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Rapid initiation of nasal saline irrigation to reduce severity in high-risk COVID+ outpatients

Amy L Baxter, MD[1], Kyle R Schwartz, MPH[2], Ryan W Johnson, MPH, MA[3], Ann-Marie Kuchinski, PhD[1], Kevin M Swartout, PhD[4], Arni S R Srinivasa Rao, PhD[5,6], Robert W Gibson, PhD, FAOTA[1], Erica Cherian, MD[3], Taylor Giller, BA, BS[3], Houlton Boomer, BA[1], Matthew Lyon, MD[1], and Richard Schwartz, MD[1]

Abstract

Objective: To determine whether initiating saline nasal irrigation after COVID-19 diagnosis reduces hospitalization and death in high-risk outpatients compared with observational controls, and if irrigant composition impacts severity. **Methods:** Participants 55 and older were enrolled within 24 hours of a + PCR COVID-19 test between September 24 and December 21, 2020. Among 826 screened, 79 participants were enrolled and randomly assigned to add 2.5 mL povidone-iodine 10% or 2.5 mL sodium bicarbonate to 240 mL of isotonic nasal irrigation twice daily for 14 days. The primary outcome was hospitalization or death from COVID-19 within 28 days of enrollment by daily self-report confirmed with phone calls and hospital records, compared to the CDC Surveillance Dataset covering the same time. Secondary outcomes compared symptom resolution by irrigant additive. **Results:** Seventy-nine high-risk participants were enrolled (mean [SD] age, 64 [8] years; 36 [46%] women; 71% Non-Hispanic White), with mean BMI 30.3. Analyzed by intention-to-treat, by day 28, COVID-19 symptoms resulted in one ED visit and no hospitalizations in 42 irrigating with alkalinization, one hospitalization of 37 in the povidone-iodine group, (1.27%) and no deaths. Of nearly three million CDC cases, 9.47% were known to be hospitalized, with an additional 1.5% mortality in those without hospitalization data. Age, sex, and percentage with pre-existing conditions did not significantly differ by exact binomial test from the CDC dataset, while reported race and hospitalization rate did. The total risk of hospitalization or death (11%) was 8.57 times that of enrolled nasal irrigation participants (SE = 2.74; $P = .006$). Sixty-two participants completed daily surveys (78%), averaging 1.8 irrigations/day. Eleven reported irrigation-related complaints and four discontinued use. Symptom resolution was more likely for those reporting twice daily irrigation ($X^2 = 8.728$, $P = .0031$) regardless of additive. **Conclusion:** SARS-CoV-2+ participants initiating nasal irrigation were over 8 times less likely to be hospitalized than the national rate.

Keywords

COVID-19, coronavirus, SARS-COV-2, nasal lavage, povidone-iodine

Introduction

Pharmacologic and immunologic COVID-19 therapeutics seek to inhibit mechanical binding of the SARS-CoV-2 spike protein-receptor to the ACE2 receptor and spike segment furin cleavage necessary for cell entry. Sungnak et al. localized the necessary co-expression of ACE2 and protease TMPRSS2 primarily in the ciliated nasal epithelia,[1] supporting the clinical correlation of nasal viral load and severity and suggesting a location for early intervention. The increased infectiousness resulting from physical changes with viral spike

[1]Department of Emergency Medicine, Augusta University, Augusta, GA, USA
[2]Edinburgh Napier University, Edinburgh, UK
[3]Medical College of Georgia, Augusta University, Augusta, GA, USA
[4]Department of Psychology, Georgia State University, Atlanta, GA, USA
[5]Laboratory for Theory and Mathematical Modeling, Department of Medicine-Division of Infectious Diseases, Medical College of Georgia, Augusta University, Augusta, GA, USA
[6]Department of Mathematics, Augusta University, Augusta, GA, USA

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Corresponding Author:
Amy L Baxter, MD, Department of Emergency Medicine, Augusta University, 1120 15th St, Augusta, GA 30912, USA.
Email: abaxter@augusta.edu

protein mutations support a mechanical opportunity to interrupt viral particle receptor binding and entry.[2] The observation that saline can inhibit furin cleavage[3] suggests a mechanical therapeutic option—nasal irrigation—may be particularly effective against this pathogen.

Nasal irrigation under pressure, or "nasal lavage," has been demonstrated to safely reduce the duration and severity of both *Coronaviridae* and illnesses like flu with shorter incubation periods.[4-7] Repeated irrigation should be most effective for pathogens with prolonged incubation, local non-hematogenous spread, and variolation where viral load impacts severity.

Given research supporting the virucidal activity of povidone-iodine against MERS and SARS-CoV-2[8-10] and the possible impact of alkalinization to reduce SARS-CoV-1 viral cell fusion and entry,[11] patients were randomized to add alkalinization or povidone-iodine to pressurized nasal lavage. We hypothesized rapid initiation of nasal irrigation after testing positive would reduce the severity of COVID-19. Our primary outcome was COVID-19 hospitalization or death, with secondary outcomes of symptom duration, severity, and household spread.[12,13] If clinically effective, irrigation could be an inexpensive option rapidly available worldwide.

Participants and methods

High-risk outpatients aged 55 and older[14] who recently were PCR positive for SARS-CoV-2 were randomized to either 240 mL saline nasal irrigation supplemented 2.5 mL of either sodium bicarbonate or 240 mL saline nasal irrigation supplemented with 10% povidone-iodine. The comparative observational arm comprised laboratory-confirmed cases in the CDC COVID-19 Case Surveillance Dataset 50 and older during the same time interval.[15] Primary outcomes were hospitalization or death within 28 days.

