**Should we rinse, gargle and nebulise saline to treat and contain SARS-CoV-2 infection?**

**Table.** Clinical studies or reports on the use of saline as nasal rinse and/or gargle (irrigation), with or without antimicrobial or anti-inflammatory additions, and/or aerosol (nebulisation) in COVID-19: population/patients studied, assessments, formulations /dose regimen used and outcomes.

<table>
<thead>
<tr>
<th>Target (population) assessed (Country of assessment)</th>
<th>Assessment(s)</th>
<th>Trials design &amp; Saline protocol</th>
<th>Outcome</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preventive treatment – Health Care Workers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COVID-clinic, upon high-risk contact, China</td>
<td>Protection by nasal rinse add-on to other PPE in hospital HCWs</td>
<td>Case control study in COVID-ward: <strong>nasal (nasopharyngeal) rinse after contact with infectious insult</strong> (composition NS) n=477 - Cases : n=51 - Controls: n=426</td>
<td>Applying nasal rinse (n=9/193): <strong>4.7%</strong> infected Not applying nasal rinse (n=42/284): <strong>14.8%</strong> infected (p&lt;0.00002) Nasal rinse was the highest statistically significant impacting factor among the interventions tested, but also several other protective measures were significantly effective</td>
<td>Liu et al.¹</td>
</tr>
<tr>
<td>COVID-ward versus non-COVID ward, Rajasthan Hospital, Jaipur, India</td>
<td>Protection by Jal Neti, add-on to other hygiene measures in hospital HCWs</td>
<td>Prophylactic Jal Neti <strong>nasal rinse + gargling</strong> 3x daily in the COVID-ward compared to no saline in the non-COVID facilities; usual PPE n=300 - Saline, COVID facility: n=100 - Controls, non-COVID facility: n=200</td>
<td>% qPCR+: - Saline rinse (COVID-facility): <strong>1%</strong> - Controls (Non-COVID facility): <strong>10%</strong> [Weakness: so far only published in local journal]</td>
<td>Singh et al.²</td>
</tr>
<tr>
<td>Front-line HCWs (nurses, physicians), Mexico</td>
<td>Treatment response to prophylaxis with neutral electrolyzed (saline) water, called SESc</td>
<td>Prospective, randomised, open-label, controlled trial in general hospital Prophylactic <strong>naso- and oropharyngeal rinse protocol</strong>: 3x daily, 4 weeks add-on to PPE, versus control s (standard PPE):</td>
<td>COVID-19 incidence (PCR+): - Rinse protocol: <strong>1.2%</strong> - Controls: <strong>12.7%</strong> (p= 0.0039) [To note: differences are not due to comorbidities: 29.8% in the saline group, 16.5%]</td>
<td>Gutiérrez-García et al.³</td>
</tr>
</tbody>
</table>
### Physicians/care personal – Dept Infectiology, Dept Cardiology, Primary care

- **Observational feedback from clinical practices**
  - Anecdotal feedback from prophylaxis nasal and oral rinse among users versus non-users in various clinical practices (Dept Cardiology, Primary care)
  - 3 clinical practices + their working environment, exposed to patients

- **Anecdotal feedback**
  - No infection among saline users
  - Infected: saline non-users (4 other cardiologists; receptionist, 2 other providers in these exposed practices)

+ Author and family physician also reports to have observed success of the saline protocol in many patients with COVID-19 infection

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### COVID-19 patients or asymptomatic carriers (any age, ambulant)

#### Mild COVID-symptoms, US

<table>
<thead>
<tr>
<th>Time to symptom relief (TTSR)</th>
<th>Open-label randomised controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nasal irrigations</strong> (250 mL, twice daily): n= 45</td>
<td>Faster symptom resolution with HS vs controls: TTSR was significantly shorter with saline:</td>
</tr>
<tr>
<td>- Hypertonic saline (HS, NeilMed): n=14</td>
<td>- nasal congestion: HS (5 days)&lt; HSS (7 days)&lt; controls (14 days) (p=0.04)</td>
</tr>
<tr>
<td>- HSS: HS+surfactant (=½ teaspoon Johnson’s Baby Shampoo): n=14</td>
<td>- headache: HS (3 days)&lt; HSS (5 days)&lt; controls (12 days) (p=0.02)</td>
</tr>
<tr>
<td>- Controls (no intervention): n=17</td>
<td>Trend for relief of:</td>
</tr>
<tr>
<td></td>
<td>- cough: HS, HSS ≤ controls (p=0.19)</td>
</tr>
<tr>
<td></td>
<td>- fatigue: HS, HSS ≤ controls (p=0.17)</td>
</tr>
<tr>
<td></td>
<td>[No significant benefit of adding shampoo]</td>
</tr>
<tr>
<td></td>
<td>[Weakness: effect on viral load not published]</td>
</tr>
</tbody>
</table>

