Nasal disinfection as a front-line defense in future pandemics

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MILITARY MEDICINE: PLANNING FOR THE UNEXPECTED

Disclosures

- The following presentation is the view of the presenter and does not represent the views of the Australian Defence Force
- I was medical advisor and medical monitor for the two COVID-19 clinical trials described in this presentation, and I receive consultancy fees from the sponsor of the trials and the company behind the product referred to in this presentation (Firebrick Pharma Ltd)

The case of COVID-19

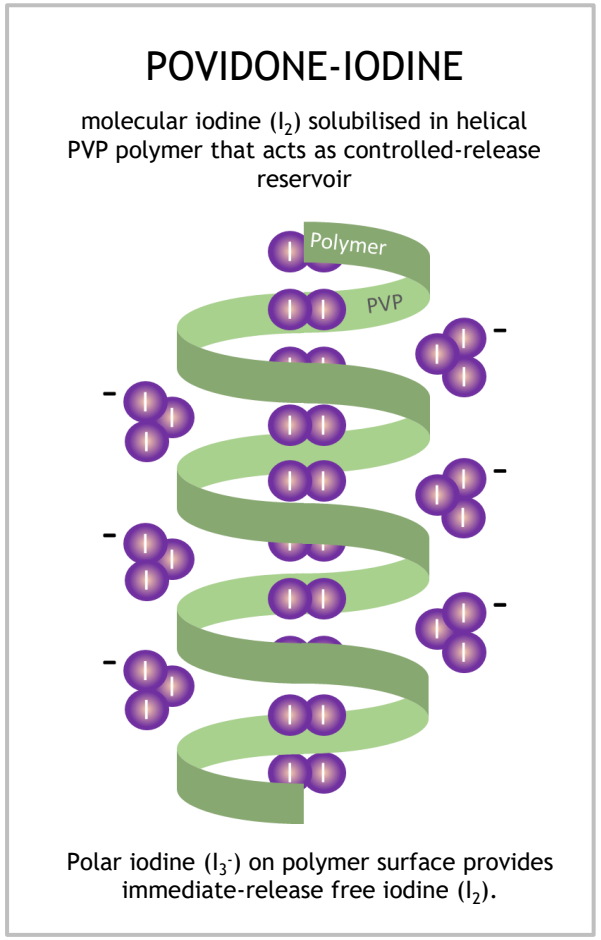
- SARS-CoV-2 is a respiratory virus
  - Enters primarily through the nose, where an initial infection is established
  - Likely through aspiration of the virus from the upper respiratory tract, the virus enters the lungs causing a more serious infection that in some cases is associated with ARDS (acute respiratory distress syndrome)
- The emergence of COVID-19 triggered interest in a range of pandemic management strategies (apart from vaccination):
  - Masking, social distancing and lockdowns to minimise spread
  - Advocacy of early treatment strategies involving various controversial agents (ivermectin, hydroxychloroquine, zinc)
  - Multiple clinical trials aimed at assessing the value of nasal and oral disinfection with povidone-iodine – an established, broad-spectrum, topical skin disinfectant

Paper	Study type, location	Covid Subjects	Regimen	Results
Choudhury (2020)	RCT Malaysia	N= 606 1:1 PVP-I or water	Combined regimen: 1% PVP-I gargle, nasal drops and eye drops, applied 4 hourly for 4 weeks	PVP-I reduced (a) days to PCR-negative, and (b) rates of hospitalisation and/or death
Guenezan (2021)	Unblinded CT France	N= 24 1:1 PVP-I or no treatment	Combined regimen: 1% PVP-I gargle and nasal spray (2.5 mL per nostril) and 10% PVP-I ointment in each nostril, applied 4 times daily for 5 days	No apparent benefit for PVP-I intervention in viral titre reduction
Arefin (2021)	Unblinded CT Bangladesh	N= 189 7 groups	Nasal irrigation (NI) with 0.4%, 0.5%, or 0.6% PVP-I or control (water); and nasal spray (NS) with 0.5% or 0.6% PVP-I or water.	NI: 93% of 0.5% PVP-I subjects were PCR-negative versus 30% for controls (water); NS: 67% of 0.5% PVP-I subjects were PCR-negative versus 7% for controls
Baxter (2021)	Unblinded CT USA	N= 79 37 PVP-I, 42 control (alkaline saline)	NI twice daily for 14 days with PVP-I nasal rinse (approx. 0.1%) or control	PVP-I NI may reduce overall risk of hospitalisation
Zarabanda (2021)	RCT USA	N= 24 3 groups	0.5% and 2.0% PVP-I NS versus saline NS applied as 2 sprays (200 µL) per nostril 4 times daily for 3 days	No sig difference between either PVP-I group and saline NS
Jamir (2021)	Retrospective observational India	266 critically ill COVID-19 patients	1.0% PVP-I applied to nasal cavity with cotton buds, 2-4 times daily	PVP-I reduced COVID-19 mortality
Elsersy (2022)	RCT Egypt	N= 200 1:1 PVP-I or placebo	PVP-I 0.5% nasal spray with glycyrrhizic acid (GA) 2.5 mg/ml, 6 times daily, versus placebo	PVP-I/GA accelerated laboratory and clinical recovery of SARS-CoV-2 infected patients & reduced household spread
Sirijatuphat (2022)	Open label single arm pilot study Thailand	N= 14	Single dose of 3 sprays of 0.4% PVP-I nasal spray in each nostril	Minimal reduction in viral load at 3 min and 4 hours post-exposure
Friedland (2022)	Open label single arm South Africa	N= 14	Single dose of 4 sprays (1.12 mL) of 0.5% PVP-I nasal spray in each nostril	Reduced culturable virus in 5/6 subjects (83%) and in 2/6 (33%), eliminated culturable virus for up to 60 min