Study setting and recruitment

The trial was conducted in Augusta, Georgia. Patients testing positive for COVID-19 by nasal swab or saliva PCR processed at a single lab at the Augusta University were recruited from September 24, 2020 to December 21, 2020. The 28-day follow-up was completed January 18, 2021 (See Appendix 1). The daily laboratory-generated list of COVID-19 tests was screened for age, first positive test in the system, and location within 25 miles of Augusta University. Prospective participants were called consecutively between the hours of 9:00 am through the early afternoon five to six days a week. When test results exceeded staffing, the list was randomized for calling order. Interested participants were assessed over the phone for inclusion criteria, and remote informed consent was completed per IRB policy.

Using COVID-19 precautions (masks, maintaining 6-foot physical distance, and door drop off), same-day home delivery of materials included a nasal irrigation device with 28+ day supplies, two gallon jugs of distilled water, the consent form, instructions, and the study additive (baking soda or povidone-iodine) with a 2.5 mL scoop. One of two high pressure[16] irrigation devices (NAVAGE [Rhinosystems Inc.] or Neilmed Sinus Rinse [Neilmed Inc.] was provided, alternating days for each brand.

Eligibility criteria

Participants had to be able to read the informed consent in English, agree to nasal lavage for 14 days with a 14-day follow-up, provide a back-up contact, and receive materials and initiate irrigation that day. Exclusion criteria included current supplemental oxygen therapy, unwillingness to try or current use of nasal irrigation, nasal surgery within the past year or chronic sinusitis, prior COVID-19 infection or positive test, symptoms longer than 7 days, inability to complete surveys by computer or smartphone, and allergies to iodine or shellfish.

Randomization

Participants were randomized to rinse with 240 cc saline including 0.5 mL 10% povidone-iodine (0.1% final concentration) or 2.5 mL sodium bicarbonate twice daily for 14 days. Randomization was stratified by sex in 10 blocks of 10 random numbers using Random.org. With odd numbers signifying alkaline and even povidone-iodine, numbered opaque envelopes were prepared in separate sequences for male or female participants to be opened after consent.

Main outcomes and measures

The primary outcome was hospitalization or death from COVID-19 within 28 days of enrollment, by self-report, phone calls, and the testing site hospital's electronic medical record. Secondary outcomes in enrolled participants compared symptom resolution, severity, household spread, adherence to nasal irrigation, and any impact of irrigant additive. Symptoms tracked included loss of smell or taste, fatigue, fever >100.4°F, chills, muscle aches, runny nose, cough (new onset or worsening of chronic cough), shortness of breath, nausea or vomiting, headache, abdominal pain, and diarrhea.

In addition to demographic data, after enrollment participants were asked pre-existing medical history as found on the CDC person of interest form, including Obesity, Chronic Lung disease (Emphysema, COPD), Asthma, Type 1 or 2 Diabetes, Cardiovascular Disease, Hypertension, Chronic Renal Disease, Immunocompromised, and weight and height to calculate obesity defined as BMI>30. Prompts were sent to participants via email from Qualtrics twice daily. To verify irrigation, patients uploaded pictures of used irrigation materials. An investigator called the patient or their designated