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#### COVID-19 patients, PCR(+) and eligible for ambulant care, Mexico

<table>
<thead>
<tr>
<th>Relief (PASS = Patient Acceptable Symptom State)</th>
<th>Prospective, 2-arm, parallel group, randomized, open-label, phase I-II clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalisation Mortality n=84</td>
<td>Overall: NES+(IV) SES &gt; NES (add-on to SOC) &gt; SOC: 43-fold increase in probability of achieving PASS on day 5 (p&lt;0.001)</td>
</tr>
</tbody>
</table>

Hospitalization:
- SES/NES (n=5/45): **11%**
- Controls (n=12/39): **30%**
- > 92% decreased risk (p<0.0001)
Symptomatic COVID-19 patients, PCR(+) and eligible for ambulant care, Mexico
Mild (79.9%), Moderate (8.9%) Severe (11.2%) at inclusion

**Disease progression/relief (PASS)**
Hospitalisation
Mortality

Prospective, 2-arm, parallel group, randomized, open-label, phase I-II clinical trial of 'neutral electrolysed saline' (SES), saline protocol add-on to SOC, starting with NES (5 mL, 4x/day for 10 days) and if not successful, applying also IV SES (for subsequent dose-levels: see ref.); +oral SES if nausea, vomiting, diarrhea +gargling RS 6x/day if intensive throat pain

<table>
<thead>
<tr>
<th>n=242</th>
</tr>
</thead>
<tbody>
<tr>
<td>-NES/SES (add-on to SOC): n=110</td>
</tr>
<tr>
<td>-controls (SOC): n= 104</td>
</tr>
</tbody>
</table>

21 days follow-up

Mortality:
- SES/NES (n=0/45): 0%
- Controls (n=5/39): 12.8%

[Weakness: too small groups to distinguish contribution of IV SES versus nebulised SES; no comparison with plain IS or HS]

Overall: NES/SES add-on to SOC > SOC; SES at higher IV dose levels > NES.

Time to PASS (days):
- NES/SES: 5.1 days
- Controls: 9.0 days (p<0.001)

-> 18-fold increase in probability of achieving PASS on day 5.

Hospitalization and/or mortality:
- NES/SES: 7.3%
- Controls: 19.2% (p=0.008)

Delayed hospitalization with NES/SES
Mortality:
- NES/SES: 1.8%
- Controls 8.7% (p=0.025)

In patients with moderate/severe disease:
- % hospitalized patients: 19% vs. 88%
- % deaths: 7.7% vs. 41%

NNT=8.3 to prevent hospitalization of 1 patient; 2.4 to achieve PASS on day 5

Viral shedding (n=10): >50% naso/oropharyngeal samples were PCR (-) on day 4; small number of patients PCR+ on day 6

