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

EVIDENCE SUMMARY

Date: 23 November 2020

Research question: Should mucolytics be used for managing hospitalised Covid-19 patients compared to no intervention or an alternative intervention?

Key findings

- A living review of two RCTs, both assessed as being of very low quality, indicates that there is insufficient evidence to recommend bromhexine for the treatment of hospitalised COVID-19 patients. Studies were underpowered to detect clinically meaningful outcomes of mortality, improvement in clinical outcomes or associated adverse effects, and were open-label, unblinded studies reporting indirect and imprecise results. It is recommended that a complete review be undertaken only if further relevant evidence is published.
- The studies investigated bromhexine at a daily oral dose of 24 to 96 mg. The formulations available on the South African market may make dosing challenging (i.e. 10mg/5ml respirator solution and a 4mg/5ml linctus with 5mg/5ml of orciprenaline) (5)
- Adverse effects associated with bromhexine include gastrointestinal effects, transient elevation in aminotransferase, allergic reactions including skin rashes, bronchospasm, angio-oedema and anaphylaxis (5).
- No studies could be sourced for N-acetylcysteine, oral or any other mucolytics.

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE 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 Sub-committee suggests that bromhexine not be used for adults with COVID-19.

Eligible patients with COVID-19 in South Africa should be considered for enrolment in relevant therapeutic trials.

Rationale: The evidence of efficacy and safety is very uncertain at this point. Studies were underpowered to detect clinically relevant outcomes of mortality or improvement in clinical outcomes; and there is an uncertain risk of serious adverse effects.

Level of Evidence: Very low certainty evidence

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

Therapeutic Guidelines Sub-Committee for COVID-19: Andy Parrish (chair), Gary Reubenson (vice-chair), Marc Blockman, Karen Cohen,), Andy Gray, Tamara Kredo, Renee De Waal, Gary Maartens, Jeremy Nel, Helen Rees.

Background: Following an advisory submitted to the Minister of Health on the lack of evidence for therapeutic bronchoscopy for mucous removal in COVID-19 patients by the Ministerially Advisory Committee for COVID-19, the MAC had recommended that the NEMLC COVID-19 Subcommittee conduct a review of the evidence for mucolytic agents in the management of COVID-19.

Mucolytic agents: Available oral formulations on the South African market includes acetylcysteine, bromhexine and carbocisteine; whilst dornase alfa is available as an inhalant solution for nebulisation.

EVIDENCE REVIEW:

Living meta-analysis:

A Cochrane supported meta-analysis(1) of two randomised controlled trials (RCTs) (2,3) showed that there remains significant uncertainty whether bromhexine is more effective and safer than standard care or placebo in treating hospitalised patients with mild or moderate COVID-19 (see Table 1 for summary of findings of the living review; and Table 2 for characteristics of the included studies[1]). The patient cohorts consisted mostly of men and the mean ages in the two RCTs were 60 years and 50 years. Two different doses of bromhexine were used in the two trials: 8 mg vs 32 mg (each 8 hourly for 2 weeks). The meta-analysis was underpowered to detect a mortality difference (RR 0.09; 95% CI 0.01 to 1.59); or whether bromhexine is of benefit in decreasing time to clinical improvement by day 28 (RR 2.50; 95% CI 0.78 to 7.97); or associated with serious adverse events. The studies did not include adolescents, pregnant or breastfeeding women. Patients in both studies also received a number of additional drugs in each arm as part of the two institutions' standard of care at the time. These drugs were either not fully listed (Ansarin et al.) or where they were, they were not balanced across the two arms (Li et al.).

The certainty of the evidence was assessed as very low, primarily due to the wide confidence intervals in the outcome measures, that were consistent with the both possibility for clinically significant benefit and clinically significant harm. In addition, there were concerns with the lack of blinding of patients, deviations from the intended intervention, randomisation and outcome reporting. Both studies were conducted in a single institution, limiting generalisability.

Guidelines:

1. *Australian guidelines for the clinical care of people with COVID-19(4) d*oes not recommend routine use of bromhexine for the treatment of COVID-19, outside of randomised trials with appropriate ethical approval.

Ongoing clinical trials:

As of 23 November 2020, 6 clinical trials investigating the role of mucolytics in the management of COVID-19 are registered on https://clinicaltrials.gov/ - study NCT04405999 has been completed, but study results have not yet been posted/published.