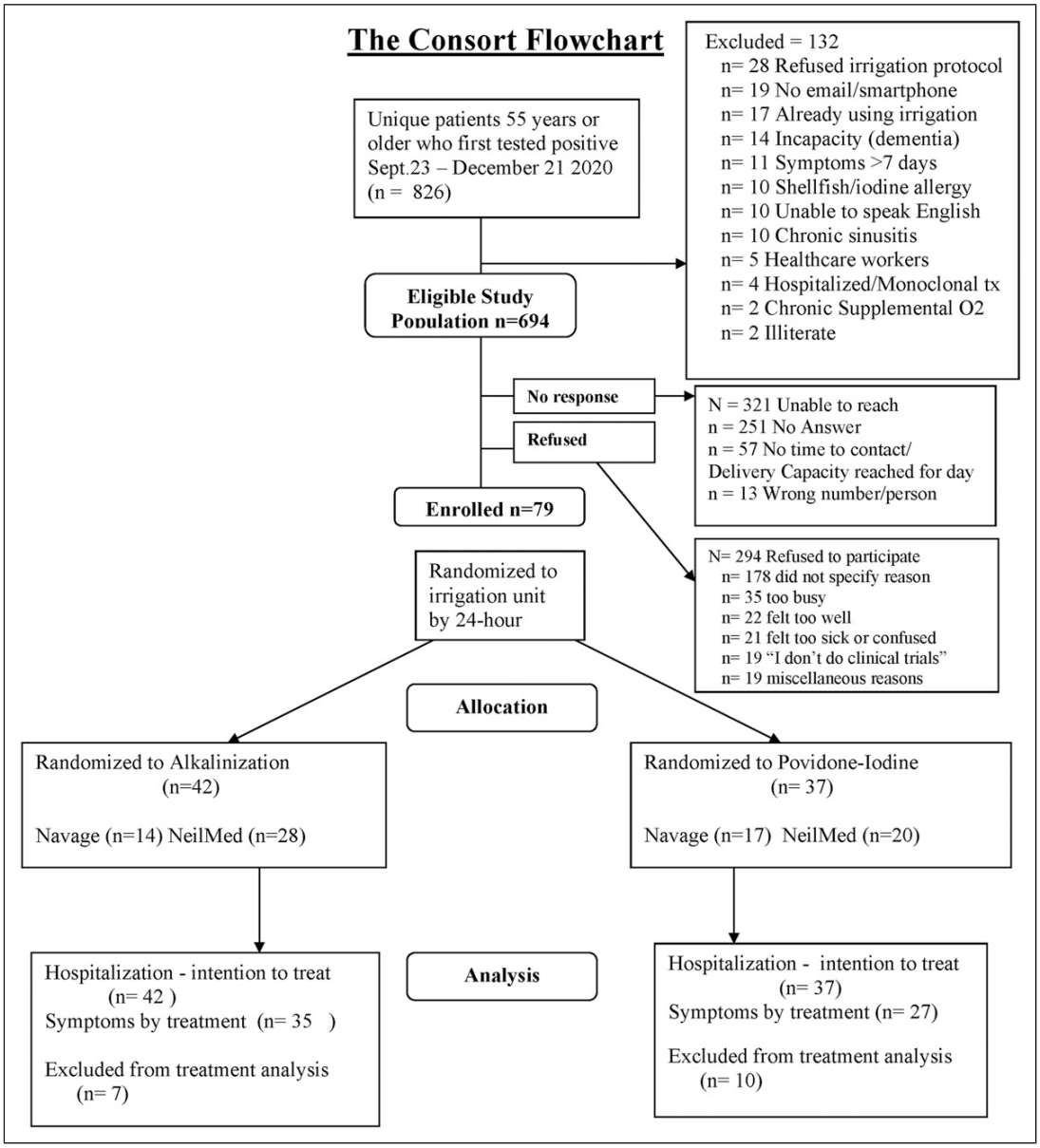

Figure 1. CONSORT diagram.

contact at day 2, 7, 14, and 28 to verify irrigation, hospitalization, or answer any questions.

Hospitalization and mortality data were compared to the National CDC Case Surveillance Public Use Dataset.[15] Twelve elements are shared with the CC for all COVID-19 cases, including date of first positive specimen, report to CDC, illness, and summary "case earliest date," laboratory-confirmed or suspected, symptom onset, and demographic data. Hospitalization, pre-existing conditions, and mortality data have four options: yes, no, unknown (marked on form), or missing (nothing recorded). Following CDC research recommendations, we matched all laboratory confirmed cases by "case earliest date" with our testing dates, and used all entries age 50+ for which hospitalization status was known.

Statistical analysis

Chi-square proportionality testing was used to evaluate differences in demographic proportions of sex, race, and age by 10-year tranche. We used an exact binomial test with Clopper–Pearson confidence intervals to compare observed hospital admission rates among participants compared with national

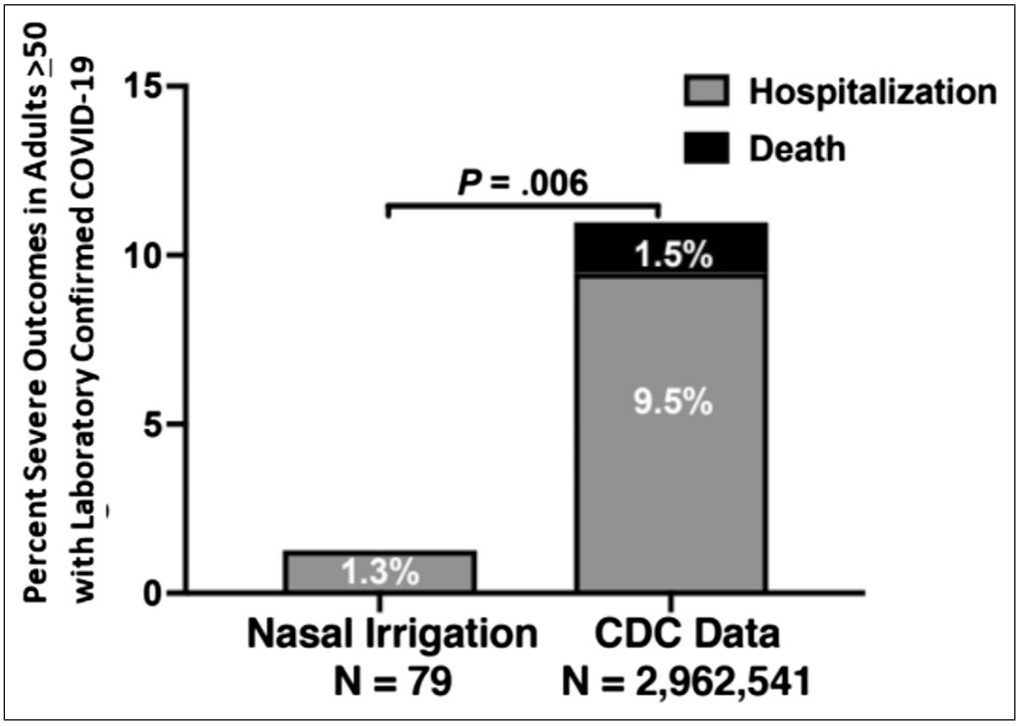

Figure 2. Percent severe outcomes in nasal irrigation group compared to CDC dataset. Percent of participants >55 in the prospective nasal irrigation group who were hospitalized compared to the number of patients age >50 in the CDC National Dataset reported hospitalized, or with death reported if hospitalization information was not reported or missing.

rates of severe disease (admission or death) published by CDC. The exact binomial test is well-suited to assess the probability of observing the proportion of participants in this study (IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp).