Delgado-Enciso et al. 2021
### COVID-19 patients: 550-plus, elderly

<table>
<thead>
<tr>
<th>Outpatients, 55-plus recruited from test &amp; trace centre if PCR+, USA (excluding: need for supplemental oxygen or cognitive barriers at start)</th>
<th>Saline rinse is started within 24 hours of + PCR test: Symptom relief Hospitalization Mortality Transmission (intention-to-treat analysis, result by day 28)</th>
<th>Open-label randomized clinical trial of 2 nasal irrigation protocols twice daily: - HS+polyvidone-iodine (PVI 10%, 2.5mL in 240mL HS) vs - HS/bicarbonate (NaHCO3) nasal rinse started within 24hrs of +PCR-test [average: symptoms 3.3 days prior to enrolment]</th>
<th>Symptom resolution of all or only one mild symptom (headache, fatigue, anosmia and congestion): more likely with HS-PVI (n=21/27) than with HS-NHCO3 (n=17/35, p=0.02) Hospitalisations - Overall with saline (n=1/79): <strong>1.26%</strong> - HS-PVI (n=0/37): 0% - HS/bicarbonate (n=1/42): 2.3% - Nested case-control: 9.14% Mortality: - HS-PVI or NaHCO3: no deaths - <strong>Nested case-control: 8.22%</strong> Total risk of hospitalization or death (10.6%) was 8.4 times that of enrolled patients (SE=2.74; P=.006). Transmission: - HS-PVI or NaHCO3 (n=10/79): <strong>12.7%</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-patients (1\textsuperscript{st} wave)</td>
<td>Relief + Hospitalization + Mortality SARS-CoV-2 (qPCR or antigen test)</td>
<td>Prospective open-label study If also breathlessness: nebulized NS/H\textsubscript{2}O\textsubscript{2} (0.04%)/l\textsuperscript{a} add-on to Vitamins (A, C, D) +/- other oxidative therapies n= 107 saline: n=107</td>
<td>85% received nebulised NS/H\textsubscript{2}O\textsubscript{2} add-on Breathlessness was reported to improve after one or 2 nebulisations; eventually applied up to every 2 hours; also effective in the 3 hospitalised patients Hospitalisation: n=3/107=2.8% Mortality: 0% [Weakness: no control group; possibly other interferring interventions] Brownstein 2020\textsuperscript{9}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Breathlessness was reported to improve after one or 2 nebulisations; eventually applied up to every 2 hours; also effective in the 3 hospitalised patients.
COVID-19 single-centre outbreak in a Long-term care (LTC) facility (Dec 28, 2020-Jan 23, 2021), USA

### Hospitalisation Mortality

<table>
<thead>
<tr>
<th>Retrospective analysis: <strong>Nasal irrigation+gargling</strong> (NSI) or, if not possible, hypertonic <strong>saline nebulization</strong> (HSNEB) during outbreak</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=29, 23 receiving saline (59% symptomatic):</td>
</tr>
<tr>
<td>- HSNEB: n=14; 9.4 days (mean)</td>
</tr>
<tr>
<td>- Nasal spray: n=10; 11.9 days (mean)</td>
</tr>
<tr>
<td>- Gargling: n=7; 9.4 days (mean)</td>
</tr>
<tr>
<td>- HSNEB + SNI and/or gargling: n=3</td>
</tr>
</tbody>
</table>

Common comorbidities: HTN(n=22); DM and CVA(n=8 each); dementia (n=6); CHF(n=3); immune-suppression (n=2) and sickle cell, CKD and CAD one each

All saline-treated patients recovered without need for hospitalization; 4/29 patients were hospitalised:
- n=2 for other reasons than COVID-19
- n=2 for COVID-19 (=2/27): n=1 with fever at the dialysis centre, n=1 hypoxemia; They had **not** started the saline intervention

Mortality: a 89-year-old male (DM, HTN, CVA, immunosuppression) expired in-house before/after saline initiation??

[To note: n=19 (70.3%) had received one dose of COVID-19 vaccine with a mean of 6.6 days from the date of PCR positivity]

### Hospitalised COVID-19 patients

<table>
<thead>
<tr>
<th>COVID-19 patients with pneumonia upon hospitalization and having high viral load (i.e. cycle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral clearance (% patients PCR-)</td>
</tr>
<tr>
<td>HRCT of lungs</td>
</tr>
</tbody>
</table>

**Prospective, open-label, randomised dose-finding study of NS nasal and oral irrigation (Jal Neti)**

| n=125 |

<table>
<thead>
<tr>
<th>Overall, % patients PCR-:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- saline: 48%; if rinsing every 3 hrs: 70% on day5</td>
</tr>
<tr>
<td>- controls: 25% (p&lt;0.05)</td>
</tr>
<tr>
<td>HRCT (n=56 reviewed): % improved or inhibition of progression:</td>
</tr>
</tbody>
</table>

[Chatterjee 2020]

[Parviz 11]
### Threshold (Ct) Value ≤25

- **NS:** n=62
- **Controls:** n=63

- **saline (n=30/34):** 91%
- **controls (n=14/22):** 63% (**p=0.028**)

[Weakness: no systematic repeated lung imaging; overall small dosing groups]