Table 1: Summary of findings for bromhexine compared to standard care for mild/ moderate/ unclear COVID-19

Patient or population: Mild/Moderate/Unclear COVID-19
Setting: Worldwide
Intervention: Bromhexine
Comparison: Standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard care	Risk with Bromhexine				
Clinical improvement D14-D28	333 per 1,000	833 per 1,000 (260 to 1,000)	RR 2.50 (0.78 to 7.97)	18 (1 RCT) [b]	⊕◯◯◯ VERY LOW [c,d,e]	
All-cause mortality D14-D28	128 per 1,000	12 per 1,000 (1 to 204)	RR 0.09 (0.01 to 1.59)	78 (1 RCT) [f]	⊕◯◯◯ VERY LOW [d,e,g]	zero events in treatment group
Adverse events	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	78 (1 RCT) [f]	⊕◯◯◯ VERY LOW [h,i,j]	zero events in both groups
Serious adverse events	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	18 (1 RCT) [b]	⊕◯◯◯ VERY LOW [c,i,j]	zero events in both groups

[1] Due to the limited data (i.e. 2 RCTs, n=96) of very low quality, the reviewers appraised the individual RCTs – and not the meta-analysis in Table 1.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Last update: November 10, 2020
b. Li T, 2020
c. Risk of bias downgraded by 1 level: some concerns in deviation from intended intervention, outcome measurement, and selection of reported result
d. Indirectness downgraded by 1 level: single study from a single institution, therefore results in this population might not be generalizable to other settings
e. Imprecision downgraded by 2 levels: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and very low number of participants
f. Ansarin K, 2020
g. Risk of bias downgraded by 1 level: some concerns in randomization and deviation from intended intervention
h. Risk of bias downgraded by 1 level: some concerns in randomization, deviation from intended intervention, and outcome measurement
i. We presume that the adverse event rates, and the corresponding relative risks, is similar across diverse settings; therefore not downgraded for indirectness
j. Imprecision downgraded by 2 levels: no events in both groups and low number of participants

CONCLUSION:

There is limited evidence for the repurposing of mucolytic agents for the treatment of COVID-19 – only two RCTs of bromhexine investigated in adult hospital COVID-19 patients were found. The evidence does not support the use of bromhexine except in a clinical trial setting. However, mucolytics could still be considered for other concomitant evidence-based indications in COVID-19 patients.

Reviewer(s): Ms TD Leong, Dr J Nel

Declaration of interests: TDL (National Department of Health, Affordable Medicines Directorate, Essential Drugs Programme), JN (Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand) have no interests to declare in respect of mucolytic therapy for COVID-19.

REFERENCES:

1. Living mapping and living network meta-analysis of COVID-19 studies: Bromhexine vs standard of care. https://covid-nma.com/living_data/index.php?comparison=84
2. Li T, Sun L, Zhang W, et al. Bromhexine Hydrochloride Tablets for the Treatment of Moderate COVID-19: An Open-Label Randomized Controlled Pilot Study. Clin Transl Sci. 2020 Sep 3. https://pubmed.ncbi.nlm.nih.gov/32881359/
3. Ansarin K, Tolouian R, Ardalan M,et al. Effect of bromhexine on clinical outcomes and mortality in COVID-19 patients: A randomized clinical trial. Bioimpacts. 2020;10(4):209-215. https://pubmed.ncbi.nlm.nih.gov/32983936/
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Table 2: Characteristics of completed RCTs included in the living review