To avoid overestimating hospitalization rates by reporting bias, the denominator included all laboratory-confirmed cases, including when hospitalization status was missing or unreported. In addition to reported hospitalizations, we included deaths in the numerator only for confirmed cases where hospitalization was unknown or missing; did not include deaths in cases where hospitalization status was known to avoid counting outcomes with increased severity twice. As an indicator of the impact of unreported hospitalizations, we report relative risk using both this most conservative denominator (underestimating hospitalizations) and for hospitalizations using only known yes or no responses in the denominator (potential for overestimating due to reporting bias) (MedCalc Software Ltd. https://www.medcalc.org/calc/relative_risk.php (Version 20.009)).

Results

During the study period, 826 unique patients aged 55 and older who tested positive for COVID-19 were screened for study eligibility. Of the 694 eligible, 321 were unable to be reached, 294 refused participation, and 79 participants were able to be enrolled and receive irrigation materials on the day of contact (Figure 1).

Admissions occurred for 1/37 assigned to povidone-iodine and 0/42 participants in the alkalinization group (1.27%). One participant in the alkalinization group reported a COVID-19 related ED visit without admission (pre-monoclonal antibody availability), one participant reported an ED visit for a minor trauma, and one participant was admitted for a syncopal episode after resolution of COVID symptoms. These events were verified in the EHR database, confirmed with the day 28 phone call, and there were no additional ED visits or hospitalizations found in consented participants.

Between September 23, 2020 and December 21, 2020, for patients 50 years and older, of 2,962,541 laboratory-confirmed cases, 280533 (9.47%) were reported hospitalized. Complete hospitalization information was available for 45%. Where hospitalization status was unknown/missing, 44,773 deaths were reported, or 1.5%. Thus, hospitalization (or death when admission status was unknown/missing) occurred in 11%, 8.57 times the hospital admission rate of nasal irrigation participants (SE = 2.74; $P = .006$) (Figure 2). The relative risk for nasal irrigation participants was .119 (95% CI: .0169–.833, $P = .032$). Using only the 1,328,778 cases where hospitalization status was reported, the relative risk of hospitalization was .0594 (95% CI: .0085–.416, $P = .0045$) when using nasal

irrigation, with a number needed to treat of 5. For the 1,002,050 CDC cases for whom both hospitalization and death were reported, 9.18% of patients expired.

The CDC dataset only reported race for 65% of confirmed cases; those reported had a lower proportion of minority patients than enrolled irrigation participants (Table 1). There was no difference in age or sex from our population. Of the 79 enrolled, 53 participants completed the initial symptom and history questionnaire (Table 2). An online daily symptom and irrigation data collection survey was completed by 62 participants (median 12 of 14 days [IQR 5,13.75]). Of those enrolled, 68% had a pre-existing condition, 45% had multiple conditions, and the average BMI was 30.27. Participants reported a median of 3.3 days [IQR 2,5] of symptoms prior to enrollment.

Presenting symptoms present in over 50% of participants included fever, muscle aches, congestion, and headache. There were no statistical differences in symptomatic outcomes by irrigation unit used or irrigant additive. Of the 29 participants who irrigated twice daily, 23 had zero or one symptom at the end of two weeks compared to 14 of 33 participants who irrigated less often (X^2 = 8.728, p = .0031). Symptoms resolved for all but 8 participants (12.9%) over the 28 day assessment period.

Of 631 daily online surveys, participants reported irrigating once per day (7.29%), twice daily (88.43%), or none (4.25%), averaging 1.79 irrigations per day (Table 3). Participants were asked to take pictures of used irrigation materials to corroborate irrigation, but the number of used packets over time became difficult to assess for confirmation. Five participants provided compliance information at phone calls due to difficulty interfacing online. Twelve participants received their materials but did not record their first irrigation until the following day. After enrollment, 11 participants complained of discomfort or spotty epistaxis, with four discontinuing irrigation (Table 3).

Ten participants (12.7% by intention-to-treat) had household contacts who tested positive at least one day after enrollment, compared to 18.8% in a published meta-analysis.[12] There was no difference in risk of household spread by additive or irrigation unit (Table 3).

Discussion

Our results support that pressurized nasal irrigation reduces the likelihood of hospitalization in high-risk COVID-19 +

Table 1.

Participant and Dataset characteristics	Nasal irrigation (n = 79)	CDC laboratory confirmed cases (n = 2,962,541)	Proportionality test
Gender no. (%)			
Female	36 (45.6)	1,550,447 (52.7)	$X^2(1) = 1.633$; $P = 0.201$
Male	43 (54.4)	1,388,911 (47.3)	
Not reported	0	23,129	
Race no. (%)			
White	56 (70.9)	1,236,640 (68.4)[a]	
Black	14 (17.7)	154,226 (8.5)[a]	
Hispanic	1 (1.2)	366,851 (20.3)[a]	$X^2(3) = 61.32$; $P < .001$
Asian or AIAN	1 (1.2)	69,058 (3.8)[a]	
Unspecified	7 (8.9)	1,036,811 (35.0)[b]	
Hospitalization no. (%)			
Yes	1	280,533 (9.5)[b]	
No	78	1,048,245 (35.4)[b]	$X^2(1) = 18.68$; $P < .001$
Missing	0	1,220,075 (41.2)[b]	SE = 2.74; $P = .006$
Unknown	0	413,688 (14.0)[b]	
Death if hospitalization missing/unknown (%)	n/a	44,773 (2.74)*	
Age in years (SD)	63.99 (7.96)	64.27**	
50–59(%)	35(44.3)	1,240,919 (41.9)[b]	
60–69	27(34.2)	894,924 (30.2)[b]	$X^2(3) = 3.15$; $P = 0.369$
70–79	13(16.4)	496,477 (16.8)[b]	
80+	4(5)	330,221 (11.1)[b]	

*For proportionality testing, all CDC hospitalizations, and deaths only when hospitalization was not reported were combined over the total number of laboratory-confirmed cases, ie, (280,533 hospitalizations + 44,773 deaths)/2,962,541. Hospitalizations occurred in 21.1% of cases where hospitalization status was reported.

