Summary Report

Sodium ascorbate

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Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IRB	Institutional Review Board
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of sodium ascorbate (UNII code: S033EH8359), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how sodium ascorbate is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how sodium ascorbate has been used historically and currently.[1-3] Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of sodium ascorbate and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATIONS

Sodium ascorbate was nominated for inclusion on the 503B Bulks List by David Smith, Fagron, and the Outsourcing Facilities Association (OFA). Sodium ascorbate was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Sodium ascorbate was nominated for:

- Vitamin deficiency via a combination intramuscular injection at a strength determined by the prescriber's request
- Vitamin C deficiency via an injection; adult supplementation is usually 50-200 mg/day
- Scurvy and adjuvant for cancer patients on chemotherapy, cold and flu, advanced colorectal cancer, and immune boost via a combination 500 mg/mL injectable product

Nominators provided references from published peer-reviewed literature to describe the pharmacology, and support the clinical use, of sodium ascorbate.[6-11]

Reasons provided for nomination to the 503B Bulks List included:

- There are no FDA-approved drug products that contain sodium ascorbate
- There are no FDA approved drug products that combine sodium ascorbate with calcium gluconate, magnesium chloride, and Vitamin B Complex in an injection form
- Sodium ascorbate is bactericidal when added to water, making it a safer form of vitamin C compared to other salt forms
- Sodium ascorbate aqueous solutions have a more basic pH compared to ascorbic acid aqueous solutions; the osmolality of the commercial product does not allow for bolus infusions due to pH
- Currently sodium ascorbate is only available as an oral laxative combination for bowel irrigation
- Compounded product may be the only product to effectively treat the indication for which it is intended
- Patient need for dosage form or strength, including greater concentration, that is not available commercially
- Patient sensitivities to dyes, fillers, preservatives or other excipients in manufactured products
- Manufacturer backorder

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of sodium ascorbate products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for sodium ascorbate; name variations of sodium ascorbate were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing sodium ascorbate. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The first search strategy used a combination of controlled vocabulary terms and keywords to describe four concepts: ascorbic acid, sodium ascorbate or vitamin C; intravenous or intramuscular administration; therapeutic or preventative use; and nominated indications for use (refer to Appendix 1 for full search strategies). An additional indication for use was identified after the first search strategy had been completed and run in each database. Therefore, a second search strategy was constructed using a combination of controlled vocabulary terms and keywords to describe three concepts: ascorbic acid, sodium ascorbate or vitamin C; intravenous or intramuscular administration; and methemoglobinemia. Terms for ascorbic acid and vitamin C were included because study authors often did not provide the specific salt form that was used, and the controlled vocabulary term for ‘sodium ascorbate’ is ‘ascorbic acid’ in both MEDLINE and Embase. Keywords for brand or proprietary products were not included in the search strategies because studies that utilized such products were excluded. Results were limited human studies in English language. Searches were conducted on March 4 and 5, 2020. The reference lists of relevant systematic reviews and meta-analyses were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on March 4, 2020 for clinical practice guidelines that recommended the use of sodium ascorbate and provided sufficient dosing and administration instructions. ClinicalTrials.gov was searched on June 3, 2020 for US studies investigating the intravenous use of vitamin C, ascorbic acid or sodium ascorbate.

Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which sodium ascorbate, ascorbic acid, or vitamin C was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies that used ascorbic acid or vitamin C were included because authors often did not specify salt form, and a subject matter expert (SME) stated that they had not seen anything clinically that would differentiate sodium ascorbate and ascorbic acid. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); or designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity. Studies were also excluded if sodium ascorbate was used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; or a dosage form, ROA, or combination that was not nominated. Studies in which sodium ascorbate was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of sodium ascorbate; setting; total number of patients; number of patients who received sodium ascorbate; patient population; indication for use of sodium ascorbate; dosage form and strength; dose; ROA; frequency and duration of therapy; use of sodium ascorbate in a combination product; use and formulation of sodium ascorbate in a compounded product; use of sodium ascorbate compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances sodium ascorbate was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify the following medical specialties that would potentially use sodium ascorbate: naturopathy and nutrition. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of sodium ascorbate in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Year 1 were not contacted to distribute the project Year 2 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Sodium ascorbate is not available as an FDA-approved product. It is available as part of several oral combination products. The FDA-approved injectable formulation of vitamin C is ascorbic acid as a 500 mg/mL intravenous solution.
- Sodium ascorbate is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for sodium ascorbate.
- Sodium ascorbate is not available in the nominated dosage form and ROA in any of the national medical registries searched. However, it is available in Australia as non-scheduled intravenous injections.

Table 1. Currently approved products – US

No approved products in the US

Table 2. Currently approved products – select non-US countries and regions

No approved products in the selected non-US countries and regions

Results of literature review

Study selection

Database searches yielded 1426 references; 14 additional references were identified from ClinicalTrials.gov. After duplicates were removed, 1093 titles and abstracts were screened. After screening, the full text of 267 articles was reviewed. Finally, 60 studies were included. Two hundred seven studies were excluded for the following reasons: wrong study design (175 studies); wrong dosage form or ROA (10); sodium ascorbate, ascorbic acid, or vitamin C used as brand or proprietary product (7); wrong indication (7); sodium ascorbate, ascorbic acid, or vitamin C not used clinically (4); unable to obtain full text (3); sodium ascorbate, ascorbic acid, or vitamin C only mentioned briefly (1).

Refer to Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Characteristics of included studies

The 60 included studies were published between 1947 and 2020. There were 23 experimental studies, 11 observational studies, 30 descriptive studies, and 0 clinical practice guidelines. The 60 studies were conducted in the following countries: Australia, Brazil, Canada, China, Egypt, Indonesia, Iran, Japan, New Zealand, Spain, the UK, and the US.

A total of 2262 patients participated in the 60 included studies. The number of patients in each study ranged from 1 to 557.

Outcome measures differed among the included studies and included: tumor markers, vitamin C levels, overall survival, and progression-free survival.

Refer to Table 5 in Appendix 2 for summary of study country, design, patient population, intervention and comparator, and outcome measures.

Use of sodium ascorbate

Two hundred eighty-seven patients received sodium ascorbate, ascorbic acid, or vitamin C as an experimental treatment for cancer, administered intravenously in doses ranging from 50 mg/kg to 80 mg/kg. Duration of treatment ranged from 4 weeks to 4 years. Four hundred forty-four patients received sodium ascorbate, ascorbic acid, or vitamin C as an experimental treatment for sepsis or septic shock, administered intravenously in doses ranging from 120 mg/kg to 4500 mg/kg. Duration of treatment ranged from 72 hours to 6 days. Thirty-eight patients received sodium ascorbate, ascorbic acid, or vitamin C as an experimental treatment for scurvy or vitamin C deficiency, administered intravenously in doses ranging from 200 mg to 2000 mg. Duration of treatment ranged from 2 days to 12 weeks. Six patients received sodium ascorbate, ascorbic acid, or vitamin C as an experimental treatment for methemoglobinemia, administered intravenously in doses ranging from 2 g to 20 g. Duration of treatment ranged from 3 days to 6 days. One patient received sodium ascorbate, ascorbic acid, or vitamin C as an experimental treatment for acute respiratory distress syndrome (ARDS), administered intravenously in doses ranging from 100 mg/kg to 200 mg/kg. Two hundred eighteen patients received sodium ascorbate, ascorbic acid, or vitamin C as an experimental treatment for Epstein-Barr virus, administered intravenously in doses ranging from 7.5 g to 50 g. Duration of treatment was a mean of 9 treatments. Nineteen patients received sodium ascorbate, ascorbic acid, or vitamin C as an experimental treatment for neutrophil locomotory dysfunction due to serious trauma, administered intravenously in doses ranging from 200 mg to 500 mg. Duration of treatment was 7 days. Patients received sodium ascorbate, ascorbic acid, or vitamin C as an experimental treatment for the reduction of acute lung disease caused by SARS-Cov-2, administered intravenously in 300 mg/kg doses. Duration of treatment is up to 72 hours.

