] comparing doxycycline to placebo. Doxycycline has been registered in South Africa for many years and is currently procured in the public sector for various indications listed in the Standard Treatment Guidelines/Essential Medicines List. The National Essential Medicines List (NEML) Ministerial Advisory Committee (MAC) on COVID-19 Therapeutics decided that an evidence summary was needed because doxycycline is a widely available antibiotic, used in ambulatory settings. Irrational use of doxycycline would contribute to the development of antimicrobial resistance.

EVIDENCE REVIEW:

An evidence summary was prepared, rather than a rapid review, as there is very limited evidence in the form of randomised controlled trials of doxycycline in the treatment of COVID-19. Nonetheless, a PICO question was agreed, as follows:

- **Population:** Patients with confirmed COVID-19, not requiring oxygen therapy and treated in ambulatory care settings, no restriction to age or co-morbidity.
- **Intervention:** Doxycycline. No restriction on dose, frequency.
- **Comparators:** Standard of care/placebo.
- **Outcomes:** Resolution of symptoms; time to resolution of symptoms; progression to hospitalisation; duration of hospitalisation; progression to requiring oxygen; progression to requiring mechanical ventilation; mortality; adverse events, adverse reactions.
- **Study designs:** Randomised controlled trials and systematic reviews of randomised controlled trials.

In October 2021, three RCTs were identified on COVID-NMA.[2] Two RCTs were excluded as they did not meet the eligibility criteria: one compared doxycycline in combination with ivermectin to placebo,[3] and the other compared doxycycline to active comparators (hydroxychloroquine and azithromycin), which may be associated with poorer outcomes because of a risk of additive toxicity.[4]

One RCT, Butler *et al*., met the eligibility criteria and is summarised here.[1]

Randomised-controlled trial:

The PRINCIPLE trial was an open label, multi-arm, adaptive platform (multiple treatments for the same disease are trialled simultaneously) randomized trial conducted in the United Kingdom primary care setting. The study enrolled older patients (≥65 years) or those aged ≥50 years, with comorbidities. The comorbidities included weakened immune system, heart disease, hypertension, asthma or lung disease, diabetes, mild hepatic impairment, stroke or neurological problems, and self-reported obesity or body mass index of ≥35 kg/m². Eligible patients had to have been unwell (for ≤14 days) with suspected COVID-19 or a positive PCR test for SARS-CoV-2 infection, but not hospitalised.

Participants were randomised to usual care only, usual care plus oral doxycycline (200 mg on day 1, then 100 mg once daily for the following 6 days), or usual care plus other interventions. However, only the usual care plus doxycycline and usual care only intervention was reported on in the publication cited here.[1]

The initial primary endpoint was hospitalisation or death. However, due to a low rate of hospitalisations, the trial management group recommended adding an outcome of disease duration. Therefore, the final co-primary endpoints were time to first self-reported recovery (the first instance that a participant reported feeling recovered), and hospitalisation or death related to COVID-19, both measured at 28 days from randomisation. Bayesian methods were used in the primary analysis, with each null hypothesis rejected if the Bayesian posterior probability of superiority exceeded 0.99 for the time to recovery endpoint and 0.975 for the hospitalisation or death endpoint. Futility was declared if there was insufficient evidence of a clinically meaningful benefit, pre-specified as a minimum of 1.5 days difference in median time to first report of recovery and a 2% difference in hospitalisation or mortality rate.

The trial opened on 2 April 2020, and randomisation to doxycycline began on July 24, 2020. The doxycycline arm of the platform study was stopped prematurely, on 14 December 2020, because the prespecified futility criterion was met. When the doxycycline arm was stopped there were 2689 participants enrolled in the platform RCT. However, only 2508/2689 (93.3%) enrolled participants contributed follow-up data and were included in the primary analysis. Of these,

a total of 1792 participants were analysed in the usual care + doxycycline group (n=780; 31.1%) and usual care only group (n=948; 37.8%). The mean age of participants was 61.1 years (SD 7.9) and most were female (n=999; 55.7%).

Reported primary outcomes:

Self-reported recovery: *usual care plus doxycycline group vs usual care only group*

- ***Median time to first self-reported recovery*:** 9.6 [95% Bayesian Credible Interval [BCI] 8.3 to 11.0] days *vs* 10.1 [8.7 to 11.7] days; hazard ratio 1.04 [95% BCI 0.93 to 1.17].
- ***Time to alleviation of all symptoms:*** 3 days (2-7) vs 2 days (1-8) (95% CI, 0.86 to 1.09; p=0.55)
- ***n (%) reported first feeling recovered within 28 days after randomization***: 596/780 (76.4%) *vs* 717/948 (75.6%)

Hospitalisation or death related to COVID-19: *usual care plus doxycycline group vs usual care only group*

- **Hospitalisations:** 41 (crude percentage 5.3%) *vs* 43 (4·5%) (estimated absolute percentage difference –0.5% [95% BCI –2.6 to 1.4])
- **Mortality:** 5 (0.6%) *vs* 2 (0.2%)

Serious adverse events: *usual care plus doxycycline group vs usual care only group*

- 5 participants were hospitalized for reasons unrelated to COVID-19, all of whom were in the usual care only group

Guidelines:

- *National Institutes of Health (USA)*[5] **"**recommends against the use of antibacterial therapy (e.g. azithromycin, doxycycline) for outpatient treatment of COVID-19 in the absence of another indication".
- *Australian guidelines for the clinical care of people with COVID-19*[6]: On the 15th October 2021 indicated "that it remains unclear whether doxycycline is more effective than standard care in treating patients with COVID-19. Their recommendation is that doxycycline should not be used for the treatment of COVID-19 outside randomised trials".