### ARDS Requiring Non-invasive Oxygen Support

**Need for invasive ventilation**

Open-label study

NS nebulized daily add-on to SOC

n=60 patients with ARDS, requiring non-invasive oxygen support

**Mortality**

Patients needing invasive ventilation in ARDS:

- n=3/60 (5%)  

Mortality: 1/60 (1.7%) of ARDS patients

[Weakness: no control group; age distribution not communicated]

Voshaar 2020

### SARS-CoV2-induced Hypoxia

**Sodium ibuprofenate (50 mg) in hypertonic saline (NaIHS) in hypoxic patients**

Nebulization/inhalation of NaIHS, tid, add-on to SOC until oxygen saturation levels of > 94% achieved on ambient air

n=578

NS: n=383; n=56 on mechanical ventilation (MV)

Controls: n=195; 21 on MV at baseline

**Oxygen saturation:**

- Nebulised NaIHS was associated with rapid improvement in hypoxia and vital signs
- Acute rapid reversal of deterioration in oxygenation and of NEWS2 scores after initiation of NaIHS therapy, irrespectively of +/-MV

Mortality: lower compared with controls:

- No MV at baseline: 10.7%, vs 18.4% in controls (**p < 0.03**).
- MV at baseline: 19.6% vs 86.7% in controls (**p < 0.001**)

[To note: Patients wore a containment hood to diminish aerosols by nebulization]

Salva 2021

### Viral shedding and transmission: viral load/infectiousness in vitro after a single or repeated exposure (gargles) – PCR/antigen results

After 1-3 applications
| Hospitalized patients in an intensive care unit (without need of intubation, n=1), or in an isolation ward (n=11) | Gargle for diagnostic purpose (PCR) | Oropharyngeal specimens after: **20 mL NS gargle for 30 sec** repeated 30 min after H₂O₂ gargle (20 mL of 1% hydrogen peroxide for 30 sec) | Results after:  
1) first 20 mL NS gargling:  
- 10/12 PCR (+); 2/12 (16%) PCR (-);  
- viral culture positive in 1 case (8.3%)  
2) second NS gargle after H₂O₂:  
- 10/12 PCR (+); 2/12 (16%) PCR (-);  
- no longer viral culture positive  
[To note: only samples with high copy numbers were cultured for life virus (n=5)]  
[Weakness: one gargle + repeated gargle after H₂O₂ per patient] |
|---|---|---|---|

**Repeated applications (treatment)**

| PCR(+) subjects | Reduction in viral load | Hypertonic **nasal rinse** (5%), 3-4 washes daily  
n=not reported | Reduction in:  
Removes SARS-CoV-2 viral load by up to 25%, (n=20) within 6 hours with 3-4 nasopharyngeal saline washes  
[Weakness: reporting by investigator on internet news] |
| COVID_19 asymptomatic physician (54 years), Italy | Viral clearance (nasopharyngeal, PCR identified) Treatment response | **HTS nasal rinsing and gargling** several times /day from the first signs onwards  
n=1 | Case report: becomes **PCR(-)** after 3 days of rinsing and remaining asymptomatic  
[Weakness: only one case report published] |
| Asymptomatic COVID-19 patients, Italy | Duration of viral shedding (nasopharyngeal, PCR-identified)  
n=172 | Open-label controlled pilot study in households  
HS (3%) +xylitol/ HMW hyaluronate as aerosol/ nebulization  
n=172:  
- n=72 performing saline rinse from day | At start, COVID-19 patients with:  
-1 cohabitant asymptomatic qPCR+: n=16  
-2 cohabitants asymptomatic qPCR+: n=24  
-3 cohabitants asymptomatic qPCR+: n=36  
Faster clearance of virus (qPCR-negative) in all patients after 7 days of saline use:  
- Nebulisation: on day 14, if rinsing day 7 to