**Weighted average by midpoint of age, eg, 41.9% x 54.5 years, halfway between 50 and 59.

[a]Percentage of all laboratory confirmed patient with race/ethnicity specified.

[b]Percentage of all laboratory confirmed patients.

Table 2. All participants with completed intake surveys (n = 53).

Patient characteristics	Nasal irrigation (n = 53)	CDC laboratory confirmed cases (n = 2,962,541)
Days of illness prior [IQR]	4 (2, 6)	n/a
Age years (SD)	63.7 (8.34)	64.27
BMI kg/m^2 (SD)	30.3 (6.75)	n/a
Pre-existing condition No. (%)	Any (68)	Any (62) Yes: 236701 No: 144359 Missing data: 2556239 (87%)
Obesity by self-report	11 (20.8)	n/a
Obesity by self-report or BMI*	24 (45)	n/a
Hypertension	23 (43.4)	n/a
Asthma	3 (5.7)	n/a
Diabetes	6 (11.3)	n/a
Immunocompromised	2 (3.8)	n/a
None	17 (32)	n/a
Multiple conditions	22 (41.5)	n/a

*Mean BMI 30.3. Median 28.9 [IQR 25.6, 33.1].

Table 3. Outcomes by irrigant and unit.

Irrigator unit		
Complaint (n = 11)	Alkalinization (n = 42)	Povidone-iodine (n = 37)
Navage (Rhinosystems Inc.) (n = 31)	**+C4. Pain, spotting***	C3. Spotting C10. "Burning"
Neilmed (Neilmed Inc.) n = 48	**C2. "Nose too clean", unpleasant water up nose feeling, no pain.** **C6. Spotting** C8. Spotting **C11. Device discomfort**	C1. Pain C5. "Irritation" C7. "Stinging" C9. "Mild burning"
Daily Reporting (n = 62)	**Alkalinization** (n = 35)	**Povidone-Iodine** (n = 27)
Irrigation compliance		
Navage (n = 28)	1.78	1.82
Neilmed (n = 34)	1.73	1.82
Households with new cases		
Navage (n = 28)%	1	2
Neilmed (n = 34)%	5	2
Clinical outcome		
Hospitalization	0	1
ED visit	1	0

There were no significant differences between irrigant and device.
+Patients who discontinued irrigation highlighted in bold.
*Four patients noted spotting (mild epistaxis or fluid tinged with blood).

outpatients, suggesting a safe and over the counter measure with potentially vital public health impact. The reduction from 11 to 1.3% as of November 2021 would have corresponded in absolute terms to over 1,000,000 fewer older Americans requiring admission. If confirmed in other studies, the potential reduction in morbidity and mortality worldwide could be profound.

A dose response was noted with twice daily irrigation, with 80% of those irrigating twice daily having zero or one mild symptom, compared to 42% of those irrigating less frequently. While one study found almost half of those 50 and older had continued symptoms 14–21 days after diagnoses,[17,18] only 13% of participants in our study had symptoms at day 28.

Clinically ancestral COVID-19 differ notably from previous *Coronaviridae*: children are less impacted; obesity, diabetes, African American race, and hypertension are independent risk factors; the relatively pathognomonic symptom of anosmia is present in up to 80% of patients[19,20]; and the duration from infection to severe symptoms is prolonged.

The clinical differences in presentation reflect SARS-CoV-2's primarily nasal entry and nasopharyngeal replication. Olfactory neuroepithelium ACE2 is expressed at 700 times the expression in lungs.[20,21] Conditions increasing nasal ACE2 expression (obesity, hypertension, and pollution) or sinus size (age and male sex) correlate with increased severity, further supporting targeting viral fusion in the nasopharynx.[22-26] In contrast, populations lacking fully developed sinus area (children), with a high baseline practice of nasal irrigation (Laos, Vietnam), or higher mask compliance have decreased severity.[27,28] Together, the nasal cavity size, ACE2 expression and variolation explanation could account for lower pediatric severity and spread.[29] The degree of methylation of the ACE2 receptors (and thus stiffness and ease of viral attachment) is related to both race and epigenetic stress.[30,31] Thus, increased virulence correlating with increased area, quantity, and stability of the spike proteins supports the mechanical target hypothesis.

Given the local cell-to-cell rather than hematogenous spread and delay in activation of lung TMPRRS2,[32] mechanically debriding viral particles lodged in the ACE2 receptor, but not yet fused, could reduce severity. Furthermore, the variation in severity with methylation implies that not all particles become securely attached.[31] The size variations in the entire nasal cavity, rather than just anterior nares, support the concept that full nasal cavity irrigation may be superior to nasal spray. Finally, the number of asymptomatic cases and the correlation of illness severity with viral load implied that even after PCR positivity, a window exists wherein lowering the infectiousness or viral load through irrigation could be clinically advantageous.