CONCLUSION:

Treatment with doxycycline was not associated with reductions in time to recovery, hospitalisations or deaths related to COVID-19, and therefore should not be used as a routine treatment for COVID-19, unless indicated for other reasons.

Reviewer(s): A Gray, M Reddy

Declaration of interests: AG (Division of Pharmacology, Discipline of Pharmaceutical Sciences, University of KwaZulu Natal) & MR (Better Health Programme, South Africa), declared no interests in respect of doxycycline for COVID-19.

Table 2: Characteristics of completed RCT(s)

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
Butler *et al.*, (2021) https://doi.org/10.1016/S2213-2600(21)00310-6 ISRCTN, 86534580	RCT: National, Open-Label, Multi-Arm, Adaptive Platform Trial Setting: Primary Care Centres in UK Funding: UK Research and Innovation, Department of Health and Social Care, National Institute for Health Research Randomisation was 1:1:1 - usual care + doxycycline; usual care only; usual care + other interventions Data was reported for usual care + doxycycline and usual care only groups Follow-up duration (days): 28	Trial stopped due to prespecified futility criterion being reached: n=2689 enrolled n=2508 (93·3%) contributed follow-up data. n=1792 part of the usual care+ doxycycline grp (n=780; 31.1%) vs usual care only grps (n=948; 37.8%). Mean Age: 61.1 years N=999 females (55.7%) & n=790 males (44.1%) *Inclusion criteria:* ≥65 yrs; ≥ 50 years with comorbidities (weakened immune system, heart disease, hypertension, asthma or lung disease, diabetes, mild hepatic impairment, stroke or neurological problem, & self-reported obesity or body mass index of ≥35 kg/m²), who had been unwell (for ≤14 days). Symptoms classified in accordance with UK National Health Service [NHS] definition of high temperature, new continuous cough or change *Exclusion criteria:* Inpatient, almost recovered (general condition improved i.e., COVID-19 symptoms mild/almost absent), Previously in PRINCIPLE trial. Taking antibiotics for an acute condition/ if doxycycline was contraindicated	Oral doxycycline (200 mg on day 1, followed by 100 mg once daily for the following 6 days) and usual care only. Total duration of therapy: maximum of 7 days followed by usual care.	*Primary outcomes:* • Self-reported recovery time, reduced hospital admission, or deaths related to COVID 19	*Primary outcomes:* *Self-Reported Recovery:* *Usual care + doxycycline vs usual care alone* • n=596/780 (76.4%) reported first feeling recovered within 28 days after randomisation, vs n=717/948 (75.6%) • Median time to first recovery: 9.6 days vs 10.1 days (hazard ratio [HR] 1.04 [95% Bayesian Credible Interval (BCI) 0.93 to 1.17]; median benefit of 0.5 days (95% BCI –0.99 to 2.04). • Probability that median time to recovery was shorter in the usual care + doxycycline grp vs usual care only grp (i.e., probability of superiority) was 0.74 & did not meet the 0.99 threshold to declare superiority. • Probability of a clinically meaningful benefit (≥1.5 days) in time to recovery was 0.10. Hospitalisation related to COVID-19 within 28 days of follow-up: (41 [crude percentage 5.3%] vs 43 [4.5%]; estimated absolute % difference –0.5% [95% BCI –2.6 to 1.4] Mortality: 5 deaths (0.6%) vs 2 (0.2%) Serious adverse events: 5 participants hospitalised for	**Overall judgement with regards to risk of bias:** MODERATE *Randomisation:* Randomisation was conducted & stratified by age and comorbidity - **LOW RISK** *Selection Bias:* Included patients without PCR-confirmed SARS-CoV-2 infection (753 (42·0%)) - **HIGH RISK** *Performance:* Open label study - **HIGH RISK**. *Missing outcome data:* 93·3% of those enrolled contributed follow-up data (<10% without follow up data) - **LOW RISK** *Measurement of the outcome:* There was a high proportion of individuals who reported recovery on day 1 among those without a positive SARS-CoV-2 test due to difficulties obtaining data to confirm eligibility from some general practices. Delays between trial screening and randomisation might have resulted in some reporting recovery sooner after randomization. An adjustment was made for this limitation in the primary analysis - **MODERATE RISK** *Selection of the reported results:* Trial analysed as pre-specified for the outcome. However due to low hospitalisations a duration of illness endpoint was added to the study. **MODERATE RISK**

					reasons unrelated to COVID-19, all in the usual care group	

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