**Gottsauner**  
**Poulas 2021**  
**Rosati et al.**  
**Ciprandi et al.**
### Mild symptomatic COVID-19 patients, Italy

**Symptoms no more than 3 days prior to inclusion**

<table>
<thead>
<tr>
<th>Duration of viral shedding (nasopharyngeal, PCR-identified)</th>
<th>Open-label controlled pilot study</th>
<th>Faster clearance of virus after 7 days of saline use -&gt; all treated patients were PCR(-) after 10 days while none in the control group.</th>
</tr>
</thead>
</table>
| **7 to 14**
- n=72 performing saline rinse from day 14 to 21
- n= 37 using no saline | **HS (3%)** +xylitol/ HMW hyaluronate as aerosol/ nebulization with a device creating a **nasal douche**, twice daily, 7 days
PCR testing repeated after 10 days
n=76 subjects;
n= ? PCR+ co-habitants (without treatment as controls) | Weakness: unclear protocol, number of controls (untreated co-habitants) is not mentioned, and treated patients seem to have also received antibiotics (tobramycin/lincomycin mentioned between the lines in the discussion)

[To note: Use of a device with a containment chamber to collect the liquid returning from the nasal cavity] |

[Varricchio et al. 19]

### SARS-CoV-2 positive case reports +/- pneumonia, Japan

| Speed of viral clearance from saliva (saliva, antigen –identified) | Superacidic electrolysed saline (pH 2.7) (SAS⁴)
**Gargling** + bilateral 2-ml **nasal rinses** upon admission (Day 1); gargling half a glass of ES +/- nasal rinses t.i.d., 4 days; add-on to remdesivir if pneumonia; favipiravir if no pneumonia n=3 | **Reduction**: salivary level of the SARS-CoV-2 antigen (Ag) decreased markedly **overnight** (Day 2) by gargling SES and faded on **day 7** after admission

**PCR(-)**: nasal swabs at **day 14** were negative. |

[Nakamoto et al. 20]

### Hospitalised SARS-CoV-2 patients with pneumonia, India

| Speed of viral clearance (nasopharyngeal, PCR-identified) | **NS (Jala Neti)** – for details: see listing under Hospitalised COVID-19 patients
- **NS**: n=62
- Controls: n=63 | Overall, % patients PCR-:
- saline: 48%; if rinsing every 3 hrs: 70% on day5
- controls: 25% (p<0.05) |

[Weakness: case reports, use of antiviral agents as SOC; no control group] |

[Chatterjee 12]

### Transmission: COVID-19 outcomes

| Ecological regression analysis of COVID-19 (1)Regression analysis: | Field 2021 21 |
| Population-based study, USA | upon exposure to elevated airborne salt + Upper airway variations in salt and water balance following humidification of air, mask wearing and salt exposure | 19 cases in the United States between Jan 2020-March 2021 on (Gulf and Pacific) US coastlines vs inland counties (data corrected for ten potential confounding environmental, physiological, and behavioural variables including humidity) + Randomized 4-arm study of effects of saline compositions on aerosols exhaled by healthy human subjects: n=21 | ~25%–30% (P < 0.05) lower COVID-19 incidence and deaths per capita on coastlines relative to the inland (2) Aerosol behaviour upon exhaling (delivery of sodium, calcium, and magnesium chloride droplets: - salts similarly reduce exhalation of respiratory droplets by ~50% (P < 0.05) within 10 min following nebulisation (= magnitude of breathing humid air or of wearing of cotton masks - respiratory droplet generation returns to relatively high baseline levels within 60–90 min on return to dry air, but calcium and magnesium ions show longer suppression (continued for 4–5 hours)

**Abbreviations:** NS=not specified; PASS = Patient Acceptable Symptom State = TTSR= Time to symptom relief; NNT=number needed to treat; HRCT = high resolution computed tomogram; PPE = personal protective equipment. **Treatments:** SOC=standard of care; NS=normal saline =IS= isotonic saline (0.9% NaCl); HS=hypertonic saline (3-7% NaCl); NES= nebulised electrolysed saline; Jal Neti (~1%); PVI=polyvidone iodine (*I=iodine=1 drop of Lugol®’s iodine in 250cc NS, mixed with 3 mL H₂O₂); SES = neutral electrolyzed saline (^SES formula pH 6.5–7.5 has 0.0015% of active chlorine and oxygen species (hypochlorous acid or hypochlorite); IV=intravenous; NES = nebulized electrolyzed saline; MV: mechanical ventilation.
References


11 Parviz S, Jackson J, Teweldebrhan Y. Saline nasal irrigation gargling, and hypertonic saline nebulization in a COVID-19 LTC outbreak. Abstract submitted to and received by personal communication.....


