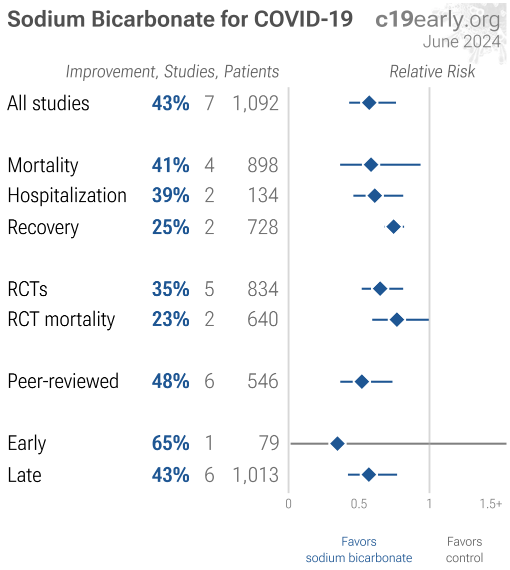
Sodium Bicarbonate for COVID-19: real-time meta analysis of 7 studies

@CovidAnalysis, June 2024, Version 1
https://c19early.org/sbmeta.html

Abstract



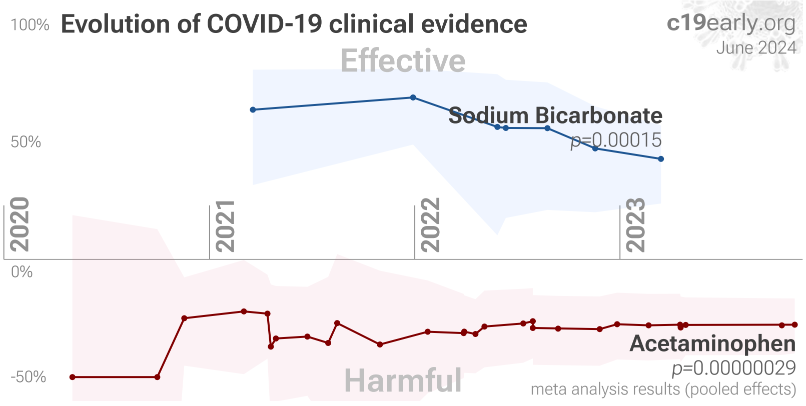
Statistically significant lower risk is seen for mortality, hospitalization, and recovery. 6 studies from 5 independent teams in 5 countries show significant improvements.

Meta analysis using the most serious outcome reported shows 43% [24-57%] lower risk. Results are similar for Randomized Controlled Trials and peer-reviewed studies. Early treatment is more effective than late treatment.

SARS-CoV-2 requires acidic pH for fusion[1]. Alkalinization of the respiratory mucosa may reduce risk.

No treatment or intervention is 100% effective. All practical, effective, and safe means should be used based on risk/benefit analysis. Multiple treatments are typically used in combination, and other treatments may be more effective. We also present an analysis covering other alkalinization treatments[2]. Sodium Bicarbonate may affect the natural microbiome, especially with prolonged use.

All data to reproduce this paper and sources are in the appendix. *Shafiee* present another meta analysis for sodium bicarbonate, showing significant improvements for mortality and recovery.



SODIUM BICARBONATE FOR COVID-19 — HIGHLIGHTS

Sodium Bicarbonate reduces risk with very high confidence for pooled analysis, high confidence for mortality, and low confidence for hospitalization and recovery.

Outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor.

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 74 treatments.

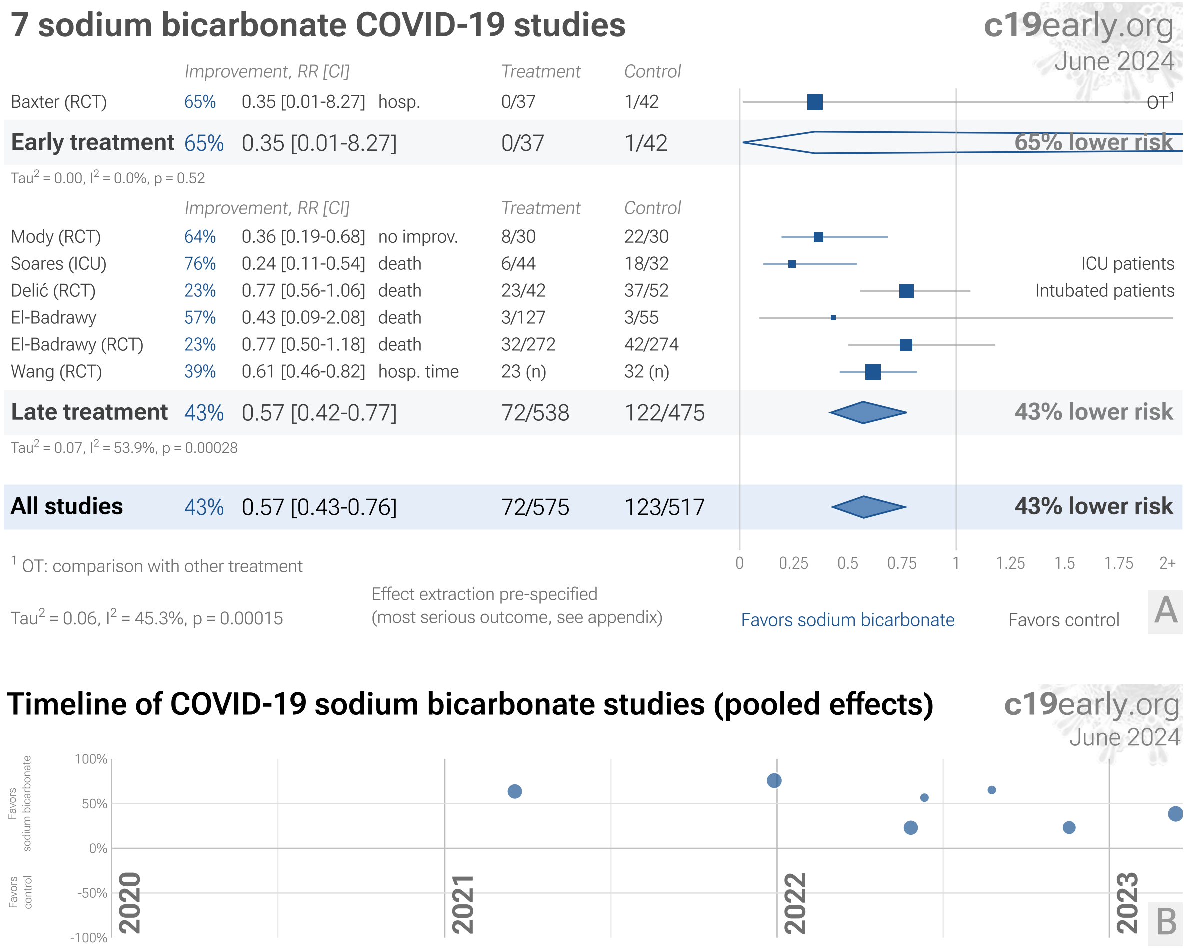


***Figure 1.* A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in sodium bicarbonate studies.**

Introduction

Immediate treatment recommended. SARS-CoV-2 infection typically starts in the upper respiratory tract, and specifically the nasal respiratory epithelium. Entry via the eyes and gastrointestinal tract is possible, but less common, and entry via other routes is rare. Infection may progress to the lower respiratory tract, other tissues, and the nervous and cardiovascular systems. The primary initial route for entry into the central nervous system is thought to be the olfactory nerve in the nasal cavity[4]. Progression may lead to cytokine storm, pneumonia, ARDS, neurological injury[5-10] and cognitive deficits[7], cardiovascular complications[11], organ failure, and death. Minimizing replication as early as possible is recommended. Logically, stopping replication in the upper respiratory tract should be simpler and more effective. Early or prophylactic nasopharyngeal/oropharyngeal treatment can avoid the consequences of viral replication in other tissues, and avoid the requirement for systemic treatments with greater potential for side effects.

Many treatments are expected to modulate infection. SARS-CoV-2 infection and replication involves the complex interplay of 50+ host and viral proteins and other factors[A,12-16], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 7,000 compounds may reduce COVID-19 risk[17], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Acidic pH enhances infection, alkalinization may inhibit infection. *Kreutzberger et al.* showed that SARS-CoV-2 requires acidic pH for fusion. The mean pH of the airway-facing surface of the nasal cavity was 6.6, compatible with fusion, while pH is neutral in other parts of the nasopharyngeal cavity and in the lung[18], suggesting no viral fusion in those locations prior to endocytic uptake. *Liu et al.* found that a more acidic pH significantly increased SARS-CoV-2 pseudovirus infection and cell surface ACE2 levels, mediated by pH-dependent inhibition of actin polymerization. Treatments that increase the pH of respiratory mucosa may inhibit fusion and reduce risk for COVID-19.

Analysis. We analyze all significant controlled studies of sodium bicarbonate for COVID-19. Search methods, inclusion criteria, effect extraction criteria (more serious outcomes have priority), all individual study data, PRISMA answers, and statistical methods are detailed in Appendix 1. We present random effects meta-analysis results for all studies, studies within each treatment stage, individual outcomes, peer-reviewed studies, and Randomized Controlled Trials (RCTs).

Treatment timing. Figure 2 shows stages of possible treatment for COVID-19. **Prophylaxis** refers to regularly taking medication before becoming sick, in order to prevent or minimize infection. **Early Treatment** refers to treatment immediately or soon after symptoms appear, while **Late Treatment** refers to more delayed treatment.

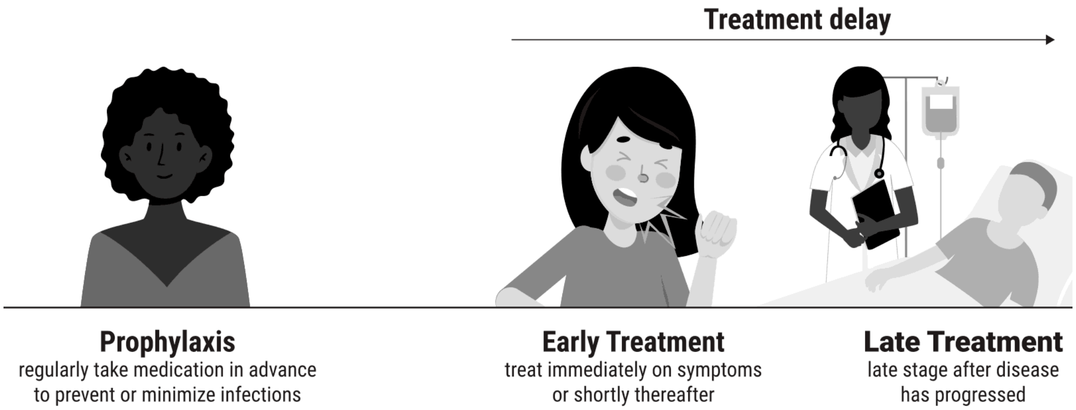


Figure 2. Treatment stages.