Refer to Tables 6 and 7 for summaries of dosage by indication.

Sodium ascorbate, ascorbic acid, or vitamin C was used as a compounded product, and was used in a combination product (refer to Tables 8-10).

In 18 studies, the authors' concluding statement recommended the use of sodium ascorbate, ascorbic acid, or vitamin C for the treatment of acute respiratory distress syndrome (ARDS), cancer and symptoms, Epstein-Barr virus, methemoglobinemia, neutrophil locomotory abnormality, sepsis/septic shock, and vitamin C deficiency/scurvy via intravenous ROA.[7,12-28] In 1 study, the authors concluded that the use of sodium ascorbate, ascorbic acid, or vitamin C was not recommended for the treatment of sepsis/septic shock via intravenous ROA.[29] In 23 studies, the authors concluded that further studies were necessary for the use of sodium ascorbate, ascorbic acid, or vitamin C for the treatment of cancer, sepsis/septic shock, and vitamin C deficiency/scurvy via intravenous ROA.[30-52] In 2 studies, the authors did not provide a definitive conclusion for the recommendation of sodium ascorbate, ascorbic acid, or vitamin C for the treatment of cancer via intravenous ROA.[53,54] In 4 studies, the authors' conclusion did not address the use of sodium ascorbate, ascorbic acid, or vitamin C.[55-58] In 12 studies, there was no conclusion for the use of sodium ascorbate, ascorbic acid, or vitamin C for the treatment of cancer, sepsis/septic shock, and SARS-Cov-2 since the trials were still ongoing.[59-70]

Refer to Table 5 in Appendix 2 for summary of authors' conclusions.

Pharmacology and historical use

In addition to the 60 included studies, 10 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of sodium ascorbate.

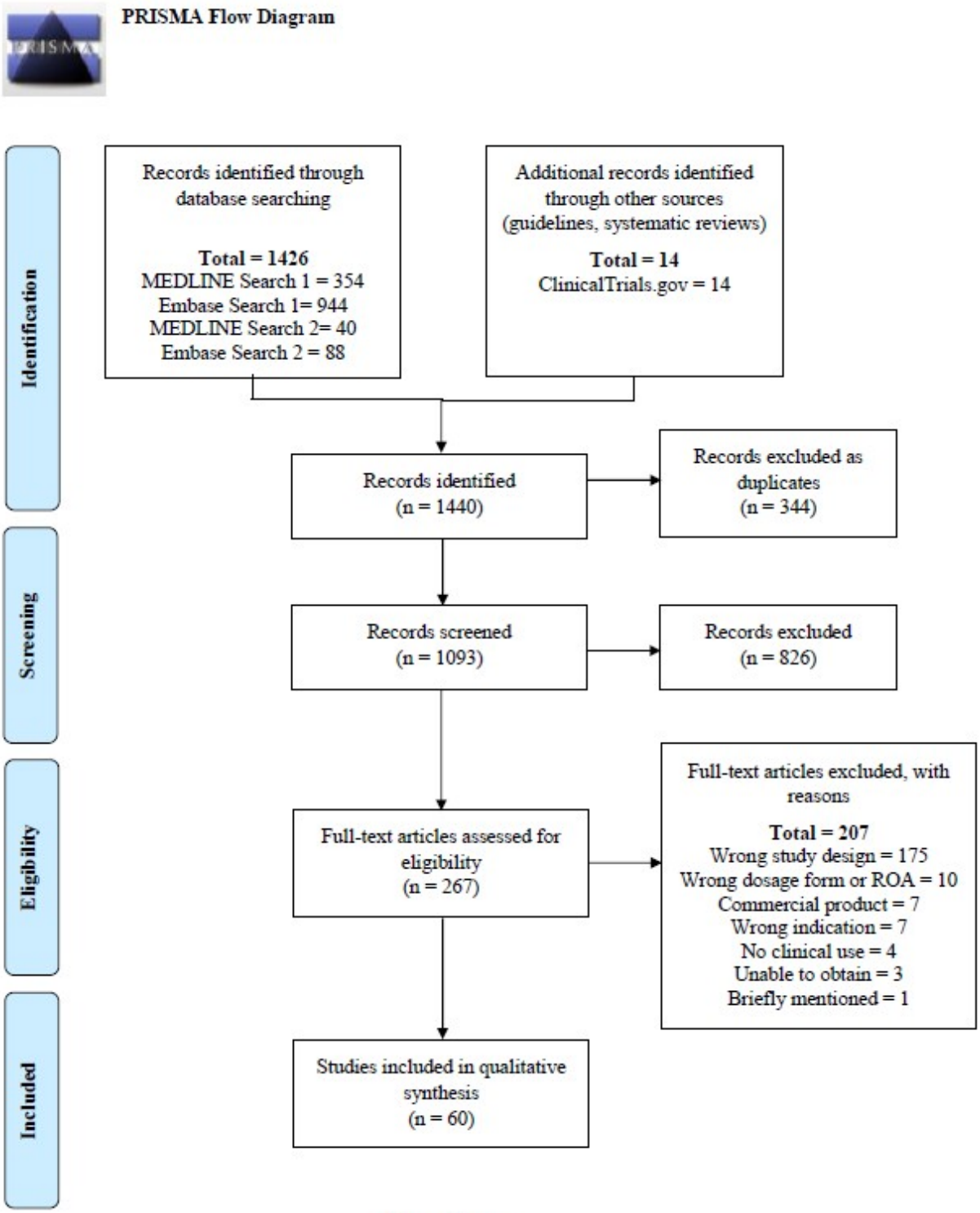
There are some concerns that high doses of intravenous ascorbic acid have the potential to cause oxalate kidney stones and oxalate nephropathy; this is because ascorbic acid is broken down to oxalic acid, and is especially an issue in patients with pre-existing renal dysfunction.[7,71] Additionally, high-dose intravenous ascorbic acid should be avoided in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, as they are at risk for hemolysis with high doses of intravenous ascorbic acid, due to the production of hydrogen peroxide.[7,72] That being said, several studies that were included in the literature review recommend using ascorbic acid to resolve methemoglobinemia in patients with G6PD deficiency, as an alternative to methylene blue therapy.[23,24,58]

When vitamin C is used in patients with cancer, there were some studies that suggested it may "improve clinical symptoms such as fatigue or nausea associated with either the cancer itself or resulting from the effects of chemotherapy medications."[7] There is also some thought that vitamin C is helpful in treating cancer because it breaks down into hydrogen peroxide and is especially toxic to cancer cells due to them being catalase-deficient: "healthy noncancerous cells produce enough catalase to protect themselves from the toxic effects of hydrogen peroxide, resulting in no adverse effects to them."[72] Another theory that was studied in colorectal cancer cells with KRAS and BRAF mutations is that vitamin C increases cancer cell death by increased uptake of the oxidized form (dehydroascorbate), which is "believed to cause an oxidative stress by depleting glutathione and inactivating glyceraldehyde phosphate dehydrogenase, resulting in an energetic crisis and cell death."[72]