Rationale for nasal disinfection with povidone-iodine (PVP-I)

Why sanitising the nasal passages makes sense as an extension of PPE and hand sanitising in at-risk environments

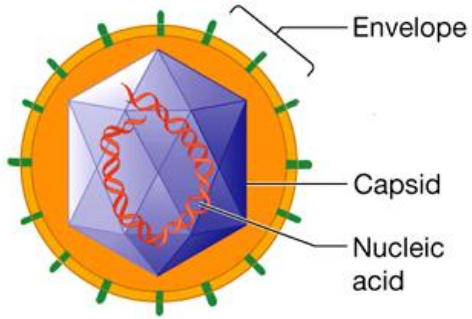
Why povidone-iodine (PVP-I)?



- PVP-I has been available and widely used for at least 6 decades as an antiseptic, including nearly 40 years in Australia as a popular gargle for sore throats (Betadine® Sore Throat Gargle)
- PVP-I is a controlled release system for free iodine (I_2)
- Free iodine is a broad-spectrum microbicide that oxidises unsaturated bonds
  - » Bacteria: destroys cell wall and functions
  - » Viruses: irreversible damage to envelope, capsid, nucleoproteins
- Action is ‘cidal – leads to permanent loss of infectivity
- Action is non-selective – does not select for resistant mutants, resistance never been reported

Antiviral activity and spectrum

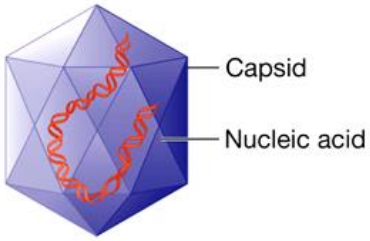
- Viruses classified as enveloped or non-enveloped (‘naked’) viruses
- PVP-I (at low concentration) inactivates both types
  - » Damages viral envelope and capsid
  - » Attacks nucleoproteins
- Enveloped viruses are acutely sensitive to PVP-I; naked viruses slightly less sensitive
  - » Historically, all serious respiratory viral pandemics caused by enveloped viruses



Enveloped virus

Coronaviruses
Influenza, RSV

≥99.99% (4 log) reduction in 15-30s with 0.5% PVP-I



Naked virus

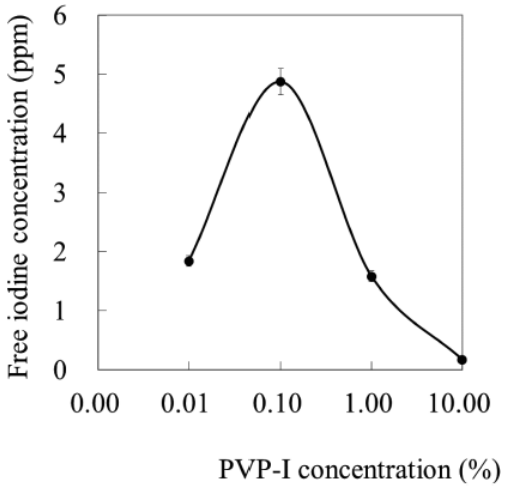
Rhinovirus
Adenovirus

90-99% reduction in 15-60s
≥99.99% reduction in 1-5 min with 0.5% PVP-I

PVP-I's unique chemistry: benefits and challenges

- Adverse effects of PVP-I are related to concentration
  - » Ciliotoxicity at ≥2.5% and cytotoxicity at 5-10%
  - » Risk of sensitivity and iodine absorption increase with PVP-I concentration
- Paradoxical chemistry makes it ideal for nasal use
  - » PVP-I is non-toxic yet more potent at lower concentrations (<1.0%)
    - – As PVP polymer is diluted, it opens up to release more free iodine, so the instantaneous potency is increased
  - » 0.5% concentration is optimum for nasal use
    - – Maximum antiviral potency combined with high tolerability and low risk of any adverse effects
- Challenges
  - » PVP-I is unstable in aqueous solution at <1.0% concentration
  - » Free iodine migrates through most plastics, causing staining and loss of stability of PVP-I solutions