Results

Table 1 summarizes the results for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, and for specific outcomes. Table 2 shows results by treatment stage. Figure 3 plots individual results by treatment stage. Figure 4, 5, 6, 7, 8, and 9 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, hospitalization, progression, recovery, and peer reviewed studies.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	43% [24-57%] ***	7	1,092	69
Peer-reviewed studies	48% [26-63%] ***	6	546	62
Randomized Controlled Trials	35% [19-48%] ***	5	834	45
Mortality	41% [6-63%] *	4	898	43
Hospitalization	39% [19-54%] ***	2	134	25
Recovery	25% [18-32%] ****	2	728	14
RCT mortality	23% [0-41%] *	2	640	19

Table 1. **Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, and for specific outcomes.** Results show the percentage improvement with treatment and the 95% confidence interval. * $p<0.05$ *** $p<0.001$ **** $p<0.0001$.

	Early treatment	*Late treatment*
All studies	65% [-727-99%]	43% [23-58%] ***
Peer-reviewed studies	65% [-727-99%]	48% [25-64%] ***
Randomized Controlled Trials	65% [-727-99%]	35% [17-50%] ***
Mortality		41% [6-63%] *
Hospitalization	65% [-727-99%]	39% [18-54%] ***
Recovery		25% [18-32%] ****
RCT mortality		23% [0-41%] *

Table 2. **Random effects meta-analysis results by treatment stage.** Results show the percentage improvement with treatment, the 95% confidence interval, and the number of studies for the stage. * $p<0.05$ *** $p<0.001$ **** $p<0.0001$.

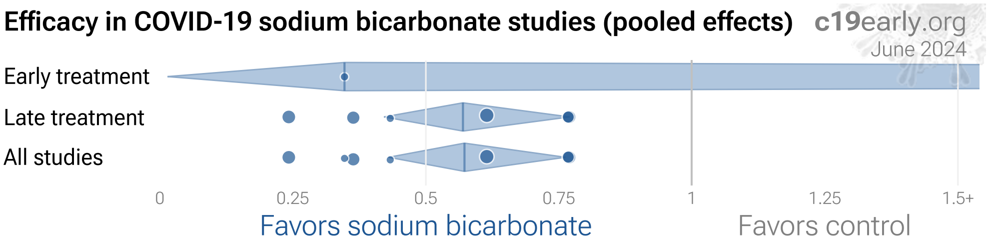
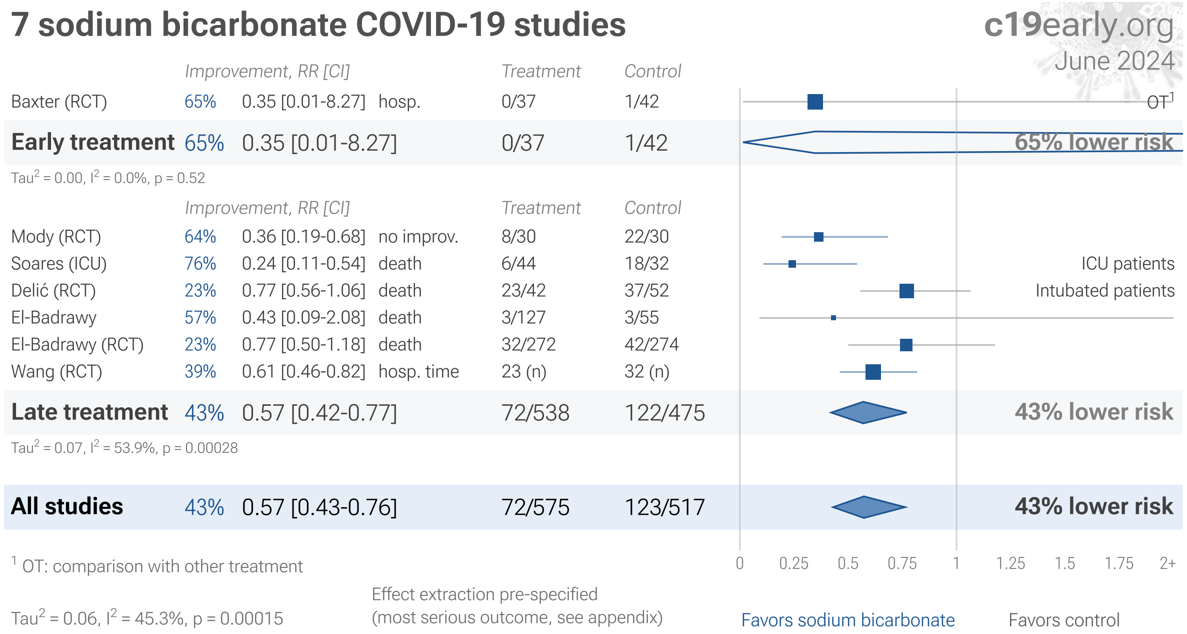


Figure 3. **Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.



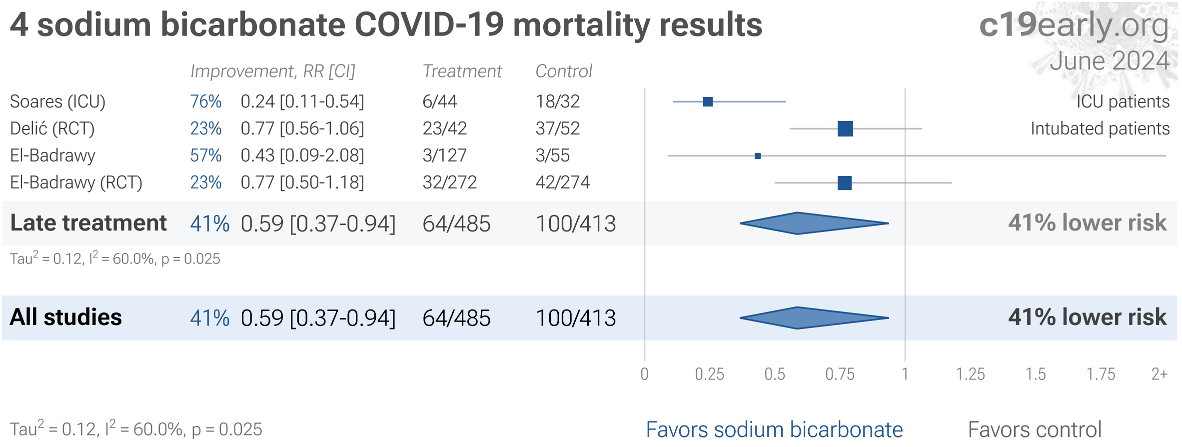
	Improvement, RR [CI]			Treatment	Control
Baxter (RCT)	65%	0.35 [0.01-8.27]	hosp.	0/37	1/42
Early treatment	65%	0.35 [0.01-8.27]		0/37	1/42
Tau² = 0.00, I² = 0.0%, p = 0.52					
Mody (RCT)	64%	0.36 [0.19-0.68]	no improv.	8/30	22/30
Soares (ICU)	76%	0.24 [0.11-0.54]	death	6/44	18/32
Delić (RCT)	23%	0.77 [0.56-1.06]	death	23/42	37/52
El-Badrawy	57%	0.43 [0.09-2.08]	death	3/127	3/55
El-Badrawy (RCT)	23%	0.77 [0.50-1.18]	death	32/272	42/274
Wang (RCT)	39%	0.61 [0.46-0.82]	hosp. time	23 (n)	32 (n)
Late treatment	43%	0.57 [0.42-0.77]		72/538	122/475
Tau² = 0.07, I² = 53.9%, p = 0.00028					
All studies	43%	0.57 [0.43-0.76]		72/575	123/517

[1] OT: comparison with other treatment

Tau² = 0.06, I² = 45.3%, p = 0.00015

Effect extraction pre-specified
(most serious outcome, see appendix)

Figure 4. **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.



	Improvement, RR [CI]		Treatment	Control
Soares (ICU)	76%	0.24 [0.11-0.54]	6/44	18/32
Delić (RCT)	23%	0.77 [0.56-1.06]	23/42	37/52
El-Badrawy	57%	0.43 [0.09-2.08]	3/127	3/55
El-Badrawy (RCT)	23%	0.77 [0.50-1.18]	32/272	42/274
Late treatment	41%	0.59 [0.37-0.94]	64/485	100/413
Tau² = 0.12, I² = 60.0%, p = 0.025				
All studies	41%	0.59 [0.37-0.94]	64/485	100/413

Tau² = 0.12, I² = 60.0%, p = 0.025

Figure 5. Random effects meta-analysis for mortality results.

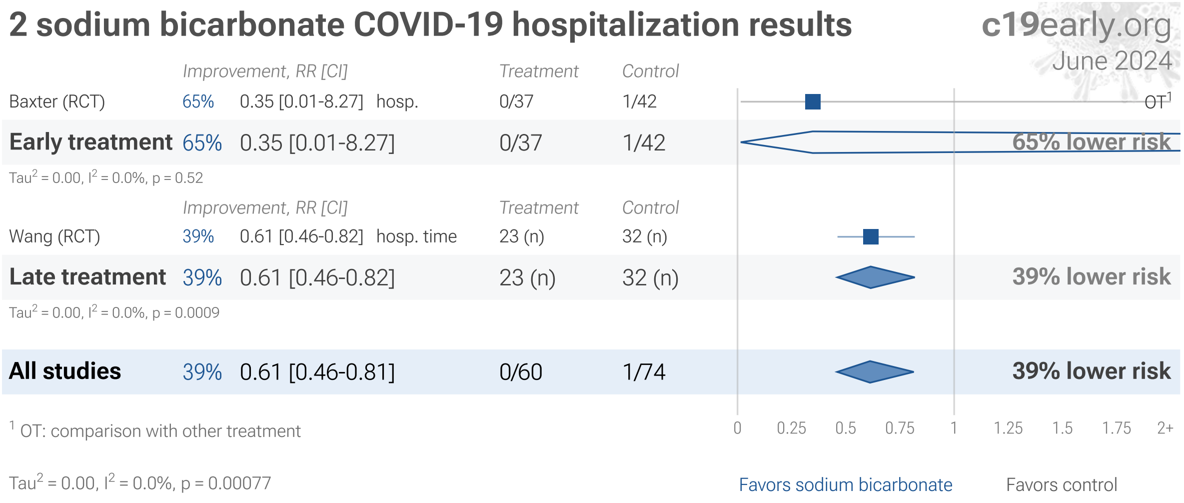


Figure 6. Random effects meta-analysis for hospitalization.