Ignaz Semmelweis pioneered handwashing to remove bacteria in 1847. In emergency medicine and surgery, debriding infectious material with copious high-powered irrigation is standard practice. While nasal irrigation reduced symptoms of other *Coronaviridae*, flu,[4] and bacterial carriage in otolaryngology,[33,34] pathology from local spread and aspiration and the continued production of viral load locally suggest a potentially greater impact on COVID-19. Association of viral load with severity[28,35,36] suggests a different kind of cumulative pathology related to immune response, as well as the potential for reducing severity after the fact by debridement. Multiple studies have demonstrated immediate viral load reductions in vitro and in vivo with direct oral or nasal application of antivirals,[8-10] or the theoretical benefit of lavaging and gargling.[37-39] One study of povidone-iodine gargles and sprays in 24 participants did not show a significant reduction in viral load, but the age difference of 23 years between control and intervention groups calls randomization into question.[40]

The focus on viral load may be too narrow a measure when clinical outcomes matter. An interim analysis of a twice daily nasal irrigation trial in 45 adults showed a significant reduction in symptom duration.[18] The final analysis of 72 enrolled patients, however, focused exclusively on the failure of additive surfactant to be virucidal. It reported the pharmacokinetic failure of the intervention to reduce viral load but did not discuss the apparently superior resolution of clinical symptoms apart from one graph without statistical parameters.[41] Huijghebaert et al raise multiple plausible mechanisms by which a salinated nasal biome might reduce symptoms irrespective of viral load: improved mucociliary clearance, reduced risk of microaspiration, and two mechanisms reducing viral ACE2/TMPRSS2 uptake, reduced furin cleavage and shunting viral particles to the mucosal surface.[42] A study of 170 hospital workers found only 1.2% of those doing oral and nasal rinses became symptomatic and PCR positive, compared to 12.7% in the control group ($P = 0.0039$).[43] The fact that the rinse group was older and had more co-morbidities may imply spot-checked viral load is not synonymous with symptom severity.

To our knowledge, this is the largest prospective clinical trial using both twice daily large volume irrigation with a virucidal arm and with documented adherence to irrigation. Moreover, the older and higher risk population in this study may be most relevant to reducing morbidity and mortality.

Limitations

The primary limitations to our study are generalizability and risk of bias in the comparison dataset. Without a matched control group, our sample may differ from the CDC database. Sex and age were not significantly different, but too many entries in the CDC dataset were missing race/ethnicity and pre-existing conditions to meaningfully evaluate. However, where there were differences, our sample was historically more at risk: obesity prevalence exceeded the national average, and over 25% of our participants were Black or did not want to report race, almost double the national average.

The greatest risk of bias comes from preferential reporting of cases with hospitalization or death to the CDC dataset, artificially raising the appearance of severity.[44] Mortality rates are likely to be over-reported compared to the general population. However, our conservatively calculated CDC admission rate of 9.47% reflects the outcomes in other prospective randomized controlled trials: in a younger, thinner group of participants described as high risk (average age 50 and BMI 29), fluvoxamine reduced hospitalization or death from 16% to 11%.[45] In a healthier cohort evaluating monoclonal antibodies, Chen et al found a 15% admission rate in participants 65+ or with BMI > 35, similar to our population

with average age 64 and BMI >30.[46] Socioeconomic challenges and larger minority populations have higher admission rates. In a similar health system to ours, Price-Haywood et al found a 39.7% admission rate; a Cochrane database of minority patients' admission rates in similar time periods and demographic location to our enrollment period consistently found admission rates as high as 60%.[47,48]

While irrigation could be an effective mechanical protection against variants in vaccinated people, adoption of a new hygiene intervention—or any intervention—is a barrier. Of the 537 patients contacted, 28 (5.2%) did not want to perform nasal irrigation. Of those who initiated irrigation, most continued twice daily use, but 11 had concerns about irrigating that were communicated to our staff. While only four discontinued irrigation, without the frequent calls and coaching adherence in the general population could be lower. The need for boiled, distilled, or filtered water to prevent amoebic *N fowleri* infection[49] could also be ignored, introducing a new risk. In addition, much older patients may have an increased potential for aspiration or could require assistance increasing the risk for their caregivers.

Our study was underpowered to detect improvement by additive. While low povidone-iodine concentrations are safe up to 5 months,[7] studies using tenfold higher concentrations for gargling noted transient thyroid stimulating hormone changes.[40] For prolonged use, thyroid function testing may be warranted. Studies of alkalinity have not supported efficacy in reducing viral fusion, however recent evaluation of the Omicron variant suggest hypertonic saline may add benefit to irrigation.[3]

Huijghebaert et al suggest multiple mechanisms for symptom reduction with saline irrigation.[42] While our study did show a dose response with irrigation and symptom resolution, some of this may be that those who reported more regularly were either less sick or more medically adherent overall. Prospective research on currant variants with different dosing in allocation arms is needed to confirm this finding.

Conclusion

As an intervention, pressurized nasal irrigation showed promise to reduce the severity of COVID-19 infection in high-risk patients when initiated within 24 hours of a positive test. As large unvaccinated populations pressure evolution of variants, an effective mechanical outpatient intervention to reduce viral entry and hospitalizations can save lives and reduce the stress on hospital staff. Irrigation is simple and standard of care in many developing countries where the population is too remote for rapid access to medical care. Because device instruction is available on the internet, and coaching can be done remotely, this is a feasible and inexpensive treatment for remote areas, as a preventative or in the context of rapid antigen testing.

Further research into the frequency and adjuvants of irrigation will be important not just for this pandemic, but for future viruses to come.

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Declaration of conflicting interests

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Ethical approval

The study was approved by the institutional review board at Augusta University in Augusta, Georgia and was registered at ClinicalTrials.gov NCT04559035.