0.5% PVP-I has greater antimicrobial potency than 5% PVP-I but lower residual 'capacity' due to the diminished reservoir



Source: Wada *et al* (2016). Relationship between Virucidal Efficacy and Free Iodine Concentration of Povidone-Iodine in Buffer Solution. Biocontrol Sci. 2016;21(1):21-7.

Development of a PVP-I Nasal Spray

- Development started in 2012 by Melbourne-based Firebrick Pharma Ltd
  - Initial goal was for use as a treatment for the common cold
  - Hypothesis: reducing nasal viral load leads to a reduction in cold duration and/or severity
  - Formulation work completed over 2014-2016 at labs in Melbourne
- Challenges – addressing the inherent instability of PVP-I at low concentration
  - 1% PVP-I is relatively stable and used as a gargle (Betadine® Sore Throat Gargle)
    - But 1% causes unacceptable nasal discomfort, odour and increased risk of iodine absorption
  - 0.5% was selected as the optimum concentration for nasal use, but stability was an issue
    - Addressed through excipients and buffers; menthol was added to mask iodine odour
  - Packaging was also critical to avoid staining and instability
    - Developed a custom polymer bottle that resisted iodine loss and staining; iodine interactions with any metal pump components also needed to be addressed with a high-quality pump

Nasodine® Nasal Spray

- After several years, a stable product and package was developed with a 2-year shelf-life at 30°C
- GMP manufacturing established in Melbourne and a complete CMC (chemistry, manufacturing, quality) package developed to support approval
- A dose of 3-4 sprays per nostril (total 0.84-1.12 mL) was determined to be optimal for dispersion in the nose and clinical use
- Basil Hetzel Institute in Adelaide employs a published, highly sensitive 'air-liquid interface' model of nasal epithelial tissue to test nasal preparations
  - » Even with extended exposure (up to 30 minutes), the formulation caused no cell toxicity (cytotoxicity) or adverse effects on cilial beat frequency (ciliotoxicity)*
- Human studies commenced in 2018

Nasodine Nasal Spray is not approved for sale (draft labelling)

* Ramezanpour, M., *et al.* (2020). In vitro safety evaluation of a povidone-iodine solution applied to human nasal epithelial cells. Int Forum Allergy Rhinol, 10(10), 1141-1148. https://doi.org/10.1002/alr.22575

Clinical experience

- 2018: Phase I study in healthy adult volunteers (N=10)
  - Conducted in Adelaide
  - 20 doses applied 4 times daily for 5 days, each dose 4 sprays per nostril (1.12 mL)
  - Iodine uptake occurred, but not clinically significant and below recommended daily upper limit for iodine in the diet
  - Treatment well-tolerated, no impact on thyroid function or other safety concerns
- 2018: Phase II study in adults with common cold (N=39)
  - Conducted in Adelaide and Brisbane
  - 20 doses applied 4 times daily for 5 days (1.12 mL dose)
  - Signals of positive clinical effect despite the small subject numbers
  - Treatment well-tolerated, no impact on thyroid function or other safety concerns

Clinical experience

- 2019: Phase III trial in adults with common cold (N=260):
  - Conducted at sites in Adelaide and Brisbane
  - 20 doses applied 4 times daily for 5 days, dose reduced to 3 sprays per nostril (0.84 mL)
  - Placebo was saline nasal spray; cold symptom impact measured using WURSS-21
  - Nasodine demonstrated clinical benefit on overall cold severity and functional impairment
- 2022/23: Phase III trial in adults with common cold (N=497):
  - Same protocol and dosage as 2019; placebo changed to water nasal spray
  - Nasodine did not demonstrate a clinical benefit on cold severity or functional impairment
  - Results are still being reviewed and development for the common cold will continue, along with other potential therapeutic indications*
- Overall safety conclusions
  - Product is well tolerated with no safety concerns based on four-times-daily use over 5 days
  - Transient rhinalgia/nasal discomfort was reported at least once over 5 days by 30-40% of subjects

* Hale, S. J. M., *et al.* (2023). In vitro Nasodine Can be an Effective Antibiofilm Agent for Biofilms that May Cause CRS. Laryngoscope. https://doi.org/10.1002/lary.30558