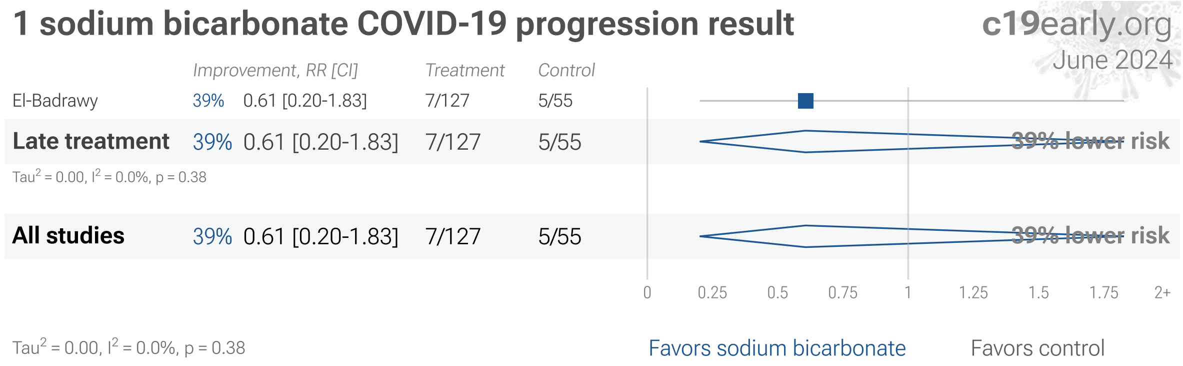


Figure 7. Random effects meta-analysis for progression.

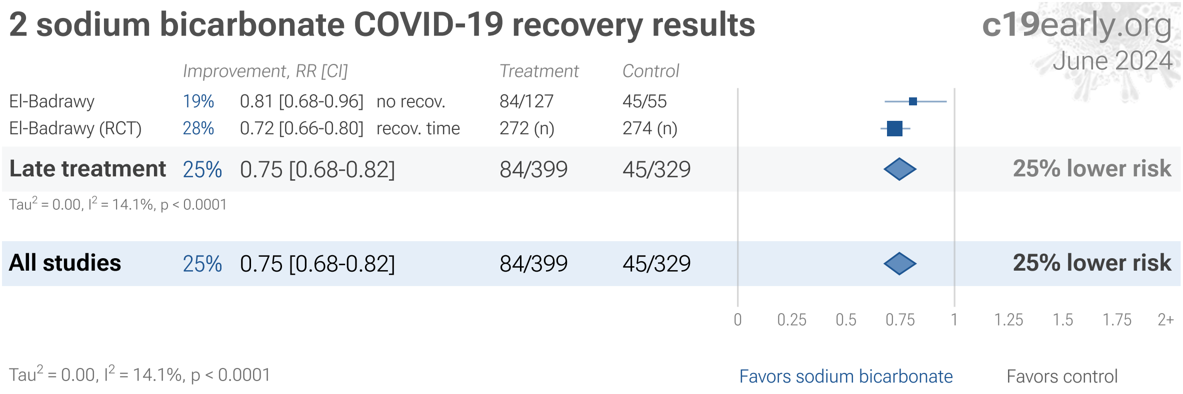


Figure 8. Random effects meta-analysis for recovery.

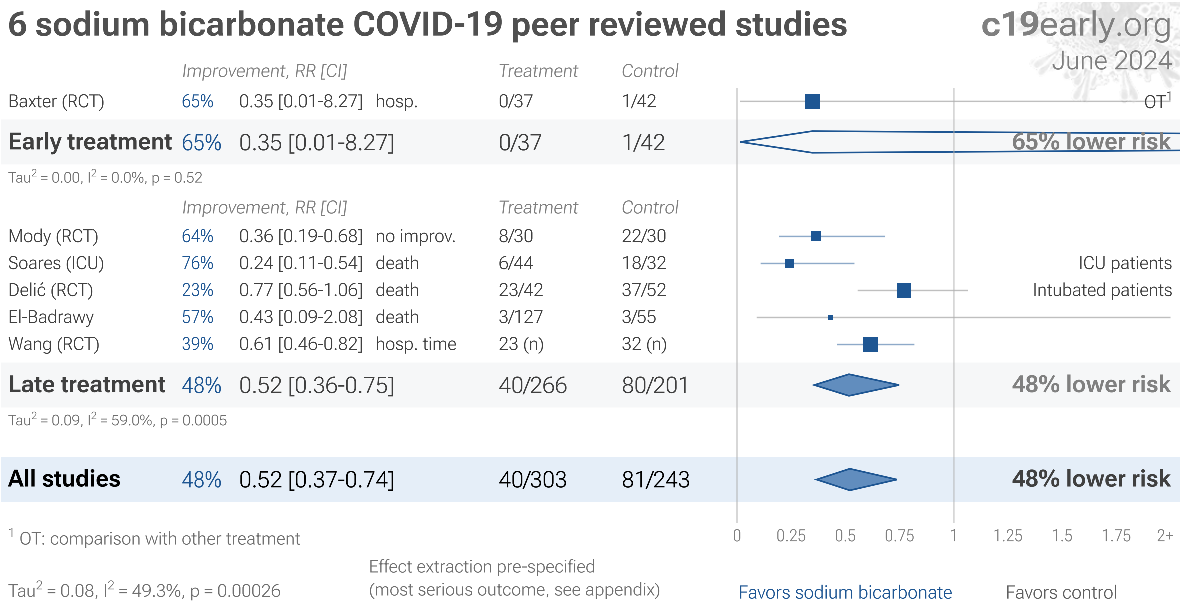


Figure 9. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with peer-reviewed studies. They also show extremely long peer-review delays, with a median of 6 months to journal publication. A six month delay was equivalent to around 1.5 million deaths during the first two years of the pandemic. Authors recommend using preprint evidence, with appropriate checks for potential falsified data, which provides higher certainty much earlier. *Davidson et al.* also showed no important difference between meta analysis results of preprints and peer-reviewed publications for COVID-19, based on 37 meta analyses including 114 trials.

Randomized Controlled Trials (RCTs)

Figure 10 shows a comparison of results for RCTs and non-RCT studies. Figure 11 and 12 show forest plots for random effects meta-analysis of all Randomized Controlled Trials and RCT mortality results. RCT results are included in Table 1 and Table 2.

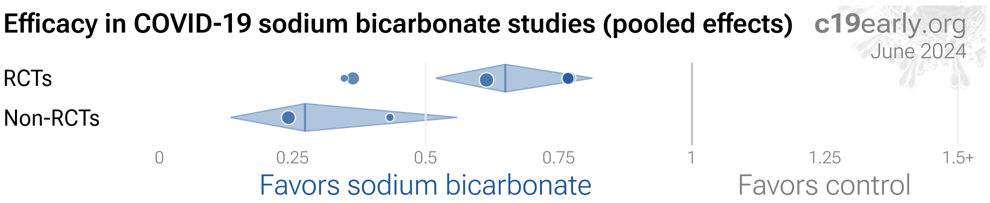


Figure 10. Results for RCTs and non-RCT studies.

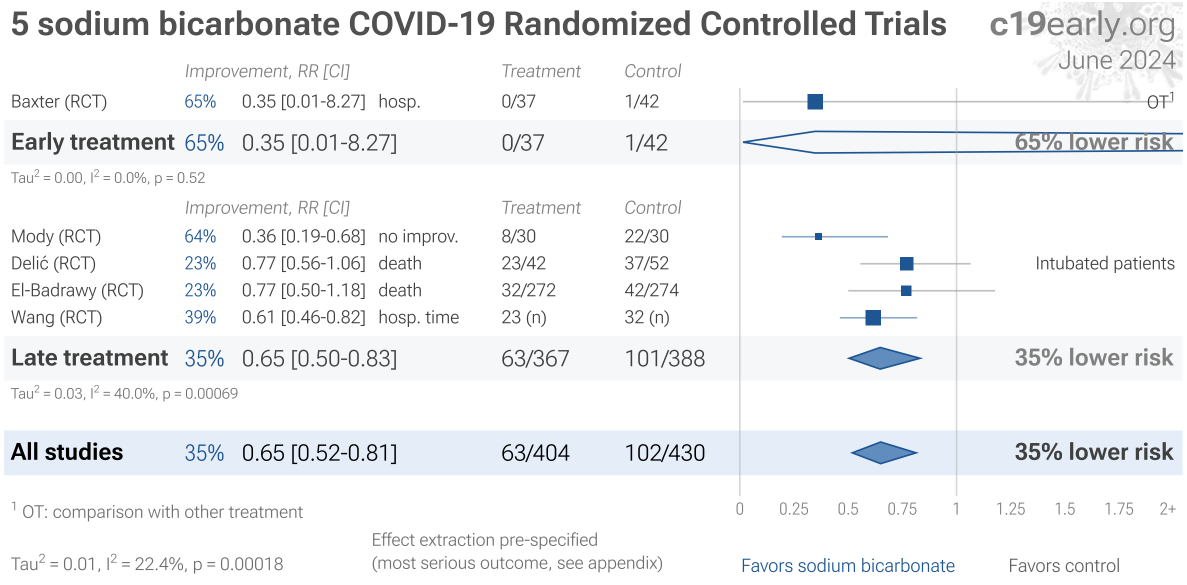


Figure 11. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

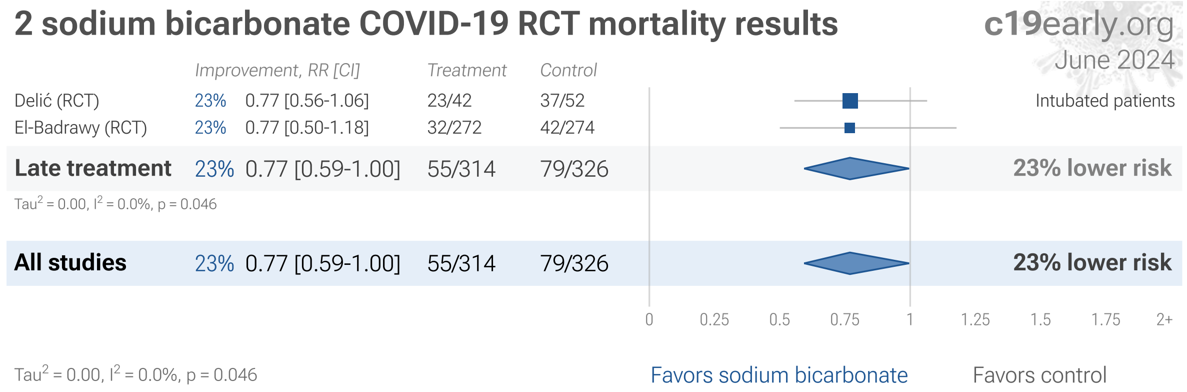


Figure 12. **Random effects meta-analysis for RCT mortality results.**

RCTs have many potential biases. RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases[22], and analysis of double-blind RCTs has identified extreme levels of bias[23]. For COVID-19, the overhead may delay treatment, dramatically compromising efficacy; they may encourage monotherapy for simplicity at the cost of efficacy which may rely on combined or synergistic effects; the participants that sign up may not reflect real world usage or the population that benefits most in terms of age, comorbidities, severity of illness, or other factors; standard of care may be compromised and unable to evolve quickly based on emerging research for new diseases; errors may be made in randomization and medication delivery; and investigators may have hidden agendas or vested interests influencing design, operation, analysis, reporting, and the potential for fraud. All of these biases have been observed with COVID-19 RCTs. There is no guarantee that a specific RCT provides a higher level of evidence.