Since patients presenting with sepsis typically are deficient in vitamin C, and "sepsis is characterized by the excessive production of reactive oxygen species," this has emerged as a potential indication for vitamin C administration.[73,74] The purpose behind using vitamin C for sepsis is to reverse organ dysfunction and microcirculatory injury.[74] A 2019 retrospective cohort study in South Korea led the authors to conclude that "adjunctive intravenous vitamin C therapy alone did not reduce hospital mortality in mechanically ventilated patients with severe sepsis or septic shock."[75] In 2019, a randomized, double-blind, placebo-controlled, multicenter trial was conducted to evaluate the effect of vitamin C infusion on organ failure and biomarkers in patients with sepsis and severe acute respiratory failure (ClinicalTrials.gov Identifier: NCT02106975).[76] This study was excluded due to using a commercial product; however, the authors concluded that while there was no significant improvement in the primary endpoints, further research is needed to evaluate vitamin C for other outcomes.[76] A 2020 review on nutrition in sepsis also came to the conclusion that currently there is "insufficient evidence [to support] routine vitamin C administration in sepsis."[77] Several ongoing studies on the administration of intravenous vitamin C in patients with sepsis were included in the literature review.

Vitamin C supplementation has also been investigated in children who have end stage renal disease and are on maintenance hemodialysis; in this patient population, it was shown to have a significant reduction in serum uric acid levels.[51] According to a review, intravenous ascorbic acid has been shown to help with hemodialysis patients resistant to epoetin with functional iron deficiency, despite being overloaded with iron.[78]

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

Types of Studies	**Number of Studies**
Descriptive[12-15,17-26,28,30,31,33,34,46,50,53-58]	27
Observational[7,32,39-43,45,47,68]	10
Experimental[16,27,29,35-38,44,48,49,51,52,59-67,69,70]	23

Table 4. Number of studies by country

Country	**Number of Studies**
Canada[60]	1
China[35]	1
Egypt[51]	1
Indonesia[16]	1
Iran[49]	1
Spain[37]	1
UK[38]	1
US[7,12-15,17-28,30-34,36,39-48,50,52-59,61-70]	52
Multiple Countries • Australia, New Zealand, Brazil[29]	1
	Total US: 52 Total Non-US Countries: 8

Table 5. Summary of included studies

Refer to Appendix 2

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Cancer[7,12-15,28,30-34,54,59,63-70]	10-150 g/infusion	–	–	Intravenous	5-39 infusions 7-10 days
		5-15%	Solution		
	7.5-375 g/week 5 g/kg/week	0.06-0.12%	–		11 days – at least 2.5 years Until disease progresses
		7.5-10%	Solution		
	15-30 g/1-3 months – 420 g/week	–	–		10 months – 4 years
Sepsis, septic shock[36,39-48,52,55,61]	6 g/day 120-200 mg/kg/day	–	–	Intravenous	72 hours – 4 days 24 hours post-last pressor dose Until ICU discharge
		1.5%	Solution		
Scurvy, vitamin C deficiency[17-20,50,56,57]	Loading 2 g 200 mg-1 g/day	–	–	Intravenous	2-10 days
Methemoglobinemia[21-24,58]	2-5 g/dose	–	–	Intravenous	1-6 doses 3 days
Acute respiratory distress syndrome (ARDS)[25]	100-200 mg/kg/day	–	–	Intravenous	7 days
Epstein-Barr virus (EBV)[26]	7.5-50 g/dose	–	Solution	Intravenous	1-23 doses
Neutrophil locomotory dysfunction due to serious trauma[27]	200-500 mg/day	0.2-0.5%	Solution	Intravenous	7 days
Reduce acute lung injury caused by SARS-Cov-2[62]	300 mg/kg/day	–	Solution	Intravenous	Up to 72 hours

Abbreviations: "–", not mentioned; ICU, intensive care unit.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Sepsis, septic shock[16,29,37,38,49,60]	0.45-6 g/day	–	–	Intravenous	Once – 10 days
	100-200 mg/kg/day	50 mg/kg/mL	Solution		Until shock resolution or ICU discharge
Cancer[35]	50-80 mg/kg/day	–	–	Intravenous	Days 0-9, up to 2 cycles
Scurvy, vitamin C deficiency[51]	750 mg/week	–	–	Intravenous	12 weeks

Abbreviations: "–", not mentioned; ICU, intensive care unit.

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Sodium ascorbate / Calcium gluconate / Magnesium chloride / Vitamin B Complex – intramuscular injection	0
	Sodium ascorbate 27.9% / Ascorbic acid 25% – injectable	0

Table 9. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Cancer[7]	2018	• Ascorbic acid mixed in a 1 L bag of 5% dextrose in water with 1 g magnesium chloride and 1 g calcium gluconate	Solution	0.05-0.15%

Table 10. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Sepsis, septic shock[49]	• Ascorbic acid (25 mg/kg) diluted in 50 mL of dextrose 5% solution	Solution	–

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Twenty-four SMEs discussed sodium ascorbate Amongst these 24 SMEs, there were 4 medical doctors, 17 pharmacists, 1 nurse practitioner, and 2 naturopathic doctors. The SMEs specialized and/or were board-certified in critical care, infectious disease, naturopathic medicine, nutrition, occupational medicine, oncology/hematology, palliative care, pediatrics, and primary care/family practice, working in academia, academic medical centers, consulting, hospitals/health system, pharmacy/pharma company, and private practice/clinics. The SMEs had been in practice for 6 to 44 years.

There has been a renewed interest in the use of vitamin C after a recently published study by Paul Marik.[42] This was a retrospective analysis that saw a reduction in patient mortality with a combination of hydrocortisone, thiamine, and intravenous ascorbic acid early in therapy for patients in septic shock who had not responded effectively to fluid and vasopressors. The hope was that with repletion of vitamins or co-factors, the patients' cellular functions might work more effectively. However, some SMEs noted that not only was it uncertain if the effect was from vitamin C, thiamine, or both, but subsequent large prospective randomized controlled trials have refuted the claims for intravenous vitamin C. They said that it was a typically given as intermittent large doses, 1500 mg of ascorbic acid every 6 hours, though one study did look at it as a continuous infusion. Other doses brought up included 25-50 mg/kg/dose and 3 g over 6 hours. Some SMEs said that while they have not been using it as a standard of practice, they have seen physicians who have "jumped on board with the vitamin C severe sepsis train and others who are waiting for more data." One SME said that their organization has actually come up with guidance around it, but that they have only used it in a handful of patients as a last resort when there is nothing left to do for those patients: "a lot of these patients expired." Another SME said that they did not think their institution had any vitamin C stock, that they felt the data was not strong enough to support its use, and it was not approved through the pharmacy and therapeutics committee.