Clinical experience in COVID-19

Nasodine’s potential role as a nasal disinfectant

Virucidal pilot study of Nasodine® (povidone-iodine 0.5%) nasal spray in people with COVID-19 and confirmed nasal shedding of SARS-CoV-2 virus

Open-label human trial in South Africa to assess the impact of a single dose of Nasodine® on shedding of SARS-CoV-2 over one hour post-dose in patients with COVID-19 symptoms

Friedland, P., et al (2022). “In vivo (human) and in vitro inactivation of SARS-CoV-2 with 0.5% povidone-iodine nasal spray.” Australian Journal of Otolaryngology, 5, 2-2. https://doi.org/10.21037/ajo-21-40

Study overview

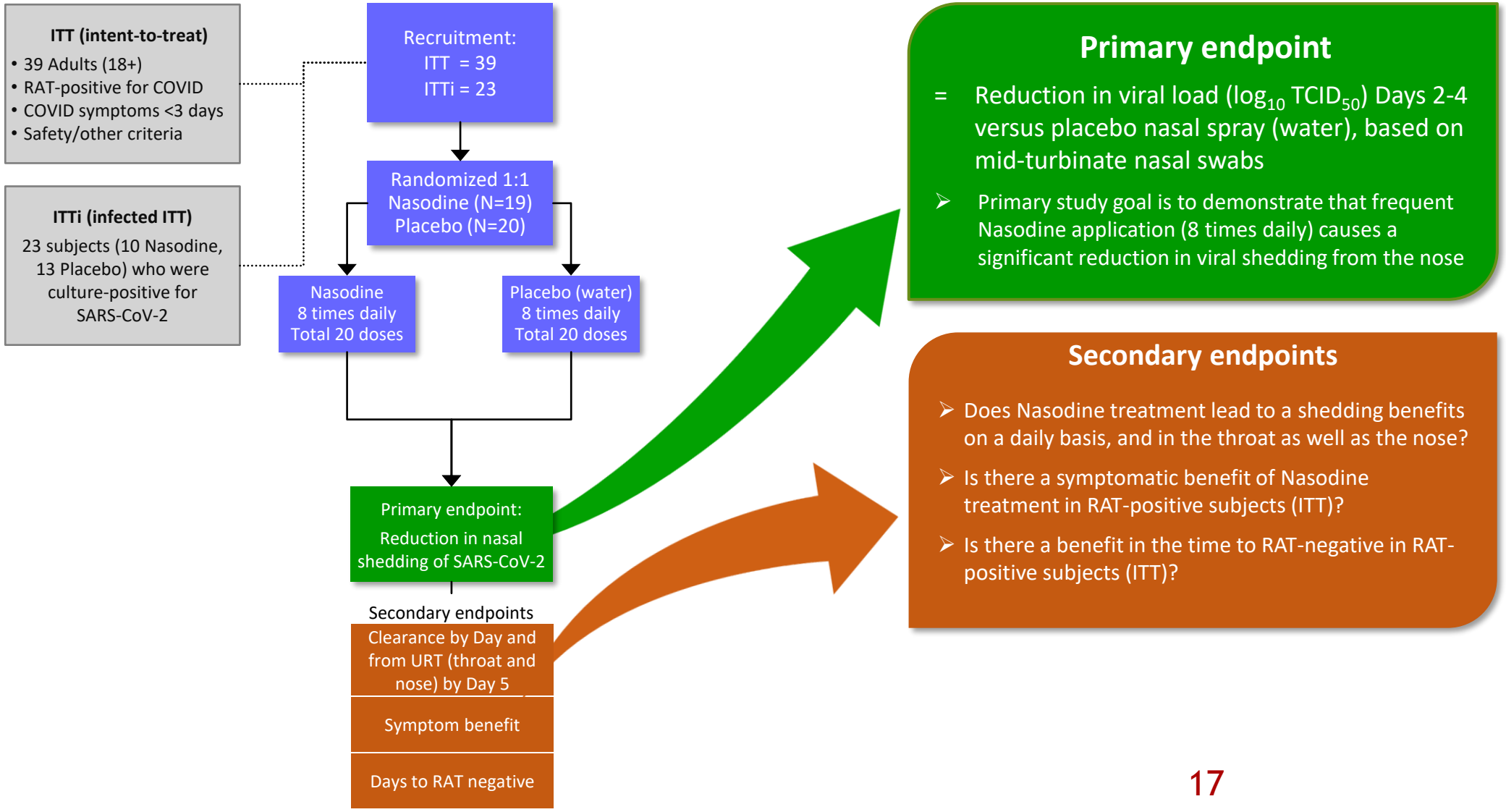
- Objective
  - To assess impact of a single dose of Nasodine on viral shedding of SARS-CoV-2 over 1 hour post-dose
- Subjects and methods
  - Enrolled 23 adults with symptoms of COVID-19; baseline nasal swabs collected for PCR and viral culture
  - All received a single dose (1.12 ml) of Nasodine, nasal swabs taken at 5, 15 and 60 minutes post-dose
  - Impact on viral load was measured by TCID50 assay in tissue culture*
- Results
  - 14 subjects proved to be PCR-positive for COVID-19 and 6 of these had culturable virus
  - 5 minutes post-dose, mean viral titre 65% below baseline; 5/6 subjects had reduced or no shedding
  - 60 minutes post-dose, mean viral titre 79% below baseline; all subjects' viral titres were below baseline
  - Confirmed in a small cohort of culture-positive subjects, that Nasodine reduced viral shedding