Conflicts of interest for COVID-19 RCTs. RCTs are expensive and many RCTs are funded by pharmaceutical companies or interests closely aligned with pharmaceutical companies. For COVID-19, this creates an incentive to show efficacy for patented commercial products, and an incentive to show a lack of efficacy for inexpensive treatments. The bias is expected to be significant, for example Als-Nielsen *et al.* analyzed 370 RCTs from Cochrane reviews, showing that trials funded by for-profit organizations were 5 times more likely to recommend the experimental drug compared with those funded by nonprofit organizations. For COVID-19, some major philanthropic organizations are largely funded by investments with extreme conflicts of interest for and against specific COVID-19 interventions.

RCTs for novel acute diseases requiring rapid treatment. High quality RCTs for novel acute diseases are more challenging, with increased ethical issues due to the urgency of treatment, increased risk due to enrollment delays, and more difficult design with a rapidly evolving evidence base. For COVID-19, the most common site of initial infection is the upper respiratory tract. Immediate treatment is likely to be most successful and may prevent or slow progression to other parts of the body. For a non-prophylaxis RCT, it makes sense to provide treatment in advance and instruct patients to use it immediately on symptoms, just as some governments have done by providing medication kits in advance. Unfortunately, no RCTs have been done in this way. Every treatment RCT to date involves delayed treatment. Among the 74 treatments we have analyzed, 64% of RCTs involve very late treatment 5+ days after onset. No non-prophylaxis COVID-19 RCTs match the potential real-world use of early treatments. They may more accurately represent results for treatments that require visiting a medical facility, e.g., those requiring intravenous administration.

RCT bias for widely available treatments. RCTs have a bias against finding an effect for interventions that are widely available — patients that believe they need the intervention are more likely to decline participation and take the intervention. RCTs for sodium bicarbonate are more likely to enroll low-risk participants that do not need treatment to recover, making the results less applicable to clinical practice. This bias is likely to be greater for widely known treatments, and may be greater when the risk of a serious outcome is overstated. This bias does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable.

Non-RCT studies have been shown to be reliable. Evidence shows that non-RCT studies can also provide reliable results. *Concato et al.* found that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. *Anglemyer et al.* summarized reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. *Lee et al.* showed that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases. Limitations in an RCT can outweigh the benefits, for example excessive dosages, excessive treatment delays, or Internet survey bias may have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see[28,29].

Using all studies identifies efficacy 7+ months faster (8+ months for low-cost treatments). Currently, 45 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. Of these, 29 have been confirmed in RCTs, with a mean delay of 7.1 months. When considering only low cost treatments, 24 have been confirmed with a delay of 8.5 months. For the 16 unconfirmed treatments, 3 have zero RCTs to date. The point estimates for the remaining 13 are all consistent with the overall results (benefit or harm), with 10 showing >20%. The only treatments showing >10% efficacy for all studies, but <10% for RCTs are sotrovimab and aspirin.

Summary. We need to evaluate each trial on its own merits. RCTs for a given medication and disease may be more reliable, however they may also be less reliable. For off-patent medications, very high conflict of interest trials may be more likely to be RCTs, and more likely to be large trials that dominate meta analyses.

Heterogeneity

Heterogeneity in COVID-19 studies arises from many factors including:

Treatment delay. The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours[30,31]. Baloxavir studies for influenza also show that treatment delay is critical — *Ikematsu et al.* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden et al.* show a 33 hour reduction in the time to alleviation of symptoms for treatment within 24 hours and a reduction of 13 hours for treatment within 24-48 hours, and *Kumar et al.* report only 2.5 hours improvement for inpatient treatment.

Treatment delay	*Result*
Post-exposure prophylaxis	86% fewer cases[32]
<24 hours	-33 hours symptoms[33]
24-48 hours	-13 hours symptoms[33]
Inpatients	-2.5 hours to improvement[34]

Table 3. **Studies of baloxavir for influenza show that early treatment is more effective.**

Figure 13 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 74 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

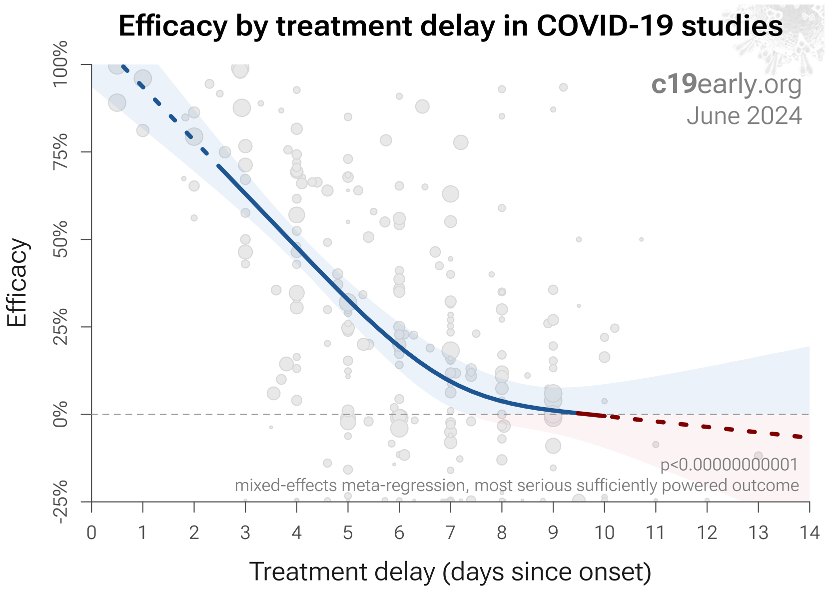


Figure 13. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 74 treatments.

Patient demographics. Details of the patient population including age and comorbidities may critically affect how well a treatment works. For example, many COVID-19 studies with relatively young low-comorbidity patients show all patients recovering quickly with or without treatment. In such cases, there is little room for an effective treatment to improve results, for example as in López-Medina et al.

Variants. Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants[36], for example the Gamma variant shows significantly different characteristics[37-40]. Different mechanisms of action may be more or less effective depending on variants, for example the degree to which TMPRSS2 contributes to viral entry can differ across variants[41,42].

Regimen. Effectiveness may depend strongly on the dosage and treatment regimen.

Other treatments. The use of other treatments may significantly affect outcomes, including supplements, other medications, or other interventions such as prone positioning. Treatments may be synergistic[43-53], therefore efficacy may depend strongly on combined treatments.

Medication quality. The quality of medications may vary significantly between manufacturers and production batches, which may significantly affect efficacy and safety. Williams et al. analyze ivermectin from 11 different sources, showing highly variable antiparasitic efficacy across different manufacturers. Xu et al. analyze a treatment from two different manufacturers, showing 9 different impurities, with significantly different concentrations for each manufacturer.

Effect measured. Across all studies there is a strong association between different outcomes, for example improved recovery is strongly associated with lower mortality. However, efficacy may differ depending on the effect measured, for example a treatment may be more effective against secondary complications and have minimal effect on viral clearance.

Meta analysis. The distribution of studies will alter the outcome of a meta analysis. Consider a simplified example where everything is equal except for the treatment delay, and effectiveness decreases to zero or below with increasing delay. If there are many studies using very late treatment, the outcome may be negative, even though early treatment is very effective. All meta analyses combine heterogeneous studies, varying in population, variants, and potentially all factors above, and therefore may obscure efficacy by including studies where treatment is less effective. Generally, we expect the estimated effect size from meta analysis to be less than that for the optimal case. Looking at all studies is valuable for providing an overview of all research, important to avoid cherry-picking, and informative when a positive result is found despite combining less-optimal situations. However, the resulting estimate does not apply to specific cases such as early treatment in high-risk populations. While we present results for all studies, we also present treatment time and individual outcome analyses, which may be more informative for specific use cases.

Pooled Effects

Combining studies is required. For COVID-19, delay in clinical results translates into additional death and morbidity, as well as additional economic and societal damage. Combining the results of studies reporting different outcomes is required. There may be no mortality in a trial with low-risk patients, however a reduction in severity or improved viral clearance may translate into lower mortality in a high-risk population. Different studies may report lower severity, improved recovery, and lower mortality, and the significance may be very high when combining the results. "*The studies reported different outcomes*" is not a good reason for disregarding results.

Specific outcome and pooled analyses. We present both specific outcome and pooled analyses. In order to combine the results of studies reporting different outcomes we use the most serious outcome reported in each study, based on the thesis that improvement in the most serious outcome provides comparable measures of efficacy for a treatment. A critical advantage of this approach is simplicity and transparency. There are many other ways to combine evidence for different outcomes, along with additional evidence such as dose-response relationships, however these increase complexity.

Using more information. Another way to view pooled analysis is that we are using more of the available information. Logically we should, and do, use additional information. For example dose-response and treatment delay-response relationships provide significant additional evidence of efficacy that is considered when reviewing the evidence for a treatment.

Ethical and practical issues limit high-risk trials. Trials with high-risk patients may be restricted due to ethics for treatments that are known or expected to be effective, and they increase difficulty for recruiting. Using less severe outcomes as a proxy for more serious outcomes allows faster collection of evidence.

Improvement across outcomes. For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, which follows from a reduction in PCR positivity. We can directly test this for COVID-19.

Validating pooled outcome analysis for COVID-19. Analysis of the the association between different outcomes across studies from all 74 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 14 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly,

Figure 15 shows that improved recovery is very strongly associated with lower mortality ($p < 0.000000000001$). Considering the extremes, Singh et al. show an association between viral clearance and hospitalization or death, with $p = 0.003$ after excluding one large outlier from a mutagenic treatment, and based on 44 RCTs including 52,384 patients. Figure 16 shows that improved viral clearance is strongly associated with fewer serious outcomes. The association is very similar to Singh et al., with higher confidence due to the larger number of studies. As with Singh et al., the confidence increases when excluding the outlier treatment, from $p = 0.0000014$ to $p = 0.000000005$.