Several SMEs had also seen patients who had received enormous doses of vitamin C (20-50 g) as a homeopathic treatment for cancer, though they were not aware of any studies supporting this use, with one SME remarking, "In my mind, there is no basis for why you would use something like that." Vitamin C seems to be a last-ditch effort or adjunct to other chemotherapy regimens. Another SME said that high-dose vitamin C is standard therapy for most of their oncology patients, though not everyone gets it. They said that in patients receiving potent and effective chemotherapy with evidence of a good response, using vitamin C as a cytotoxic therapy is redundant and therefore will withhold it. According to this SME, high-dose vitamin C is prescribed for cancers due to its oxidative effect on tumor cells through the production of hydrogen peroxide; this is not a profound effect and they "rarely see tumor shrinkage with vitamin C being the sole or primary cytotoxic therapy." However, it seems to improve the quality of life in patients, regardless of if the patient is receiving chemotherapy, radiotherapy, or neither, by mitigating side effects, helping patients heal from surgery, and "basically helping people with better energy and mental clarity, less depression and anxiety." This SME said that they administer intravenous high-dose vitamin C in their office and will often add other agents such as fermented mistletoe extract, an adjunctive immune supportive therapy that is common in Germany.

One SME said that they have used vitamin C in a few scurvy cases amongst patients so malnourished that "you could see it in their gumline." Some SMEs said that they do not look for vitamin C deficiency in their patients, so they have not had to administer any treatment for it yet.

Another SME said that they have used ascorbic acid and zinc for wound healing as the standard additive for almost every total parenteral nutrition (TPN); exceptions were made if the patient had kidney stones or

other renal dysfunction. If being administered for wound healing or pressure ulcers, then vitamin C was typically a short course, and the SME preferred to administer enterally or orally if possible, though intravenous was sometimes required. Other SMEs said that they have also seen a few requests to add vitamin C for the healing of severe wounds that have not responded to other standard measures. However, they said that there is no good evidence for the use of vitamin C to support wound healing unless the patient was truly deficient in vitamin C.

There was one SME who said there have been some thoughts in the cardiac surgery intensive care unit (ICU) regarding levels of ascorbic acid and vasoplegia being affected by cardiopulmonary bypass procedures. They have seen ascorbic acid used occasionally in that unit, "but it's also being evaluated from a research standpoint to further elaborate on evidence in that population." As such, vitamin C is kept in stock in the pharmacy, and usually administered as 1500 mg every 6 hours. The SME said that they used to use it as partial vials, but to reduce waste, they thought the pharmacy started to make multiple bags in their production lab.

One SME said that vitamin C is great and should be available in multiple forms since "people like to take it and some people can't take an oral tab." They said that they use it for colds since patients like to think that you are giving them an immune boost; it is probably a placebo effect, but vitamin C "can't hurt you." Another SME said that they have not seen sodium ascorbate used for cold and flu or as an injectable immune boost. A few SMEs brought up vitamin C in SARS-Cov-2. One SME said that they have seen its use resurface in this patient population; another said "there's been some data indicating that some critical care patients and even COVID patients could benefit from intravenous sodium ascorbate." However, neither report having used it themselves.

One SME said that they do not give just vitamin C alone, but always with vitamin B complex, magnesium, and maybe some other minerals. They had also administered vitamin C and thiamine together. Another SME said that they are not generally in favor of combination products, since they can make it difficult to find the correct dose for each individual component.

Regarding availability, one SME said that they were not sure why anyone would use sodium ascorbate over the commercially available ascorbic acid (Ascor®). Other SMEs said that they do not know how sodium ascorbate compares, but that ascorbic acid has very limited stability (beyond use date of 2-4 hours after being opened) and degrades quickly when exposed to light and air. This can cause a lot of waste, since the commercially available product comes in a very large 50 mL vial at a concentration of 500 mg/mL. One SME said that they would make intermittent infusions from the commercial product and make enough to last for 24 hours. Ascorbic acid can cause the formation of nephroliths and calcium carbonate crystallization in urine, so while not directly nephrotoxic, it can have negative effects in patients and result in acute renal failure. Another SME said that while they had heard of the potential for nephrotoxicity, the patients they have used ascorbic acid in were so critically ill that they were already on renal replacement therapy; however, because the patients were so ill, they cannot say whether or not the vitamin C made their condition worse.

Another SME said that they have not seen anything that would differentiate sodium ascorbate and ascorbic acid, so long as the compatibility has been validated and given as equivalent doses. However, they also said it brought up a few questions: "depending on the dose you're using or how long you're using it, would the patient be more likely to develop metabolic acidosis? If that's a concern, I guess in a long-term PN [parenteral nutrition] patient, you worry about metabolic bone disease that they're already at risk for. Could it affect any of their electrolyte elimination as well?"

It was also noted that there is a shortage of sodium ascorbate in the commercial market, so they see compounders producing it, but it is a difficult product to get intravenously; “some hospitals order it because it’s part of their protocols for sepsis or critical patients.”

Results of survey

Zero people responded to the survey distributed via professional medical associations and available on the project website.

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which sodium ascorbate prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded sodium ascorbate

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded sodium ascorbate

No respondents to survey distributed via professional medical associations

CONCLUSION

Sodium ascorbate was nominated for inclusion on the 503B Bulks List via injection to treat vitamin C deficiency, scurvy, cold and flu, advanced colorectal cancer, and as an immune boost and adjuvant for cancer patients on chemotherapy. Sodium ascorbate is not available in the nominated dosage form and ROA in any of the national medical registries searched.

From the literature review and interviews, injectable vitamin C has been used for a wide variety of indications. Most studies used ascorbic acid, or did not specify the product used beyond "vitamin C." Indications for use included: cancer treatment, sepsis or septic shock, scurvy or vitamin C deficiency, methemoglobinemia, ARDS, Epstein-Barr virus, neutrophil locomotory dysfunction, wound healing, and in the cardiac surgery intensive care unit. In addition, there were currently ongoing trials for vitamin C in the treatment of cancer, sepsis or septic shock, and SARS-Cov-2. While some practitioners were strong supporters of vitamin C utilization, others had their doubts about the strength of evidence supporting its use. In addition, there were practitioners who felt that while the data is not strong, vitamin C was unlikely to cause patient harm, and they may administer as a last resort or upon patient request. Vitamin C is commercially available as injectable ascorbic acid, but this formulation has limited stability and comes in a large, concentrated vial. There were also concerns about the formation of kidney stones and metabolic acidosis with prolonged use.

Zero people responded to the survey.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy 1

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to March 3, 2020
- Date last searched: March 4, 2020
- Limits: Humans (search hedge); English language
- Number of results: 354

1	ascorbic acid/	41724
2	as#orb$.tw.	40233
3	xyloascorb$.tw.	3
4	(vitamin$ adj2 c).tw.	20396
5	or/1-4	66350
6	exp administration, intravenous/	141842
7	infusions, parenteral/	26195
8	infusions, intravenous/	54478
9	injections/	42187
10	injections, intramuscular/	30789
11	injections, intravenous/	81384
12	inject$.tw.	654716
13	infusion$.tw.	226719
14	(parenteral$ adj2 (administ$ or therap$ or treat$ or deliver$)).tw.	11072
15	intravenous$.tw.	308002
16	intra venous$.tw.	479
17	intravascular$.tw.	43024
18	intra vascular$.tw.	254
19	intramuscular$.tw.	46814
20	intra muscular$.tw.	618