* PCR Ct scores are unsuitable for quantification of SARS-CoV-2, because PVP-I was shown *in vitro* to inactivate SARS-CoV-2 without affecting its RNA copy number

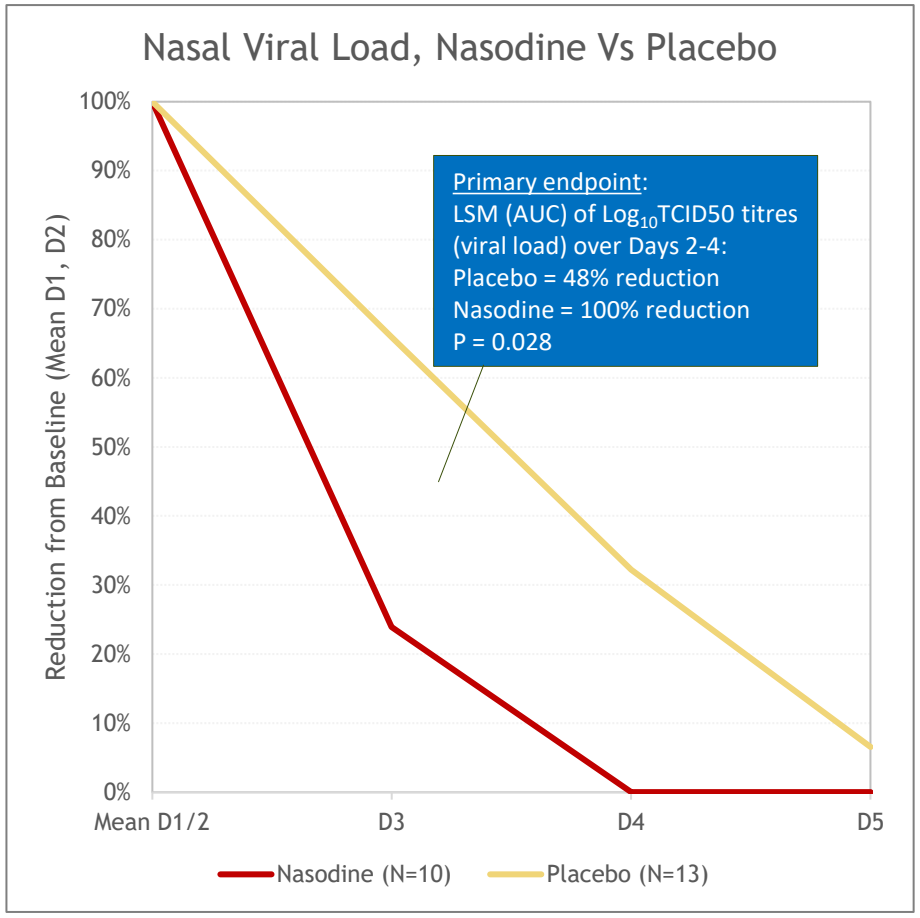
Reduction of nasal shedding of SARS-CoV-2 in COVID-19 positive patients by the use of Nasodine® (povidone-iodine 0.5%) Nasal Spray