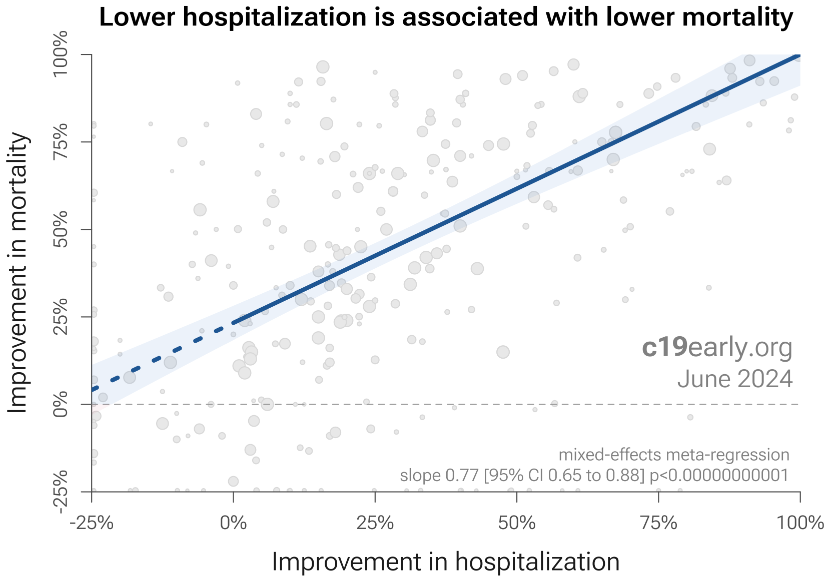


Figure 14. **Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.**

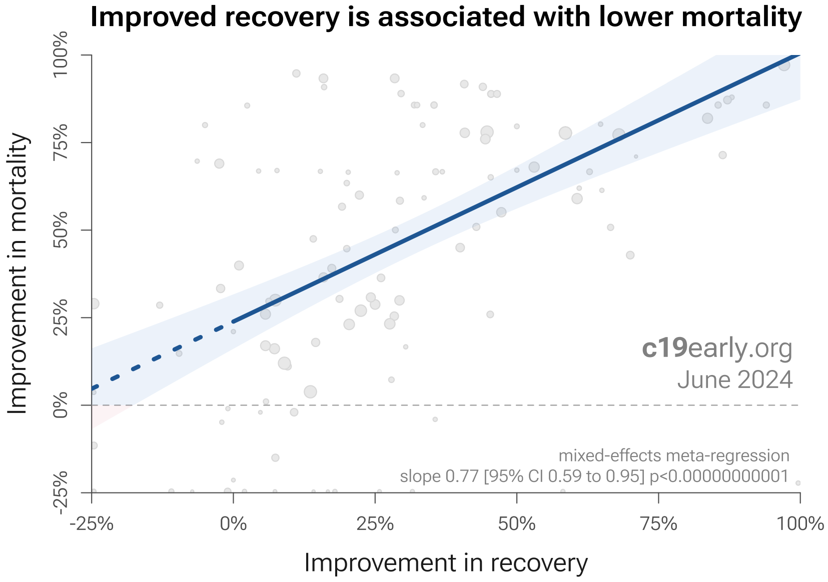


Figure 15. **Improved recovery is associated with lower mortality, supporting pooled outcome analysis.**

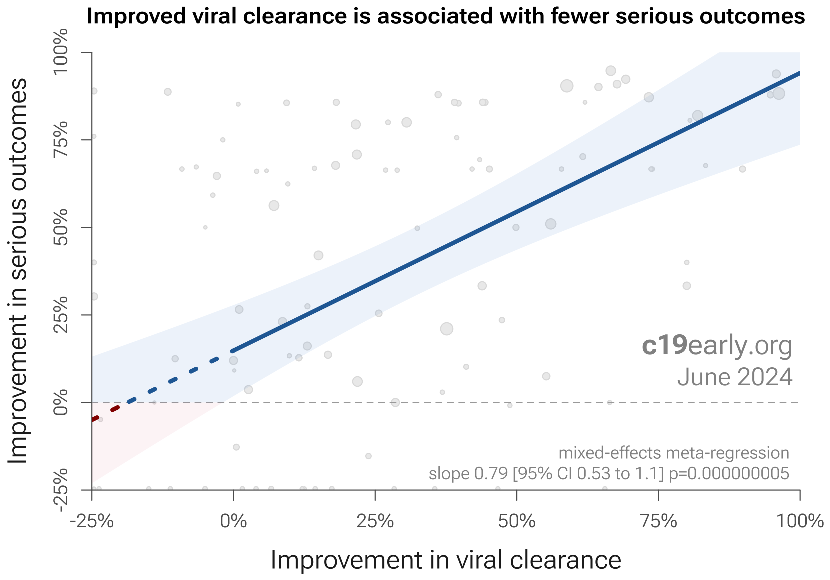


Figure 14. **Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.**

Pooled outcomes identify efficacy 5 months faster (6 months for RCTs). Currently, 45 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 90% of these have been confirmed with one or more specific outcomes, with a mean delay of 5.0 months. When restricting to RCTs only, 56% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 6.4 months. Figure 17 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

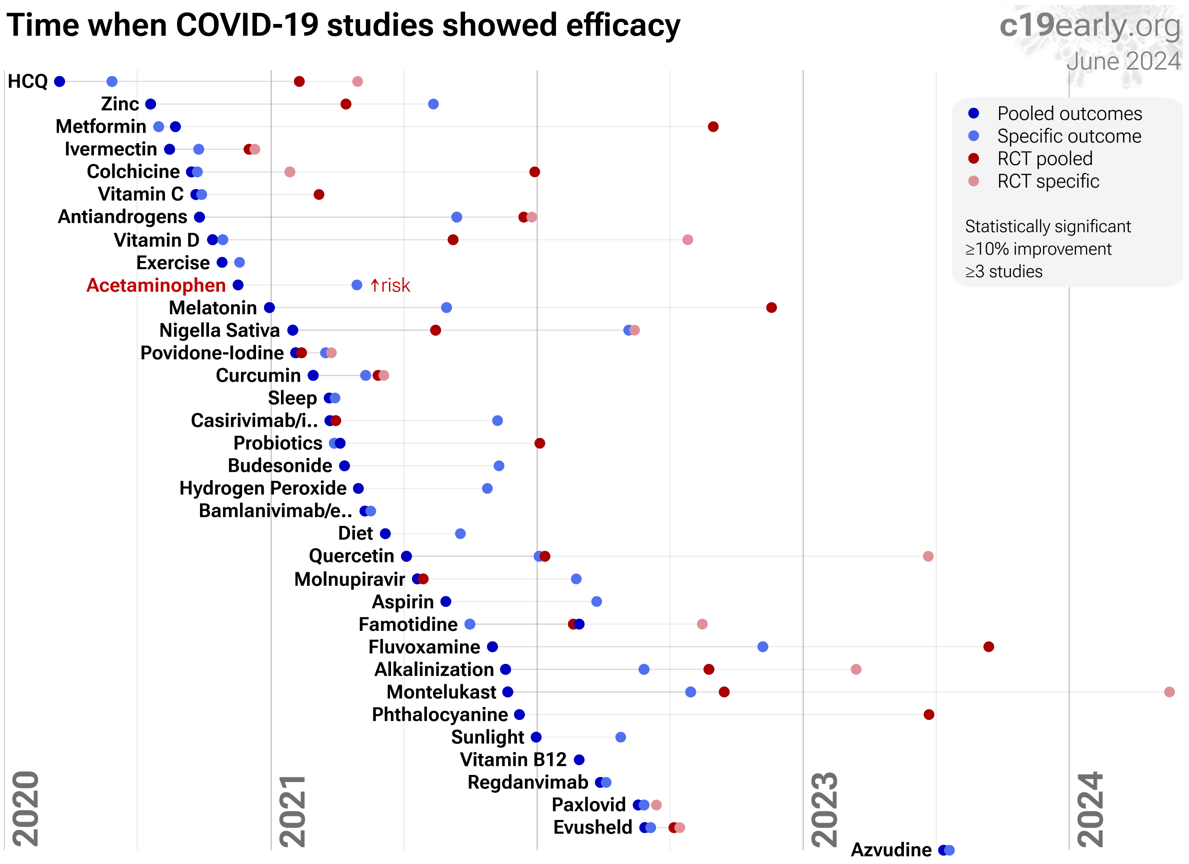


Figure 17. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

Limitations. Pooled analysis could hide efficacy, for example a treatment that is beneficial for late stage patients but has no effect on viral clearance may show no efficacy if most studies only examine viral clearance. In practice, it is rare for a non-antiviral treatment to report viral clearance and to not report clinical outcomes; and in practice other sources of heterogeneity such as difference in treatment delay is more likely to hide efficacy.

Summary. Analysis validates the use of pooled effects and shows significantly faster detection of efficacy on average. However, as with all meta analyses, it is important to review the different studies included. We also present individual outcome analyses, which may be more informative for specific use cases.

Discussion

Nasal/oral administration. Studies to date use a variety of administration methods to the respiratory tract, including nasal and oral sprays, nasal irrigation, oral rinses, and inhalation. Table 4 shows the relative efficacy for nasal, oral, and combined administration. Combined administration shows the best results, and nasal administration is more effective than oral. Precise efficacy depends on the details of administration, e.g., mucoadhesion and sprayability for sprays.

Nasal/oral administration to the respiratory tract	*Improvement*	*Studies*
Oral spray/rinse	38% [25-49%]	8
Nasal spray/rinse	56% [44-65%]	12
Nasal & oral	94% [74-99%]	6

Table 4. **Respiratory tract administration efficacy. Relative efficacy of nasal, oral, and combined nasal/oral administration for treatments administered directly to the respiratory tract, based on studies for povidone-iodine, iota-carrageenan, alkalinization, hydrogen peroxide, nitric oxide, chlorhexidine, cetylpyridinium chloride, phthalocyanine, and sodium bicarbonate. Results show random effects meta analysis for the most serious outcome reported for all prophylaxis and early treatment studies.**

Impact on the *microbiome*. Nasopharyngeal/oropharyngeal treatments may not be highly selective. In addition to inhibiting or disabling SARS-CoV-2, they may also be harmful to beneficial microbes, disrupting the natural microbiome in the oral cavity and nasal passages that have important protective and metabolic roles[57]. This may be especially important for prolonged use or overuse. Table 5 summarizes the potential for common nasopharyngeal/oropharyngeal treatments to affect the natural microbiome.