21	or/6-20	1177674
22	drug therapy/	30353
23	primary prevention/	18152
24	pre-exposure prophylaxis/	1937
25	immunomodulation/	6213
26	de.fs.	2948872
27	dt.fs.	2183728
28	ad.fs.	1393168
29	tu.fs.	2190900
30	pc.fs.	1263942
31	therap$.tw.	2355879
32	treat$.tw.	4670699
33	prevent$.tw.	1202938
34	prophyla$.tw.	144654
35	or/22-34	9778696
36	exp ascorbic acid deficiency/	3908
37	exp neoplasms/	3290888
38	exp inflammation/	330064
39	critical illness/	27797
40	common cold/	4184
41	influenza, human/	48109
42	exp antineoplastic protocols/	137787
43	chemotherapy, adjuvant/	39858
44	consolidation chemotherapy/	519
45	induction chemotherapy/	2565
46	maintenance chemotherapy/	1589

47	exp immune system/	1137127
48	((as#orb$ or vitamin c) adj3 (deficien$ or deplet$)).tw.	1874
49	avitaminosis.tw.	517
50	hypovitamin$.tw.	2125
51	hypoascorbemi$.tw.	6
52	scurv$.tw.	1413
53	scorbutus.tw.	24
54	cancer$.tw.	1472426
55	malignan$.tw.	490030
56	neoplas$.tw.	229979
57	tumo?r$.tw.	1457134
58	sepsis$.tw.	82046
59	septic?emi$.tw.	18738
60	bacter?emi$.tw.	28100
61	endotox?emi$.tw.	8476
62	(common adj3 cold).tw.	3131
63	chemotherap$.tw.	345153
64	flu.tw.	10741
65	influenza?.tw.	102079
66	or/36-65	5103172
67	and/5,21,35,66	755
68	exp animals/ not humans/	4674491
69	67 not 68	392
70	limit 69 to english language	354

MEDLINE search strategy 2

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to March 4, 2020
- Date last searched: March 5, 2020
- Limits: Humans (search hedge); English language
- Number of results: 40

1	ascorbic acid/	41726
2	as#orb$.tw.	45719
3	xyloascorb$.tw.	3
4	(vitamin$ adj2 c).tw.	23174
5	or/1-4	74182
6	exp administration, intravenous/	141850
7	infusions, parenteral/	26196
8	infusions, intravenous/	54482
9	injections/	42190
10	injections, intramuscular/	30790
11	injections, intravenous/	81385
12	inject$.tw.	727422
13	infusion$.tw.	241612
14	(parenteral$ adj2 (administ$ or therap$ or treat$ or deliver$)).tw.	11996
15	intravenous$.tw.	334632
16	intra venous$.tw.	566
17	intravascular$.tw.	46906
18	intra vascular$.tw.	296
19	intramuscular$.tw.	51469
20	intra muscular$.tw.	706
21	or/6-20	1288675
22	methemoglobinemia/	3130

23	meth?emoglobin$.tw.	6674
24	ferrih?emoglobin$.tw.	163
25	hemiglobin$.tw.	55
26	or/22-25	7585
27	and/5,21,26	50
28	exp animals/ not humans/	4675019
29	27 not 28	45
30	limit 29 to english language	40

Embase search strategy 1

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 4, 2020
- Limits: Humans (search hedge); English language
- Number of results: 944

1	ascorbic acid'/mj	36514
2	sodium ascorbic acid cotransporter'/de	213
3	ascorb*':ti,ab,tn	59489
4	askorb*':ti,ab,tn	51
5	xyloascorb*':ti,ab,tn	7
6	(vitamin* NEAR/2 c):ti,ab,tn	31787
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	92701
8	parenteral drug administration'/de	2103
9	intramuscular drug administration'/de	71554
10	intravascular drug administration'/exp	417233
11	injection'/exp	247471
12	inject*':ti,ab	1081672
13	infusion*':ti,ab	352385
14	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	18102
15	intravenous*':ti,ab	482382
16	intra venous*':ti,ab	1433
17	intravascular*':ti,ab	67425
18	intra vascular*':ti,ab	675
19	intramuscular*':ti,ab	74319
20	intra muscular*':ti,ab	1269
21	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	2062203
22	drug therapy'/de	711290

23	pre-exposure prophylaxis'/de	3891
24	immunomodulation'/de	79019
25	drug dose':lnk	621716
26	drug administration':lnk	1717677
27	drug therapy':lnk	3841536
28	prevention':lnk	1159372
29	therap*':ti,ab	4072661
30	treat*':ti,ab	7765275
31	prevent*':ti,ab	1876511
32	prophyla*':ti,ab	257381
33	#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32	13040741
34	ascorbic acid deficiency'/exp	5948
35	neoplasm'/exp	5031993
36	inflammation'/exp	3688224
37	critical illness'/de	28545
38	common cold'/de	9670
39	influenza'/exp	96198
40	antineoplastic protocol'/de	204
41	cancer chemotherapy'/exp	440847
42	immune system'/exp	2236396
43	((ascorb* OR askorb* OR 'vitamin c') NEAR/3 (deficien* OR deplet*)):ti,ab	3257
44	avitaminosis':ti,ab	1366
45	hypovitamin*':ti,ab	4256
46	hypoascorbem*':ti,ab	12
47	hypoascorbaem*':ti,ab	0
48	scurv*':ti,ab	2518

49	scorbutus':ti,ab	36
50	cancer*':ti,ab	2494950
51	malignan*':ti,ab	836835
52	neoplas*':ti,ab	368059
53	tumor*':ti,ab	1967922
54	tumour*':ti,ab	425589
55	sepsis*':ti,ab	147991
56	septicemi*':ti,ab	18422
57	septicaemi*':ti,ab	9533
58	bacteremi*':ti,ab	33827
59	bacteraemi*':ti,ab	9022
60	endotoxemi*':ti,ab	10204
61	endotoxaemi*':ti,ab	1320
62	(common NEAR/3 cold):ti,ab	5036
63	chemotherap*':ti,ab	634337
64	flu':ti,ab	19747
65	influenza*':ti,ab	141141
66	#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65	10244586
67	#7 AND #21 AND #33 AND #66	1907
68	[animals]/lim NOT [humans]/lim	5999949
69	#67 NOT #68	1198
70	#67 NOT #68 AND [english]/lim	944

Embase search strategy 2

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 5, 2020
- Limits: Humans (search hedge); English language
- Number of results: 88

1	ascorbic acid'/mj	36519
2	sodium ascorbic acid cotransporter'/de	213
3	ascorb*':ti,ab,tn	59509
4	askorb*':ti,ab,tn	51
5	xyloascorb*':ti,ab,tn	7
6	(vitamin* NEAR/2 c):ti,ab,tn	31800
7	1 OR 2 OR 3 OR 4 OR 5 OR 6	92723
8	parenteral drug administration'/de	2103
9	intramuscular drug administration'/de	71559
10	intravascular drug administration'/exp	417229
11	injection'/exp	247457
12	inject*':ti,ab	1081947
13	infusion*':ti,ab	352440
14	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	18105
15	intravenous*':ti,ab	482487
16	intra venous*':ti,ab	1434
17	intravascular*':ti,ab	67443
18	intra vascular*':ti,ab	675
19	intramuscular*':ti,ab	74336
20	intra muscular*':ti,ab	1269
21	8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20	2062639
22	methemoglobinemia'/de	6260

23	methemoglobin*':ti,ab	7225
24	methaemoglobin*':ti,ab	2172
25	ferrihemoglobin*':ti,ab	185
26	ferrihaemoglobin*':ti,ab	43
27	hemiglobin*':ti,ab	95
28	22 OR 23 OR 24 OR 25 OR 26 OR 27	11844
29	7 AND 21 AND 28	124
30	[animals]/lim NOT [humans]/lim	6001155
31	29 NOT 30	114
32	29 NOT 30 AND [english]/lim	88