Informed consent

Verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

ORCID iDs

Amy L Baxter https://orcid.org/0000-0001-7123-0733
Taylor Giller https://orcid.org/0000-0002-0350-8243
Richard Schwartz https://orcid.org/0000-0003-0947-3034

Supplemental Material

Supplemental material for this article is available online.

References

1. Sungnak W, Huang N, Becavin C, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nat Med*. 2020;26:681-687.
2. Scudellari M. How the coronavirus infects cells - and why Delta is so dangerous. *Nature*. 2021;595(7869):640-644.
3. Li C, Li AW. Hypertonic saline and aprotinin based blockage of SARS-CoV-2 specific furin site cleavage by inhibition of nasal protease activity. *bioRxiv*. 2021.
4. Ramalingam S, Graham C, Dove J, Morrice L, Sheikh A. A pilot, open labelled, randomised controlled trial of hypertonic saline nasal irrigation and gargling for the common cold. *Sci Rep*. 2019;9(1):1015.
5. Burton MJ, Clarkson JE, Goulao B, et al. Antimicrobial mouthwashes (gargling) and nasal sprays administered to patients with suspected or confirmed COVID-19 infection to

improve patient outcomes and to protect healthcare workers treating them. *Cochrane Database Syst Rev*. 2020;9:Cd013627.
6. Farrell NF, Klatt-Cromwell C, Schneider JS. Benefits and safety of nasal saline irrigations in a pandemic-washing COVID-19 away. *JAMA Otolaryngol Head Neck Surg*. 2020;146(9): 787-788.
7. Frank S, Capriotti J, Brown SM, Tessema B. Povidone-iodine use in sinonasal and oral cavities: a review of safety in the COVID-19 Era. *Ear Nose Throat J*. 2020;99(9):586-593.
8. Eggers M, Eickmann M, Zorn J. Rapid and effective virucidal activity of povidone-iodine products against middle east respiratory syndrome coronavirus (MERS-CoV) and modified vaccinia virus ankara (MVA). *Infect Dis Therapy*. 2015;4(4): 491-501.
9. Eggers M, Koburger-Janssen T, Eickmann M, Zorn J. In vitro bactericidal and virucidal efficacy of povidone-iodine gargle/mouthwash against respiratory and oral tract pathogens. *Infect Dis Therapy*. 2018;7(2):249-259.
10. Pelletier JS, Tessema B, Frank S, Westover JB, Brown SM, Capriotti JA. Efficacy of povidone-iodine nasal and oral antiseptic preparations against severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). *Ear Nose Throat J*. 2020;2020: 145561320957237.
11. Gallagher TM, Escarmis C, Buchmeier MJ. Alteration of the pH dependence of coronavirus-induced cell fusion: effect of mutations in the spike glycoprotein. *J Virol*. 1991;65(4):1916-1928.
12. Lei H, Xu X, Xiao S, Wu X, Shu Y. Household transmission of COVID-19-a systematic review and meta-analysis. *J Infect*. 2020;81(6):979-997.
13. Madewell ZJ, Yang Y, Longini IM, Halloran ME, Dean NE. Household transmission of SARS-CoV-2: a systematic review and meta-analysis of secondary attack rate. *medRxiv*. 2020.
14. Levin AT, Hanage WP, Owusu-Boaitey N, Cochran KB, Walsh SP, Meyerowitz-Katz G. Assessing the age specificity of infection fatality rates for COVID-19: systematic review, meta-analysis, and public policy implications. *Eur J Epidemiol*. 2020; 35(12):1123-1138.
15. Control CfD. *CDC COVID-19 Case Surveillance Public Use Data*. Centers for Disease Control. https://data.cdc.gov/Case-Surveillance/COVID-19-Case-Surveillance-Public-Use-Data/vbim-akqf/data (Accessed 20 August 2021).
16. Piromchai P, Puvatanond C, Kirtsreesakul V, Chaiyasate S, Thanaviratananich S. Effectiveness of nasal irrigation devices: a Thai multicentre survey. *PeerJ*. 2019;7:e7000. doi:10.7717/peerj.7000
17. Tenforde MW, Kim SS, Lindsell CJ, et al. Symptom Duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network - United States, March-June 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(30):993-998.
18. Kimura KS, Freeman MH, Wessinger BC, et al. Interim analysis of an open-label randomized controlled trial evaluating nasal irrigations in non-hospitalized patients with coronavirus disease 2019. *Int Forum Allergy Rhinol*. 2020;10(12):1325-1328.
19. Meng X, Deng Y, Dai Z, Meng Z. COVID-19 and anosmia: A review based on up-to-date knowledge. *Am J Otolaryngol*. 2020;41(5):102581.
20. Chen M, Shen W, Rowan NR, et al. Elevated ACE-2 expression in the olfactory neuroepithelium: implications for anosmia and upper respiratory SARS-CoV-2 entry and replication. *Eur Respir J*. 2020;56(3):1948.
21. Hou YJ, Okuda K, Edwards CE, et al. SARS-CoV-2 reverse genetics reveals a variable infection gradient in the respiratory tract. *Cell*. 2020;182(2):429-446.
22. Palaiodimos L, Kokkinidis DG, Li W, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. *Metabolism*. 2020;108:154262.
23. Radzikowska U, Ding M, Tan G, et al. Distribution of ACE2, CD147, CD26, and other SARS-CoV-2 associated molecules in tissues and immune cells in health and in asthma, COPD, obesity, hypertension, and COVID-19 risk factors. *Allergy*. 2020;75(11):2829-2845.
24. Loftus PA, Wise SK, Nieto D, Panella N, Aiken A, DelGaudio JM. Intranasal volume increases with age: Computed tomography volumetric analysis in adults. *Laryngoscope*. 2016; 126(10):2212-2215.
25. Brandt EB, Beck AF, Mersha TB. Air pollution, racial disparities, and COVID-19 mortality. *J Allergy Clin Immunol*. 2020;146(1):61-63.
26. Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. JAMA. 2020;323(23):2427-2429.
27. Likus W, Bajor G, Gruszczyńska K, Baron J, Markowski J. Nasal region dimensions in children: a CT study and clinical implications. *BioMed Res Int*. 2014;2014:125810.
28. Gandhi M, Rutherford GW. Facial masking for Covid-19––potential for "variolation" as we await a vaccine. *N Engl J Med*. 2020;383(18):e101.
29. Viner RM, Mytton OT, Bonell C, et al. Susceptibility to SARS-CoV-2 infection among children and adolescents compared with adults: a systematic review and meta-analysis. *JAMA Pediatr*. 2020;2020:25.
30. Keeler JA, Patki A, Woodard CR, Frank-Ito DO. A computational study of nasal spray deposition pattern in four ethnic groups. *J Aerosol Med Pulmonary Drug Deliv*. 2016;29(2): 153-166.
31. Cardenas A, Rifas-Shiman SL, Sordillo JE, et al. DNA methylation architecture of the ACE2 gene in nasal cells of children. *Sci Rep*. 2021;11(1):7107.
32. Sajuthi SP, DeFord P, Jackson ND, et al. Type 2 and interferon inflammation strongly regulate SARS-CoV-2 related gene expression in the airway epithelium. *bioRxiv*. 2020.
33. Panchmatia R, Payandeh J, Al-Salman R, et al. The efficacy of diluted topical povidone-iodine rinses in the management of recalcitrant chronic rhinosinusitis: a prospective cohort study. *Eur Arch Oto-Rhino-Laryngol*. 2019;276(12):3373-3381.