Treatment	*Microbiome disruption potential*	*Notes*
Iota-carrageenan	Low	Primarily antiviral, however extended use may mildly affect the microbiome
Nitric Oxide	Low to moderate	More selective towards pathogens, however excessive concentrations or prolonged use may disrupt the balance of bacteria
Alkalinization	Moderate	Increases pH, negatively impacting beneficial microbes that thrive in a slightly acidic environment
Cetylpyridinium Chloride	Moderate	Quaternary ammonium broad-spectrum antiseptic that can disrupt beneficial and harmful bacteria
Phthalocyanine	Moderate to high	Photodynamic compound with antimicrobial activity, likely to affect the microbiome
Chlorhexidine	High	Potent antiseptic with broad activity, significantly disrupts the microbiome
Hydrogen Peroxide	High	Strong oxidizer, harming both beneficial and harmful microbes
Povidone-Iodine	High	Potent broad-spectrum antiseptic harmful to beneficial microbes

Table 5. **Potential effect of treatments on the nasophyrngeal/oropharyngeal microbiome.**

Publication bias. Publishing is often biased towards positive results, however evidence suggests that there may be a negative bias for inexpensive treatments for COVID-19. Both negative and positive results are very important for COVID-19, media in many countries prioritizes negative results for inexpensive treatments (inverting the typical incentive for scientists that value media recognition), and there are many reports of difficulty publishing positive results[58-61]. For sodium bicarbonate, there is currently not enough data to evaluate publication bias with high confidence.

Funnel plot analysis. Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 18 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry ($p > 0.05$). In plot B, we add a single typical variation in COVID-19 treatment trials — treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry, $p < 0.0001$, with six variants of Egger's test all showing $p < 0.05$[62-69]. Note that these tests fail even though treatment delay is uniformly distributed. In reality treatment delay is more complex — each trial has a different distribution of delays across patients, and the distribution across trials may be biased (e.g., late treatment trials may be more common). Similarly, many other variations in trials may produce asymmetry, including dose, administration, duration of treatment, differences in SOC, comorbidities, age, variants, and bias in design, implementation, analysis, and reporting.

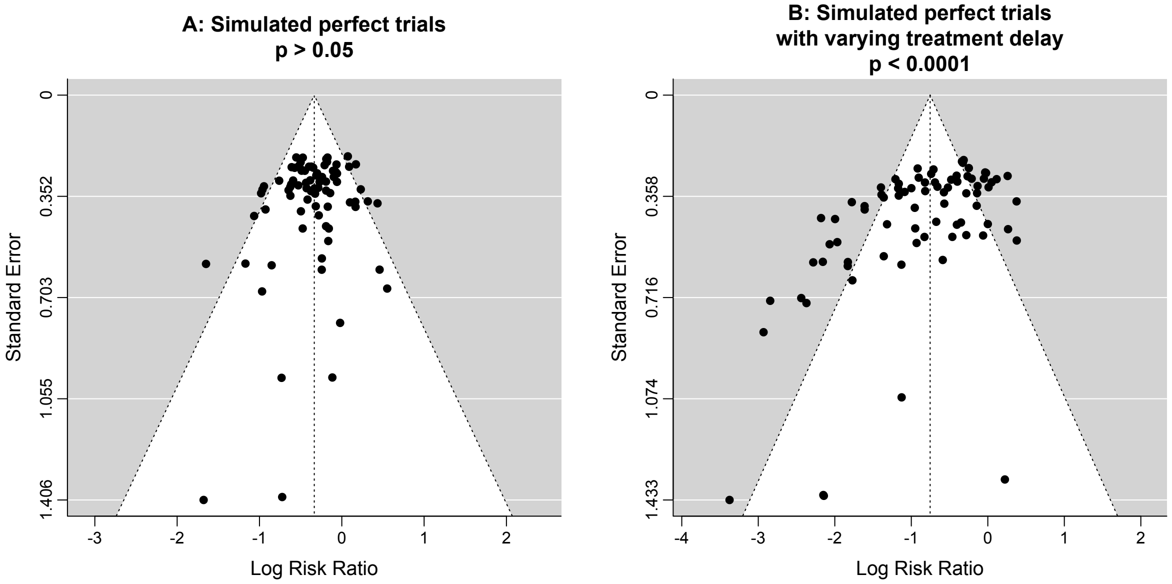


Figure 18. **Example funnel plot analysis for simulated perfect trials.**

Conflicts of interest. Pharmaceutical drug trials often have conflicts of interest whereby sponsors or trial staff have a financial interest in the outcome being positive. Sodium Bicarbonate for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 sodium bicarbonate trials have been run by physicians on the front lines with the primary goal of finding the best methods to save human lives and minimize the collateral damage caused by COVID-19. While pharmaceutical companies are careful to run trials under optimal conditions (for example, restricting patients to those most likely to benefit, only including patients that can be treated soon after onset when necessary, and ensuring accurate dosing), not all sodium bicarbonate trials represent the optimal conditions for efficacy.

Limitations. Summary statistics from meta analysis necessarily lose information. As with all meta analyses, studies are heterogeneous, with differences in treatment delay, treatment regimen, patient demographics, variants, conflicts of interest, standard of care, and other factors. We provide analyses for specific outcomes and by treatment delay, and we aim to identify key characteristics in the forest plots and summaries. Results should be viewed in the context of study characteristics.

Some analyses classify treatment based on early or late administration, as done here, while others distinguish between mild, moderate, and severe cases. Viral load does not indicate degree of symptoms — for example patients may have a high viral load while being asymptomatic. With regard to treatments that have antiviral properties, timing of treatment is critical — late administration may be less helpful regardless of severity.

Details of treatment delay per patient is often not available. For example, a study may treat 90% of patients relatively early, but the events driving the outcome may come from 10% of patients treated very late. Our 5 day cutoff for early treatment may be too conservative, 5 days may be too late in many cases.

Comparison across treatments is confounded by differences in the studies performed, for example dose, variants, and conflicts of interest. Trials with conflicts of interest may use designs better suited to the preferred outcome.

In some cases, the most serious outcome has very few events, resulting in lower confidence results being used in pooled analysis, however the method is simpler and more transparent. This is less critical as the number of studies increases. Restriction to outcomes with sufficient power may be beneficial in pooled analysis and improve accuracy when there are few studies, however we maintain our pre-specified method to avoid any retrospective changes.

Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone[43-53]. Therefore standard of care may be critical and benefits may diminish or disappear if standard of care does not include certain treatments.

This real-time analysis is constantly updated based on submissions. Accuracy benefits from widespread review and submission of updates and corrections from reviewers. Less popular treatments may receive fewer reviews.

No treatment or intervention is 100% available and effective for all current and future variants. Efficacy may vary significantly with different variants and within different populations. All treatments have potential side effects. Propensity to experience side effects may be predicted in advance by qualified physicians. We do not provide medical advice. Before taking any medication, consult a qualified physician who can compare all options, provide personalized advice, and provide details of risks and benefits based on individual medical history and situations.

Notes. 1 of the 7 studies compare against other treatments, which may reduce the effect seen. *Shafiee* present another meta analysis for sodium bicarbonate, showing significant improvements for mortality and recovery.

Reviews. *Rashedi et al.* present a review covering sodium bicarbonate for COVID-19.

Perspective

Results compared with other treatments. SARS-CoV-2 infection and replication involves a complex interplay of 50+ host and viral proteins and other factors[12-16], providing many therapeutic targets. Over 7,000 compounds have been predicted to reduce COVID-19 risk[17], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 19 shows an overview of the results for sodium bicarbonate in the context of multiple COVID-19 treatments, and Figure 20 shows a plot of efficacy vs. cost for COVID-19 treatments.

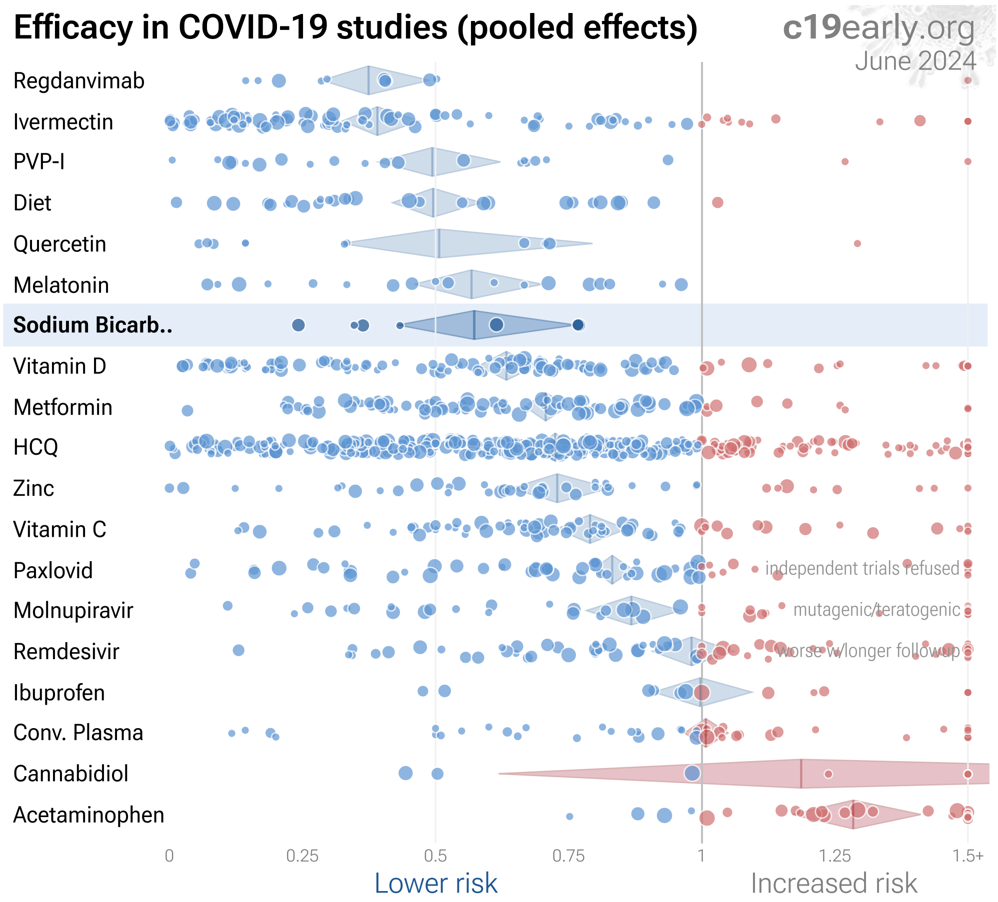
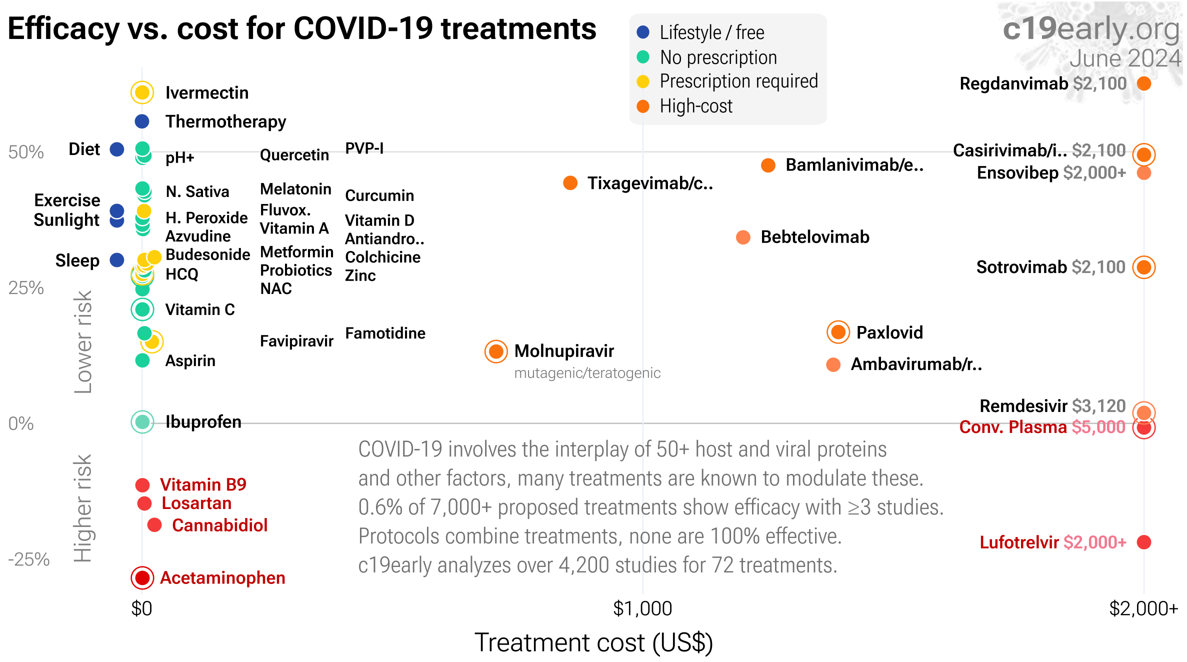