Appendix 2. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 1: Cancer					
Allen, 2015, US[63]	Open-label, phase 2 clinical trial	Out-patients >18 y with newly diagnosed glioblastoma multiforme Estimated enrollment: 90	• Ascorbic acid plus radiation therapy, temozolomide	Overall survival, progression free survival, health-related QOL	*Ongoing, estimated completion date 2024*
Bazzan *et al*., 2018, US[7]	Retrospective chart review	86 In-patients (35%, median 60 y, range 19-87 y) 32 Patients received only ascorbic acid for cancer management 53 Patients received ascorbic acid adjunct to chemotherapy	• IV ascorbic acid mixed with magnesium chloride and calcium gluconate (86)	Quality of life measures	IV ascorbic acid may be useful in symptom management and improving quality of life in cancer patients; it is generally safe and well-tolerated
Campbell *et al.*, 1991, US[12]	Case report	1 In-patient with reticulum cell sarcoma (100%, 42 y)	• Sodium ascorbate (1)	–	The double-regression in response to intravenous ascorbate can only be explained by the tumors being ascorbate-sensitive
Cullen, 2015, US[64]	Open-label, phase 2 clinical trial	Out-patients >18 y with stage IV non-small cell lung cancer Estimated enrollment: 57	• Ascorbic acid plus paclitaxel, carboplatin	Tumor response, progression free survival, overall survival	*Ongoing, estimated completion date 2027*
Cullen, 2016, US[65]	Open-label, phase 2 clinical trial	Out-patients >18 y with non-small cell lung cancer, diagnosed within past 4 weeks Estimated enrollment: 46	• Ascorbic acid plus radiation therapy, paclitaxel	Progression rate at completion of radiation and chemotherapy, tumor response, progression-free survival, overall survival	*Ongoing, estimated completion date 2026*

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Drisko *et al.*, 2003, US[13]	Case	2 Out-patients with ovarian cancer (0%, range 55-60 y)	• Ascorbic acid adjunct to chemotherapy (2)	–	Antioxidants adjunct to chemotherapy may improve chemotherapy efficacy and be safe
Drisko *et al.*, 2018, US[14]	Case report	1 Out-patient with pancreatic cancer (100%, 68 y)	• Ascorbic acid not adjunct to chemotherapy (1)	–	Current evidence is enough for targeted phase I and II clinical trials of pharmacological ascorbic acid as a complement to standard therapies for metastatic pancreatic cancer
Dusing *et al.*, 2011, US[30]	Case	1 Out-patient with prostate cancer (100%, 59 y)	• Ascorbic acid (1)	–	Recommends translating into clinical trials due to dramatic reduction in tumor metabolism
General Oncology, Inc., 2019, US[66]	Open-label, phase 2A clinical trial	Out-patients >18 y with BRCA-related metastatic pancreatic adenocarcinoma Estimated enrollment: 12	• Vitamin C plus melphalan, BCNU, low-dose ethanol, vitamin B12, autologous hematopoietic stem cell infusion	Objective response according to RECIST 1.1, overall survival, physical, social and emotional well-being as measured by Functional Assessment of Cancer Therapy: General (FACT-G)	*Ongoing, estimated completion date 2022*
Gonzalez *et al.*, 2017, US[15]	Case report	1 Patient with ER-positive, PR-positive breast cancer (0%, 45 y)	• High dose IV vitamin C protocol (1)	Decreasing tumor marker levels	Vitamin C is an effective adjunct in breast cancer treatment, and recommend continuing studying high dose IV vitamin C as adjuvant for cancer in any stage

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Jackson *et al.*, 1995, US[53]	Case report	1 Out-patient with partially resected pancreatic adenocarcinoma and hyperglycemia (100%, 68 y)	• Vitamin C (1)	Plasma vitamin C levels, follow-up CT scan	"A CT scan of the abdomen six months after the surgery failed to detect any progression of the tumor. A recurrence of the tumor occurred after the amount and frequency of I. V. vitamin C was significantly reduced so the patient could travel in his motor-home (family reunions, etc). The patient lived for 12 months after the initial diagnosis of cancer of the head of the pancreas. He received no chemotherapy or radiation treatment and enjoyed a good quality of life until the time of his death."
Kasi *et al.*, 2020, US[59]	Phase II Clinical Trial	Out-patients with metastatic pancreatic adenocarcinoma Estimated enrollment not specified	• Control • Ascorbate	Overall survival, objective response rate, progression-free survival	*Ongoing, estimated completion date 2025*
Mikirova *et al.*, 2012, US[31]	–	45 Out-patients after standard treatment with conventional methods (67%, range 25-93 y)	• Ascorbic acid (45)	Blood C-reactive protein, cytokines and vitamin C levels	IV vitamin C may reduce inflammation which is correlated with reductions in tumor markers; further investigation is needed
Mikirova *et al.*, 2016, US[32]	–	12 Outpatients with cancer after standard treatment with conventional methods (sex, age not specified) 8 Healthy volunteers as control subjects (50%, range 35-60 y)	• Vitamin C (12)	Serum concentrations of 175 cytokines Serum concentrations of 58 proteins (4 patients)	Vitamin C treatment can downregulate angiogenesis and inflammation-promoting cytokines; future studies should have a larger sample size and a greater variety of tumor types

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Monga, 2018, US[67]	Single-arm, open-label phase Ib/II clinical trial	Out-patients >18 y with locally advanced soft tissue sarcomas requiring preoperative radiation Estimated enrollment: 25	• Ascorbate plus radiation therapy	Tumor response by pathological complete response rates, incidence of dose-limiting toxicities, time to disease progression, overall response rate, overall survival	*Ongoing, estimated completion date 2022*
Padayatty *et al.*, 2006, US[33]	Case reports	3 Patient cases with renal tumor, primary bladder tumor and multiple satellite tumors, and diffuse large B-cell lymphoma (33%, range 49-51y)	• Vitamin C (3)	Survival time	Further clinical study of safety and efficacy is warranted, but data suggests that high-dose IV vitamin C may have anti-tumor effects
Riordan *et al.*, 1990, US[79] Riordan *et al.*, 1998, US[80] Riordan *et al.*, 2000, US[54] Riordan *et al.*, 2004, US[81]	Case	7 Out-patient cases with kidney cancer, stage IV colorectal carcinoma, metastatic pancreatic carcinoma, diffuse large B-cell lymphoma, non-Hodgkin's lymphoma, and end-stage breast cancer (57%, range 51-73 y)	• Ascorbic acid or Vitamin C (7)	–	High-dose vitamin C (up to 50 g/day) is not toxic in cancer patients, and some patients had complete remission after these infusions; however, infusions of 30 g vitamin C do not produce high enough concentrations to kill most tumor cells
Salerno, 2013, US[34]	Case study	1 Out-patient with prostate cancer (100%, 57 y)	• High dose vitamin C (1)	Prostate-specific antigen levels, prostate ultrasound	After 10 months of treatment, the vascular tumor was no longer detectable on ultrasound; there should be further consideration of the role of vitamin C for cancer