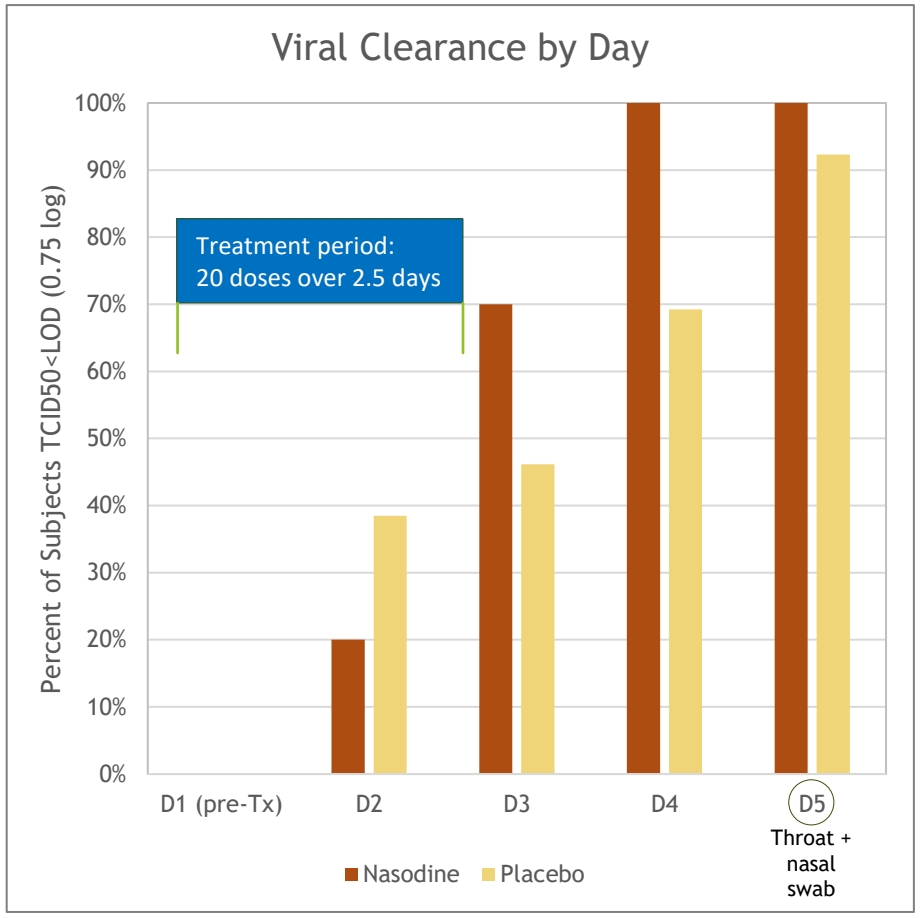
Randomised, placebo-controlled, Phase 2 trial in subjects with COVID-19 symptoms, to assess the impact of 20 doses of Nasodine on viral shedding of SARS-CoV-2 over a 5-day period