34. Rieser GR, Moskal JT. Cost efficacy of methicillin-resistant *Staphylococcus aureus* decolonization with intranasal povidone-iodine. *J Arthroplasty*. 2018;33(6):1652-1655.
35. Faíco-Filho KS, Passarelli VC, Bellei N. Is higher viral load in SARS-CoV-2 associated with death? *Am J Trop Med Hyg*. 2020; 103(5):2019-2021.
36. Goyal A, Reeves DB, Cardozo-Ojeda EF, Schiffer JT, Mayer BT. Wrong person, place and time: viral load and contact network structure predict SARS-CoV-2 transmission and superspreading events. *medRxiv*. 2020.
37. Khan MM, Parab SR, Paranjape M. Repurposing 0.5% povidone iodine solution in otorhinolaryngology practice in Covid-19 pandemic. *Am J Otolaryngol*. 2020;41(5):102618.
38. Radulesco T, Lechien JR, Saussez S, Hopkins C, Michel J. Safety and impact of nasal lavages during viral infections such as SARS-CoV-2. *Ear Nose Throat J*. 2021;100(2_suppl):188s-191s.
39. Panta P, Chatti K, Andhavarapu A. Do saline water gargling and nasal irrigation confer protection against COVID-19? *Explore*. 2021;17(2):127-129.
40. Guenezan J, Garcia M, Strasters D, et al. Povidone iodine mouthwash, gargle, and nasal spray to reduce nasopharyngeal viral load in patients with COVID-19: A randomized clinical trial. *JAMA Otolaryngol Head Neck Surg*. 2021;147(4):400-401.
41. Esther CR, Kimura KS, Mikami Y, et al. Pharmacokinetic-based failure of a detergent virucidal for severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) nasal infections: A preclinical study and randomized controlled trial. *Int Forum Allergy Rhinol*. 2022.
42. Huijghebaert S, Hoste L, Vanham G. Essentials in saline pharmacology for nasal or respiratory hygiene in times of COVID-19. *Eur J Clin Pharmacol*. 2021;77(9):1275-1293.
43. Gutiérrez-García R, De La Cerda-Ángeles JC, Cabrera-Licona A, Delgado-Enciso I, Mervitch-Sigal N, Paz-Michel BA. Nasopharyngeal and oropharyngeal rinses with neutral electrolyzed water prevents COVID-19 in front-line health professionals: A randomized, open-label, controlled trial in a general hospital in Mexico City. *Biomed Rep*. 2022;16(2):11.
44. Krantz SG, Rao A. Level of underreporting including underdiagnosis before the first peak of COVID-19 in various countries: Preliminary retrospective results based on wavelets and deterministic modeling. *Infect Control Hosp Epidemiol*. 2020; 41(7):857-859.
45. Reis G, Dos Santos Moreira-Silva EA, Silva DCM, et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. *Lancet Glob Health*. 2021;10:E42-E51.
46. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. *N Engl J Med*. 2021;384(3):229-237.
47. Mackey K, Ayers CK, Kondo KK, et al. Racial and ethnic disparities in COVID-19-related infections, hospitalizations, and deaths: a systematic review. *Ann Intern Med*. 2021;174(3): 362-373.
48. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and mortality among black patients and white patients with Covid-19. *N Engl J Med*. 2020;382(26):2534-2543.
49. Yoder JS, Straif-Bourgeois S, Roy SL, et al. Primary amebic meningoencephalitis deaths associated with sinus irrigation using contaminated tap water. *Clin Infect Dis*. 2012;55(9): e79-85.