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Shah, 2017, US[68]	Single-arm, 3-cohort, open-label trial	Out-patients >18 y with colorectal adenocarcinoma, lung cancer, or pancreatic cancer that was: Cohort A: • Resectable and had not received chemotherapy or radiotherapy Cohort B: • Inoperable, metastatic KRAS or BRAF mutant, and had received at least 1 line of treatment Cohort C: • Metastatic, with extended RAS or BRAF mutation, with liver metastases amenable to Y90 radioembolisation Estimated enrollment: 50	• Vitamin C	Cohort A: change in antitumor activity measured by pathologic response based on tumor regression grading Cohort B: 3-month disease control rate, progression-free survival Cohort C: max tolerated dose of high-dose vitamin V in combination with Y90 radioembolization, progression-free survival	*Ongoing, estimated completion date 2021*
Solís-Nolasco, 2020, US[28]	Case study	1 Patient with brainstem glioma (gender not specified, 5 y)	• Vitamin C plus endolaser therapy (1)	Reduction in size of glioma on CT	"Combining IVC [IV vitamin C] with endolaser as adjuvant therapies, we achieved a significant reduction in tumor size. This clinical therapeutic approach for glioma could be utilized as an adjuvant therapy for this deadly type of cancer."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Taylor, 2019, US[69]	Open-label clinical trial	Out-patients >18 y with cisplatin-ineligible, muscle invasive bladder cancer Estimated enrollment: 21	• Ascorbic acid added to gemcitabine/carboplatin chemotherapy	Post-treatment pathological staging (10 weeks), overall change in patient-reported QOL (8 weeks), disease-free survival (5 years)	*Ongoing, estimated completion date 2024*
Witzig, 2018, US[70]	Randomized, parallel assignment, double-blinded clinical trial	Out-patients >18 y with relapsed or refractory lymphoma Estimated enrollment: 151	• Arm A: ascorbic acid, combination chemotherapy • Arm B: Placebo, combination chemotherapy • Arm C: ascorbic acid, combination chemotherapy Arm C has different chemotherapy than arm A or B	Overall response rate (up to 2 years), clinical benefit rate, continued salvage therapy beyond cycle 2	*Ongoing, estimated completion date 2024*
Zhao *et al.*, 2018, China[35]	–	73 Patients with acute myeloid leukemia (54%, range 60-87 y)	• DCAG: decitabine, granulocyte colony-stimulating factor, cytarabine, aclarubicin (34) • Vitamin C, DCAG (39)	Complete remission rate, overall survival	Vitamin C may have a synergistic anti-neoplastic action in acute myeloid leukemia patients; larger clinical trials need to be performed to adjust vitamin C dosing and examine benefits
Indication 2: Sepsis, septic shock					
Bernardo *et al.*, 2018, US[36]	Pilot study	21 In-patients with mild septic shock (43%, mean 60.67 y ± 2.66)	• IV vitamin C, hydrocortisone, and thiamine (number not reported) • Placebo (number not reported)	Vasopressor requirements, in-hospital mortality	The use of the intervention treatment appears to be beneficial in mild septic shock, but further studies are needed to confirm the findings

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Fan *et al.*, 2019, US[52]	–	18 In-patients with septic shock (gender and age not specified)	• Placebo (9) • Vitamin C, hydrocortisone, thiamine (9)	Mortality, ICU LOS	"The combination of vitamin C, hydrocortisone, and thiamine in addition to standard ICU care may improve mortality and outcomes in patients with septic shock. These findings are currently being validated in an expanded cohort through ongoing enrollment at our center."
Ferron-Celma *et al.*, 2009, Spain[37]	Prospective, randomized, double-blinded clinical trial	20 In-patients that were septic after abdominal surgery Placebo (gender not specified, mean 65.1 y ± 3.6) Vitamin C (gender not specified, mean 67.8 y ± 4.5)	• Placebo (10) • Vitamin C (10)	Analysis of Fas (CD95) expression; measures of neutrophil apoptosis; leukocyte counts; hemoglobin levels	"Further research is required to determine whether the effects of vitamin C on neutrophil apoptosis are reflected in postsurgical recovery time for septic surgery patients, relating apoptotic parameters and neutrophil counts to postsurgical complications, the development of MODS [multiple organ dysfunction syndrome], and the mortality rate."
Fuji *et al.*, 2020, Australia, New Zealand, Brazil[29]	Open-label, parallel randomized trial	211 In-patients with septic shock Intervention (63.6%, mean 61.9 y ± 15.9) Control (62.5%, mean 61.6 y ± 13.9)	• Vitamin C, hydrocortisone, thiamine (107) • Control (104)	Time alive and free of vasopressors at day 7 after randomization	Treatment with vitamin C, hydrocortisone, and thiamine does not lead to a more rapid resolution of septic shock compared with solo hydrocortisone
Galley *et al.*, 1997, UK[38]	–	30 In-patients with septic shock (73%, range 21-89 y)	• Antioxidant: n-acetyl-cysteine, ascorbic acid, alpha-tocopherol (16) • Placebo (14)	Hemodynamic changes	Antioxidant replacement causes statistically significant hemodynamic changes in septic shock patients; further studies are required

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Grady *et al.*, 2019, US[39]	Propensity matched analysis	54 In-patients with septic shock requiring vasopressors Vitamin C (59%, mean 67 y ± 12) No vitamin C (67%, mean 63 y ± 16)	• Vitamin C, hydrocortisone, and thiamine (27) • No vitamin C (27)	Duration of vasopressors, input/output at 6 and 24 hours, percentage of patients needing renal replacement therapy, ICU and hospital mortality	The administered treatment may be helpful in patients with septic shock, but large prospective studies are needed to confirm the preliminary findings
Greenley *et al.*, 2019, US[40]	Retrospective cohort	172 In-patients diagnosed with septic shock requiring at least 1 vasopressor (gender and age not specified)	• Control (number not reported) • Ascorbic acid, thiamine, and hydrocortisone (number not reported)	ICU mortality, number of vasopressors required, ICU LOS, duration of mechanical ventilation	Patients receiving the treatment failed to demonstrate statistically significant decrease in ICU mortality over control group, though requirement of 1 vasopressor to be eligible required a higher severity of illness; further research is required to investigate efficacy prior to progression to septic shock
Long *et al.*, 2020, US[41]	Retrospective cohort	206 In-patients with sepsis, septic shock, or bacterial pneumonia Standard care (56%, 61.1 y ± 16.2) Intervention (54%, 65.5 y ± 13.9)	• Standard care (127) • Intervention: standard care plus hydrocortisone vitamin C, thiamine (79)	ICU and hospital mortality, vasopressor duration, need for renal replacement therapy, LOS	There was a time-sensitive improvement in APACHE-adjusted ICU mortality in patients with intervention, but no difference in hospital mortality; future trials should look at the relationship between timeliness of therapy and magnitude of outcome improvement
Marik *et al.*, 2017, US[42]	Retrospective before-after clinical study	94 In-patients with primary diagnosis of severe sepsis or septic shock and procalcitonin level >2ng/mL (gender and age not specified)	• Control (47) • Hydrocortisone, vitamin C, thiamine (47)	Hospital mortality, SOFA score	The intervention may effectively prevent organ dysfunction and reduce mortality in patients with sepsis and septic shock; additional studies are required to confirm findings