Study overview

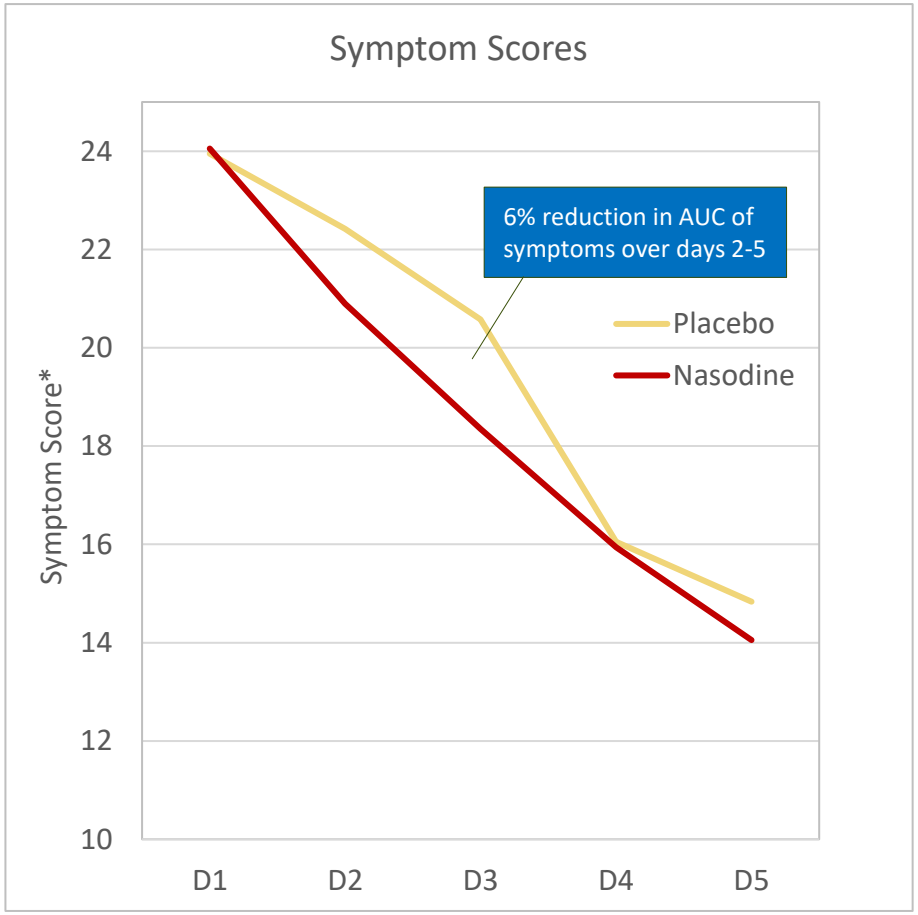


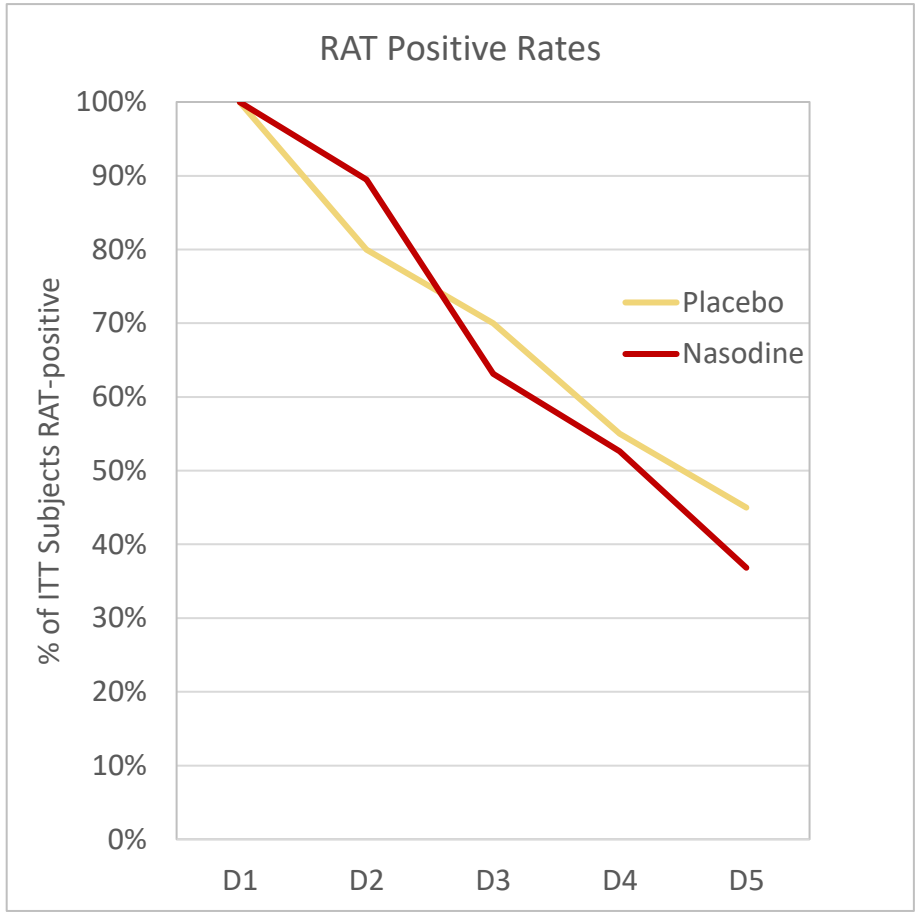
Results: Primary endpoint and clearance by day





Trial results: Symptoms and days to RAT-negative





- Based on a 10-item COVID-19 symptom severity scale consistent with US FDA Guidance for Industry (2020)