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
Li T et al, 2020 (2)	Open-label, pilot RCT Single-centre in China Follow-up duration (days): 21	n=18 Age ≥18 years but ≤80 years (mean age of 50 years); confirmed or clinically suspected mild or moderate COVID-19 (based on China's Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (Provisional 5th ed); 78% were men *Exclusion criteria:* ALT ≥5× ULN, Total bilirubin level ≥3× ULN, or creatinine ≥1.5×ULN; severe liver disease; severe or critical COVID-19 cases; previous history of severe gastrointestinal diseases; lactose intolerance; allergy to bromhexine or ingredients including starch, lactose, and magnesium stearate; pregnancy; breastfeeding.	• Bromhexine, oral (32 mg 8 hourly); n=12 in addition to standard of care ***vs*** • Standard of care alone: Antivirals (arbidol granules, 0.1 to -0.2g 8 hrly and recombinant human interferon-α2b spray, 0.083 ml 8 hrly), on the doctors' discretion according to China's Novel Coronavirus Pneumonia Diagnosis and Treatment Plan; n=6. Total duration of therapy: 14 days	*Primary outcomes:* • Clinical recovery and deterioration rate after initiation of medications. *(Clinical recovery: fever and respiratory symptoms returning to normal over 48 h; Disease deterioration: respiratory distress, respiratory rate ≥30 times/min, oxygen saturation (SpO2) ≤ 93% in the resting state, and oxygenation index ≤300 mmHg).* *Secondary outcomes:* • Virologic clearance during the study period (SARS-CoV- 2-negative conversion within 20 days, rate of SARS-CoV-2-negative conversion). • Clinical follow-up (clinical remission rate, time to fever remission, rate of improvement in chest CT, patients requiring oxygen therapy, and discharge rate within 20 days). • Adverse events (AEs).	**No significant differences in the primary and secondary outcomes between the bromhexine vs control group.** *Primary outcomes:* • **Clinical recovery & deterioration rate** - Median (interquartile) time from onset to recovery for all patients was 15.0 (13.0 to 22.0) days; clinical remission and negative SARS-CoV-2 results in both groups. - Overall time to fever remission was 11.0 (9.0 to 12.0) days: 10.5 (9.3 to 11.0) days vs 11.5 (9.5 to12.0) days, p=0.70, ns *Secondary outcomes:* • **Clinical follow-up:** - Improvement by CT imaging: 6.7% vs. 33.3%, p=0.62, ns - Requiring oxygen therapy: 16.7% vs. 33.3%, p=0.11, ns - Discharge rate within 20 days: 83.3% vs. 33.3%, p=0.12, ns • **Side effects:** Most commonly reported AE was liver injury - 3 (25.0%) vs 4 (66.7%) cases in the bromhexine group vs control groups – though no significant difference in AEs was observed between the two treatment arms.	• Open-label, pilot study analysed using an ITT analysis. • Trial registry reported treatment arms differently to the final publication – as all patients received antivirals (arbidol granules and recombinant human interferon α2b spray). • 9 patients, 8 from the bromhexine group and 1 from the control group, had treatment duration < 14 days because of disease recovery. • No patient in either group deteriorated during the observation period; all patients achieved clinical remission and negative SARS-CoV-2 results. • Deteriorated patients who progressed to severe or critical condition were withdrawn from the study (aligned with study participant exclusion criteria) **Overall judgement with regards to risk of bias: "*MODERATE RISK*"** • *Randomisation*: Allocation sequence random and allocation was concealed. **LOW RISK** • *Deviations from intervention:* Unblinded study. No information on concomitant anticoagulants and biologics. Antiviral and corticosteroid administered to all and not restricted to the control group (as reported in the registry) **MODERATE RISK** • *No missing outcome data* **LOW RISK** • *Measurement of the outcome:* Unblinded study **MODERATE RISK** • *Selection of the reported results:* Protocol and statistical analysis were not available and there were some concerns for the outcomes -incidence of clinical improvement; serious adverse events **MODERATE RISK**
Ansarin K et al, 2020 (3)	Open-label RCT Single-centre in Iran	n=78 Patients ≥18 years (mean age was 59.8 years), hospitalised with COVID-19 (unclear severity) at a single center in Iran; 55% were men.	Bromhexine, oral (8 mg 8 hourly, in addition to standard of care x14 days; n=39 ***vs***	*Primary outcomes:* Improvement in the rate of ICU admissions, intubation/mechanical ventilation, and 28-day mortality. *Secondary outcomes:*	**Bromhexine group vs control group** *Primary outcomes:* • **28-day mortality:** 0% vs 12.8%, p=0.027. • **ICU admission:** 2 patients (5.1%) vs 11 patients (28.2%), p=0.006.	• Open-label RCT using an ITT analysis. • Primary outcomes were reported in the report but not prespecified in the trial registry. • Some outcomes from the registry were omitted in the publication (e.g., period of mechanical ventilation). • Secondary outcomes (e.g., number of patients with specific symptoms) were reported in the

	Follow-up duration (days): 28	*Exclusion criteria:* Pregnancy or lactation, chronic respiratory disease/ symptoms that may interfere with diagnosis of COVID-19, allergy to bromhexine and cancer.	Standard care x 14 days; n=39 Standard therapy based on the Iranian national COVID-19 treatment protocol & best practice guidelines at that time – including hydroxychloroquine 200 mg daily x 14 days with supportive and symptomatic therapy.	Clinical improvement of symptoms (fever, dyspnea, and weakness, assessment of CRP, LDH, neutrophil/lymphocyte ratio and length of hospital).	• **Mechanical ventilation:** 2.6%(1) vs 23.1% (9), p=0.0007 *Secondary outcomes:* • **Clinical improvement of symptoms within 2 weeks:** - Dyspnea: 3.4% vs 48.3% , p≤ 0.001 - Cough: 6.9% vs 40.0%, p= 0.003. - Lassitude: 6.9% vs 34.5%, p=0.010. - LDH (363.2±83.6 vs. 445.3±115.2; p= 0.056), NLR: 1.7(1.0) vs. 3.0 (6.3); p=0.052; CRP: 0% vs. 81.8%; p<0.001) - Length of hospital stay: 7.6±3.5 days vs 8.1±5.5 days; p=0.587. No major AEs reported.	publication, but not pre-specified in the trial registry. **Overall judgement with regards to risk of bias:** **"*MODERATE RISK*"** • *Randomisation*: Allocation sequence random, but no information on allocation concealment **moderate risk** • *Deviations from intervention:* Unblinded study. No information on concomitant anticoagulants and biologics. Antiviral and corticosteroid administered to all and not restricted to the control group (as reported in the registry) **moderate risk** • *No missing outcome data* **low risk** • *Measurement of the outcome:* Unblinded study (outcome assessor). Risk assessed to be some concerns for the outcome: Adverse events. **moderate risk** • *Selection of the reported results:* Risk assessed to be low for the outcomes: Mortality. Adverse events. **low risk**