Figure 19. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 7,000+ proposed treatments show efficacy[71].



COVID-19 involves the interplay of 50+ host and viral proteins and other factors, many treatments are known to modulate these. 0.6% of 7,000+ proposed treatments show efficacy with ≥3 studies. Protocols combine treatments, none are 100% effective. c19early analyzes over 4,200 studies for 72 treatments.

Figure 20. Efficacy vs. cost for COVID-19 treatments.

Conclusion

SARS-CoV-2 infection typically starts in the upper respiratory tract. Progression may lead to cytokine storm, pneumonia, ARDS, neurological issues, organ failure, and death. Stopping replication in the upper respiratory tract, via early or prophylactic nasopharyngeal/oropharyngeal treatment, can avoid the consequences of progression to other tissues, and avoid the requirement for systemic treatments with greater potential for side effects.

Studies to date show that sodium bicarbonate is an effective treatment for COVID-19. Statistically significant lower risk is seen for mortality, hospitalization, and recovery. 6 studies from 5 independent teams in 5 countries show significant improvements. Meta analysis using the most serious outcome reported shows 43% [24-57%] lower risk. Results are similar for Randomized Controlled Trials and peer-reviewed studies. Early treatment is more effective than late treatment.

SARS-CoV-2 requires acidic pH for fusion[1]. Alkalinization of the respiratory mucosa may reduce risk.

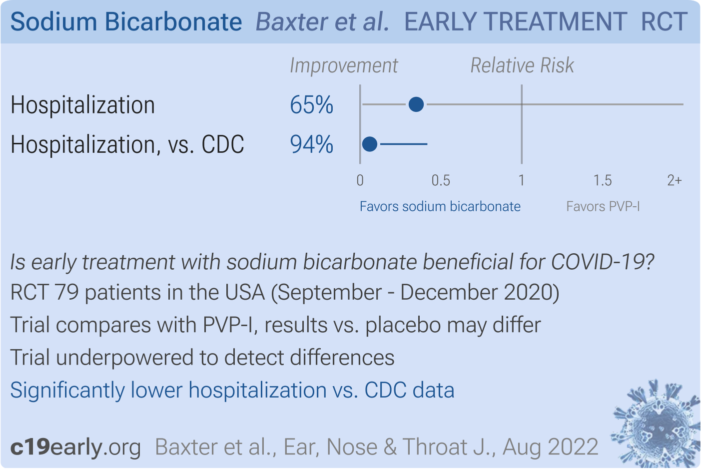
Shafiee present another meta analysis for sodium bicarbonate, showing significant improvements for mortality and recovery.

We also present an analysis covering other alkalinization treatments[2].

Sodium Bicarbonate may affect the natural microbiome, especially with prolonged use.

Study Notes

Baxter

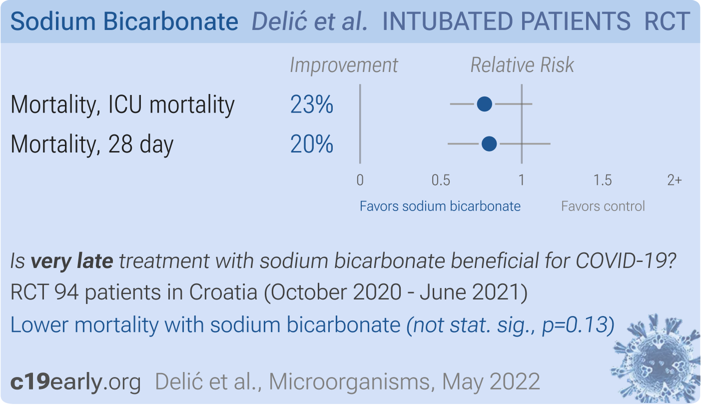

Sodium Bicarbonate *Baxter et al.* EARLY TREATMENT RCT

Is early treatment with sodium bicarbonate beneficial for COVID-19?
RCT 79 patients in the USA (September - December 2020)
Trial compares with PVP-I, results vs. placebo may differ
Trial underpowered to detect differences
Significantly lower hospitalization vs. CDC data

c19early.org Baxter et al., Ear, Nose & Throat J., Aug 2022

Baxter: Small RCT 79 PCR+ patients 55+ comparing pressure-based nasal irrigation with povidone-iodine and sodium bicarbonate, showing significantly lower hospitalization when compared with CDC data.

Delić



*Is **very late** treatment with sodium bicarbonate beneficial for COVID-19?*

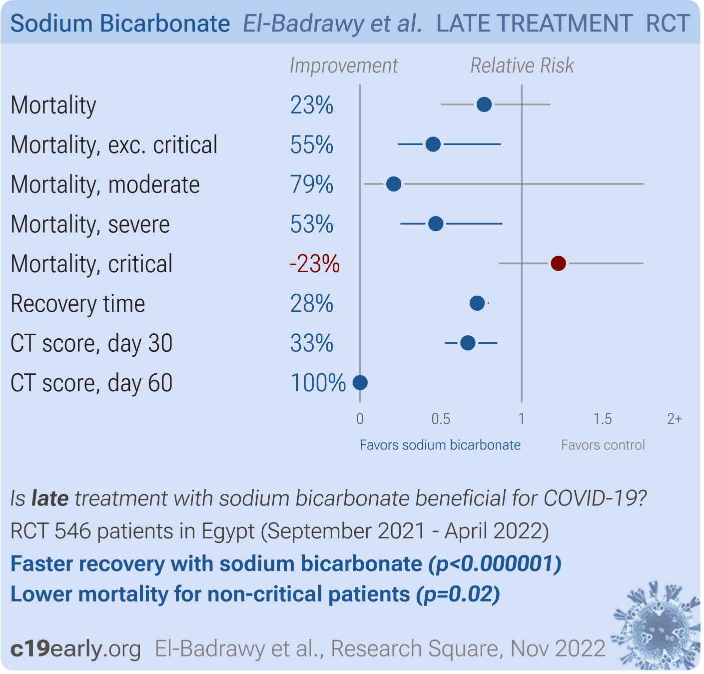
RCT 94 patients in Croatia (October 2020 - June 2021)

Lower mortality with sodium bicarbonate *(not stat. sig., p=0.13)*

c19early.org Delić et al., Microorganisms, May 2022

Delić: RCT mechanically ventilated patients in Croatia, 42 treated with sodium bicarbonate inhalation, and 52 control patients, showing no significant difference in mortality with treatment. Treated patients showed a lower incidence of gram-positive or MRSA-caused ventilator-associated pneumonia. ICU mortality results are from[74].

El-Badrawy



*Is **late** treatment with sodium bicarbonate beneficial for COVID-19?*

RCT 546 patients in Egypt (September 2021 - April 2022)

Faster recovery with sodium bicarbonate *(p<0.000001)*

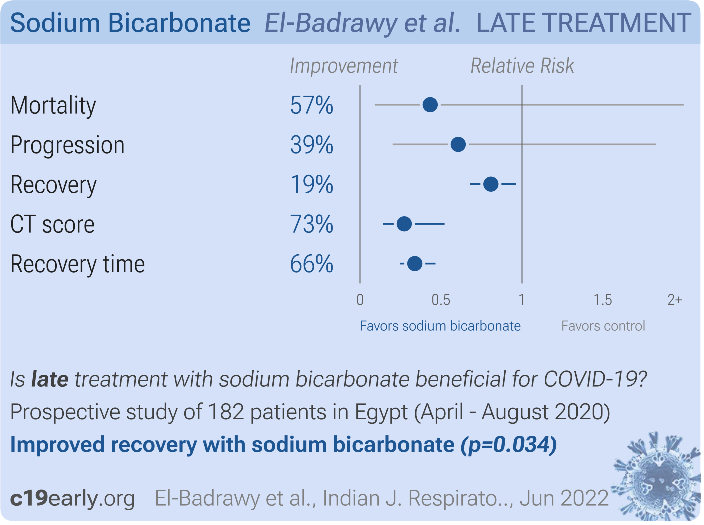
Lower mortality for non-critical patients *(p=0.02)*

c19early.org El-Badrawy et al., Research Square, Nov 2022

El-Badrawy: RCT 546 patients showing significantly faster recovery and lower mortality with sodium bicarbonate (inhaled and nasal drops). The reduction in mortality is only statistically significant when excluding baseline critical cases.

Inhalation of nebulized sodium bicarbonate 8.4% (5ml every 4h) 7:00am to 23:00pm every day for 30 days together with 8.4% nasal drops 4 times daily (three drops for each nostril).