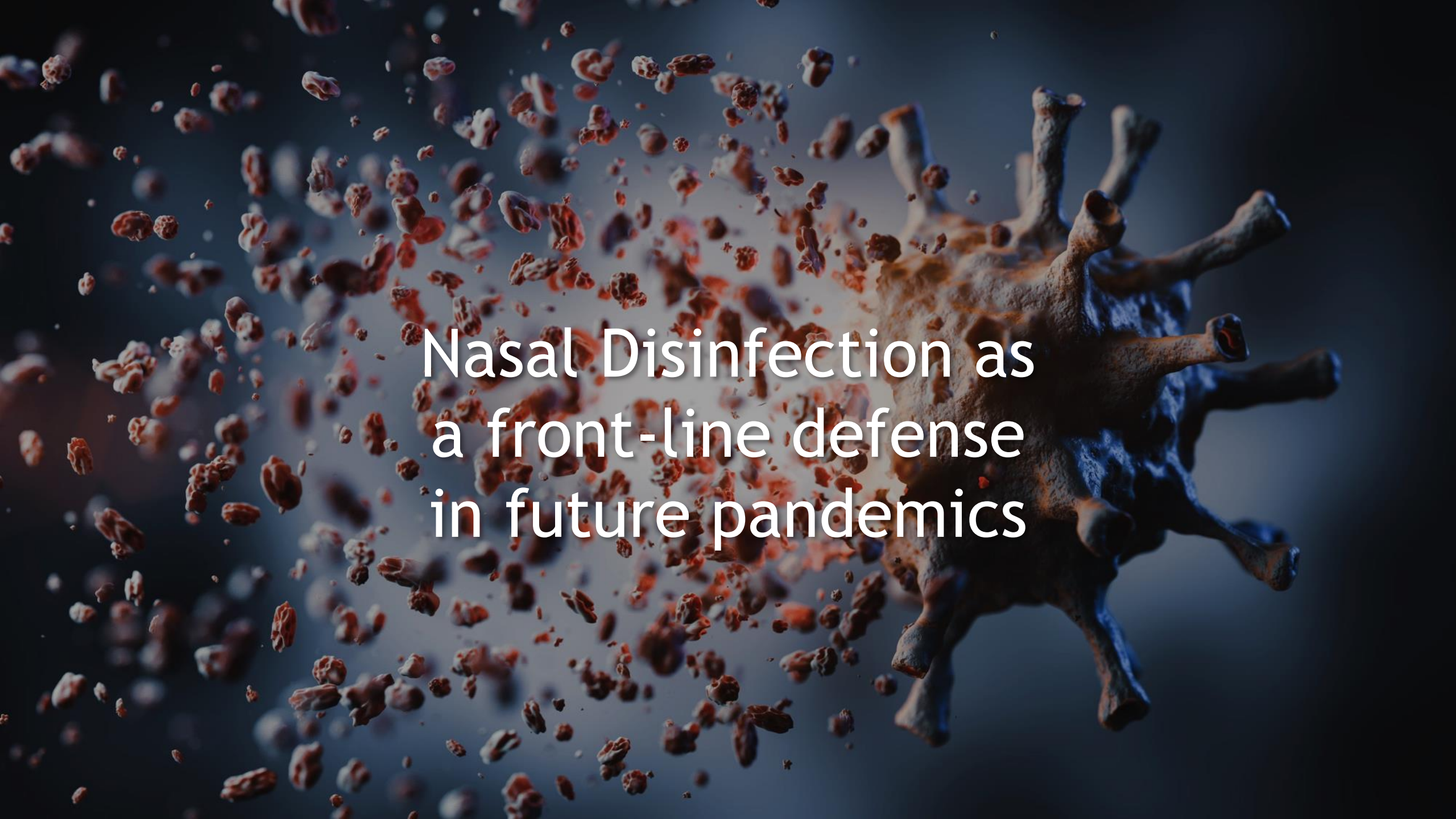
Previous studies have shown that PVP-I eliminates infectivity of SARS-CoV-2 but does not significantly affect viral RNA, so has no effect on PCR results for this virus

Key conclusions

- Primary endpoint of reduction in shedding was met (p=0.028)
- Nasodine treatment resulted in 100% reduction in viral load by day 4, after completion of the treatment regimen on day 3
- 100% of Nasodine-treated subjects had cleared the virus by day 4 based on mid-turbinate nasal swabs
- On day 5, when throat swabs were also taken, Nasodine-treated subjects had no evidence of infection; the nasal spray apparently cleared the virus from the throat as well as the nose
- There was a small positive effect (6%) on symptoms but no appreciable effect on RAT-negativity within the 5-day assessment period
- Previous human studies in healthy volunteers and those with colds confirmed safety and tolerability when used 4 times daily for 5 days at doses of 0.84-1.12 mL.
- The current study extended the safety dataset to show that it was well-tolerated when used at a dose of 1.12 mL, up 8 times daily (20 doses over 3 days)

Implications

- For COVID-19, the period of active shedding after symptom onset is 6-9 days (source: NIH); in this trial, subjects had symptoms for up to 3 days prior to enrolment, so that in most cases, there was already a natural decline in viral load occurring at start of treatment.
- It is challenging to recruit subjects early enough to make a significant impact on viral load, and through this mechanism alone, to alter clinical outcomes, such as symptoms (whether common cold or COVID-19). Although practically difficult to prove, this may not be the case in "real world" use where subjects may choose to use the nasal spray earlier
- Despite the small number of subjects in the study and a naturally declining viral load, Nasodine produced a convincing, significant reduction in viral shedding with 100% clearance by day 4
- The results support early treatment with intranasal PVP-I for maximum benefit on viral load, although impact on clinical outcomes is not established (a larger study may be required)
- The results are highly supportive of nasal disinfection with PVP-I as a productive means to reduce viral shedding and likely associated transmission risk from those infected
- The results may also support the use of nasal disinfection as a routine extension of other infection-control practices for all healthcare workers in a pandemic risk setting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