El-Badrawy



*Is **late** treatment with sodium bicarbonate beneficial for COVID-19?*

Prospective study of 182 patients in Egypt (April - August 2020)

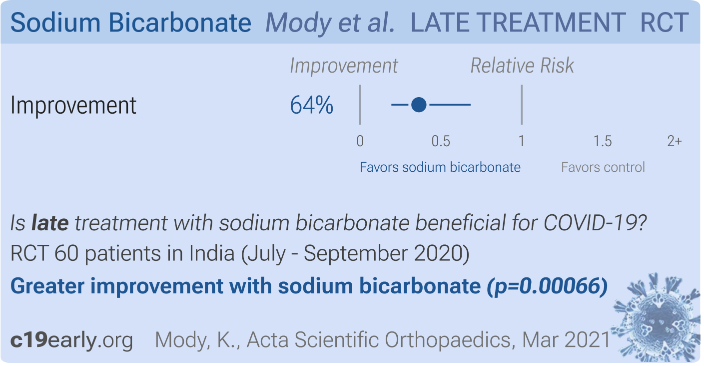
Improved recovery with sodium bicarbonate *(p=0.034)*

El-Badrawy (B): Prospective study of 182 COVID-19 pneumonia patients, 127 treated with sodium bicarbonate inhalation and nasal drops, showing significantly faster recovery and improved CT scores with treatment.

Authors note that contacts of index cases also received sodium bicarbonate treatment, with none reporting COVID-19.

Inhalation of nebulized sodium bicarbonate 8.4% (5ml every 4h) 7:00am to 23:00pm every day for 30 days together with 8.4% nasal drops 4 times daily (three drops for each nostril).

Mody



*Is **late** treatment with sodium bicarbonate beneficial for COVID-19?*

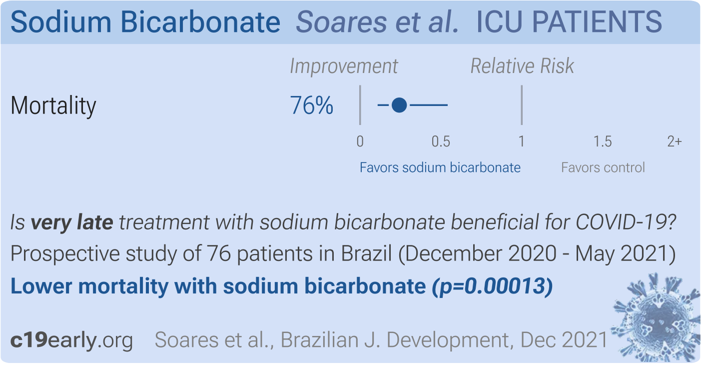
RCT 60 patients in India (July - September 2020)

Greater improvement with sodium bicarbonate *(p=0.00066)*

Mody: RCT 60 hospitalized patients in India, showing significantly greater clinical improvement with inhaled sodium bicarbonate.

Nasal and oral inhalation of nebulized 50ml 8.4% sodium bicarbonate for 5 minutes twice daily for 5 days.

Soares



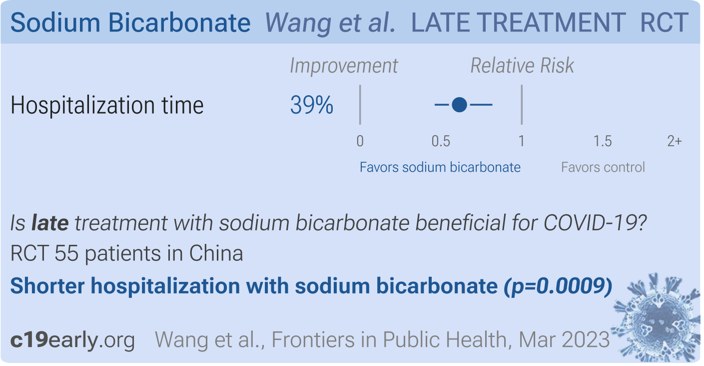
*Is **very late** treatment with sodium bicarbonate beneficial for COVID-19?*
Prospective study of 76 patients in Brazil (December 2020 - May 2021)
Lower mortality with sodium bicarbonate *(p=0.00013)*

Soares et al., Brazilian J. Development, Dec 2021

Soares: Analysis of 76 ICU patients in Brazil, 44 treated with bronchoalveolar lavage using 3% sodium bicarbonate, showing significantly lower mortality with treatment.

Bronchoalveolar lavage with 10ml of sodium bicarbonate solution directly into the tube (closed circuit), 500µl for each lung segment, followed by aspiration of the solution, performed every 6 hours for 7 days.

Wang



*Is **late** treatment with sodium bicarbonate beneficial for COVID-19?*
RCT 55 patients in China
Shorter hospitalization with sodium bicarbonate *(p=0.0009)*

Wang et al., Frontiers in Public Health, Mar 2023

Wang: RCT 55 mild/moderate patients in China, showing shorter hospitalization with sodium bicarbonate nasal irrigation and oral rinsing. Oral rinse with 5% sodium bicarbonate solution three times daily. Nasal irrigation two times with the solution entering through one nostril and exiting from the other. 30–40mL of solution was used every time and irrigation was performed for at least 30s. Details of randomization are not provided.

Appendix 1. Methods and Data

We perform ongoing searches of PubMed, medRxiv, Europe PMC, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19early.org. Search terms are sodium bicarbonate and COVID-19 or SARS-CoV-2. Automated searches are performed twice daily, with all matches reviewed for inclusion. All studies regarding the use of sodium bicarbonate for COVID-19 that report a comparison with a control group are included in the main analysis. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome specific analyses. For example, if effects for mortality and cases are both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcomes are considered more important than viral test status. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO_2 is more important than cough. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to[80]. Reported confidence intervals and *p*-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed Altman, Altman (B), and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1[83]. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.12.3) with scipy (1.13.1), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.2), and plotly (5.22.0).

Forest plots are computed using PythonMeta[84] with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. Results are presented with 95% confidence intervals. Heterogeneity among studies was assessed using the I^2 statistic. Mixed-effects meta-regression results are computed with R (4.4.0) using the metafor (4.6-0) and rms (6.8-0) packages, and using the most serious sufficiently powered outcome. For all statistical tests, a *p*-value less than 0.05 was considered statistically significant. Grobid 0.8.0 is used to parse PDF documents.

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment (for example based on oxygen status or lung involvement), and treatment started within 5 days of the onset of symptoms. If studies contain a mix of early treatment and late treatment patients, we consider the treatment time of patients contributing most to the events (for example, consider a study where most patients are treated early but late treatment patients are included, and all mortality events were observed with late treatment patients). We note that a shorter time may be preferable. Antivirals are typically only considered effective when used within a shorter timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective[30,31].

We received no funding, this research is done in our spare time. We have no affiliations with any pharmaceutical companies or political parties.

A summary of study results is below. Please submit updates and corrections at https://c19early.org/sbmeta.html.

Early treatment

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

Baxter, 8/25/2022, Randomized Controlled Trial, USA, peer-reviewed, 12 authors, study period 24 September, 2020 - 21 December, 2020, this trial compares with another treatment - results may be better when compared to placebo, trial NCT04559035 (history).	risk of hospitalization, 65.3% lower, RR 0.35, *p* = 1.00, treatment 0 of 37 (0.0%), control 1 of 42 (2.4%), NNT 42, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), vs. PVP-I.

Late treatment

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

Delić, 5/28/2022, Randomized Controlled Trial, Croatia, peer-reviewed, 12 authors, study period October 2020 - June 2021, trial NCT04755972 (history).	**risk of death, 23.0% lower, RR 0.77, p = 0.13**, treatment 23 of 42 (54.8%), control 37 of 52 (71.2%), NNT 6.1, ICU mortality.
	risk of death, 20.1% lower, RR 0.80, p = 0.30, treatment 20 of 42 (47.6%), control 31 of 52 (59.6%), NNT 8.3, 28 day mortality.
El-Badrawy, 11/18/2022, Randomized Controlled Trial, Egypt, preprint, 7 authors, study period 1 September, 2021 - 30 April, 2022, trial NCT05035524 (history).	**risk of death, 23.2% lower, RR 0.77, p = 0.26**, treatment 32 of 272 (11.8%), control 42 of 274 (15.3%), NNT 28, all cases.
	risk of death, 54.8% lower, RR 0.45, p = 0.02, treatment 12 of 247 (4.9%), control 27 of 251 (10.8%), NNT 17, mild/moderate/severe cases.
	risk of death, 79.2% lower, RR 0.21, p = 0.21, treatment 1 of 125 (0.8%), control 5 of 130 (3.8%), NNT 33, moderate cases.
	risk of death, 53.2% lower, RR 0.47, p = 0.02, treatment 11 of 63 (17.5%), control 22 of 59 (37.3%), NNT 5.0, severe cases.
	risk of death, 22.7% higher, RR 1.23, p = 0.33, treatment 20 of 25 (80.0%), control 15 of 23 (65.2%), critical cases.
	recovery time, 27.6% lower, relative time 0.72, p < 0.001, treatment mean 4.2 (±2.5) n=272, control mean 5.8 (±3.1) n=274, time to clinical improvement.
	CT score, 33.3% lower, RR 0.67, p = 0.001, treatment 238, control 229, CT score, day 30.
El-Badrawy (B), 6/12/2022, prospective, Egypt, peer-reviewed, 7 authors, study period 15 April, 2020 - 31 August, 2020, trial NCT04374591 (history).	**risk of death, 56.7% lower, RR 0.43, p = 0.37**, treatment 3 of 127 (2.4%), control 3 of 55 (5.5%), NNT 32.
	risk of progression, 39.4% lower, RR 0.61, p = 0.52, treatment 7 of 127 (5.5%), control 5 of 55 (9.1%), NNT 28, deterioration or death, day 30.
	risk of no recovery, 19.2% lower, RR 0.81, p = 0.03, treatment 84 of 127 (66.1%), control 45 of 55 (81.8%), NNT 6.4, day 30.
	relative CT score, 72.7% better, RR 0.27, p < 0.001, treatment 127, control 55, day 30.
	recovery time, 66.2% lower, relative time 0.34, p < 0.001, treatment mean 3.31 (±0.99) n=127, control mean 9.79 (±6.288) n=55, time to clinical improvement.
Mody, 3/19/2021, Randomized Controlled Trial, India, peer-reviewed, 1 author, study period July 2020 - September 2020, trial CTRI/2020/07/026535.	**risk of no improvement, 63.6% lower, RR 0.36, p < 0.001**, treatment 8 of 30 (26.7%), control 22 of 30 (73.3%), NNT 2.1.

Soares, 12/29/2021, prospective, Brazil, peer-reviewed, 17 authors, study period December 2020 - May 2021.	risk of death, 75.8% lower, RR 0.24, $p < 0.001$, treatment 6 of 44 (13.6%), control 18 of 32 (56.2%), NNT 2.3.
Wang, 3/15/2023, Randomized Controlled Trial, China, peer-reviewed, 13 authors.	hospitalization time, 38.5% lower, relative time 0.61, $p < 0.001$, treatment mean 7.7 (±4.15) n=23, control mean 12.53 (±5.56) n=32.

Supplementary Data

Supplementary Data

Footnotes

a. Viral infection and replication involves attachment, entry, uncoating and release, genome replication and transcription, translation and protein processing, assembly and budding, and release. Each step can be disrupted by therapeutics.

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