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Masse *et al.*, 2020, Canada[60]	Parallel-group, allocation concealed, blinded, superiority RCT	Patients admitted to the ICU with proven or suspected infection as the main diagnosis; treated with vasopressor continuous intravenous infusion at time of assessment Estimated enrollment: 800	• Vitamin C • 5% dextrose in water or normal saline	Composite of death or persistent organ dysfunction at 28 days after randomization	*Ongoing, estimated completion date 2022*
Mitchell *et al.*, 2019, US[43]	Retrospective, observational analysis	At least 35 in-patients with sepsis or septic shock (gender and age not specified)	• Vitamin C (35) • Historically matched control	Hospital mortality; ICU, 28-day, and 60-day mortality	"Initial study outcomes indicate an increased mortality rate in this veteran population, compared to patients in the study by Marik and colleagues, in which hospital mortality was 8.5% (n=47). These findings may be explained by the higher acuity of illness at baseline in this patient population, as demonstrated by the mean APACHE II score of 26. By continuing to collect data from historical controls, this study will elucidate the impact of the vitamin C protocol on mortality in this Veteran population."
Rahardjo *et al.*, 2013, Indonesia[16]	Prospective, randomized, placebo-controlled trial	32 In-patients with sepsis (gender not specified, range 17-60 y)	• Vitamin C (number not reported) • Normal saline (number not reported)	Lactate level, base deficit, and SvO2	Vitamin C in septic patients can improve lactate level, base deficit, and SvO2
Reilkoff, 2020, US[61]	Randomized, double-blind, placebo-controlled clinical trial	In-patients older than 18 y with septic shock Estimated enrollment: 140	• Vitamin C • Placebo	All-cause mortality (28 days), duration of vasopressor therapy, duration of ICU stay	*Ongoing, estimated completion date 2020*

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Rosini *et al.*, 2018, US[44]	Randomized, double-blind, placebo-controlled trial	24 In-patients (gender and age not specified)	• Placebo (12) • Ascorbic acid (12)	Initial serum ascorbic acid levels, change in SOFA, ICU utilization or LOS, hospital LOS, mortality	High-dose ascorbic acid does not decrease organ failure at 72 hours compared to placebo in patients with sepsis, but larger studies are needed to evaluate the efficacy
Sadaka *et al.*, 2019, US[45]	Retrospective cohort	62 In-patients with septic shock Treatment (52%, mean 67 y ± 16) Control (52%, mean 70 y ± 12)	• Ascorbic acid, hydrocortisone, and thiamine (31) • Control (31)	ICU and hospital mortality, ICU and hospital LOS, renal replacement therapy, duration of vasopressors, mechanical ventilation-free days	Patients with septic shock who received the intervention had reduced ICU mortality, complications did not differ between groups, and pending results from larger multicenter studies, the intervention may improve patient survival
Saltzman *et al.*, 2019, US[46]	Case report	1 In-patient with septic shock and cardiogenic shock (100%, 53 y)	• Vitamin C, hydrocortisone, thiamine (1)	SOFA score	While procalcitonin was decreased, and cardiac indices, SOFA score, and mortality rate improved, a randomized controlled trial is required to change management of septic shock and mortality
Schuring *et al.*, 2018, US[55]	Case	1 In-patient with history of HIV-1, noncompliant with antiretroviral therapy (100%, 31 y)	• Intravenous methylprednisolone, high-dose vitamin C (1)	Resolution of shock and vasopressor dependence within 24 hours	"The use of systemic corticosteroids is useful in this clinical scenario and we proposed it should be part of the therapeutic approach of patients with similar clinical presentation."
Teachey *et al.*, 2018, US[47]	Single-center, retrospective, multiple arm case control study	36 In-patients (gender and age not specified)	• Corticosteroids (12) • Thiamine, corticosteroids (12) • Vitamin C, thiamine, corticosteroids (12)	Mortality, LOS, vasopressor use	Addition of vitamin C had no effect on mortality or LOS; further research assessing outcomes is needed

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Wald *et al.*, 2020, US[48]	Retrospective, propensity score-matched cohort study	557 Pediatric in-patients with septic shock Control (48%, median 10.1 y [IQR 3-15]) Hydrocortisone-only (53%, median 10.5 y [IQR 4-15]) Hydrocortisone, ascorbic acid, thiamine (60%, median 8.4 y [IQR 4-14])	• Control (333) • Hydrocortisone-only (181) • Hydrocortisone, ascorbic acid, thiamine (43)	30-day mortality	Children with septic shock who receive therapy with hydrocortisone, ascorbic acid, and thiamine have lower mortality when matched with untreated control patients and matched hydrocortisone-only therapy patients; however, larger, multicenter studies are needed to confirm findings
Zabet *et al.*, 2016, Iran[49]	Double-blind randomized clinical trial	28 In-patients with septic shock who required a vasopressor drug to maintain arterial pressure Ascorbic acid (71.42%, mean 64.14 y ± 15.98) Control (78.57%, 63.71 y ± 13.84)	• Ascorbic acid (14) • Control (14)	Vasopressor dose and duration over 3 days	Ascorbic acid may be considered effective and safe in patients with septic shock; however, future studies are needed to determine the most effective dose and best time for administration
Indication 3: Scurvy, vitamin C deficiency					
De Jesus, 1947, US[50]	Report of cases	2 In-patients post-gastric resection (100%, range 32-42 y)	• Ascorbic acid (2)	Ascorbic acid levels	"As a result of this experience at least 1 Gm. of ascorbic acid is now given as routine following gastric resection. Similar findings were observed after thoracic operations. Whether such a dose is sufficient to prevent disappearance of the vitamin from the plasma after operation awaits further investigation."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
El Mashad *et al.*, 2016, Egypt[51]	–	60 In-patients with end-stage renal disease suffering from dyslipidemia and hyperuricemia Intervention (47%, mean 8.2 y ± 17.3) Control (50%, mean 9.5 y ± 3.1)	• Vitamin C (30) • Control (30)	Uric acid, ascorbic acid, and serum lipid levels	Supplementation of vitamin C causes the reduction of serum uric acid levels, improves the lipid profile, and improves ascorbic acid deficiency; further investigation is needed with larger sample size and longer duration
Joshi *et al.*, 2019, US[56]	Case report	1 Patient with vitamin C deficiency due to poor diet (100%, 69 y)	• Vitamin C (1)	Plasma vitamin C	Scurvy should be considered in patients who are at risk, but the diagnosis is frequently overlooked
Kraus *et al.*, 2017, US[17]	Case report	1 In-patient with scurvy presenting with abdominal pain, uterine bleeding, behavior change, and severe anemia (0%, 13 y)	• Vitamin C (1)	–	"Scurvy should be considered as a cause of AUB [abnormal uterine bleeding] in adolescents with selective diets; symptoms rapidly reverse with treatment which can be diagnostic. Vitamin C is essential for collagen synthesis; deficiency leads to capillary fragility as well as reduced platelet adhesiveness."
Mathbout *et al.*, 2017, US[57]	Case report	1 In-patient with uncontrolled type-1 diabetes (100%, 43 y)	• Vitamin C (1)	–	"However, in the case of this patient, scurvy was a very real issue in the setting of his malnutrition and chronic diabetic diarrhea."
Naranbhai *et al.*, 2018, US[18]	Case report	1 In-patient with chronic idiopathic gastroparesis, constipation, and migraines who presented for thigh hematoma, menorrhagia, and peri-follicular hemorrhages (0%, 39 y)	• Vitamin C (1)	Stabilized anemia, cessation of vaginal bleeding, improvement of leg pain	"Symptoms respond rapidly to oral ascorbic acid but may require parenteral administration in severe cases. The general internist should be familiar with the clinical features and risk factors for this treatable and preventable disease."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Shavit and Brown, 2013, US[19]	Case report	1 In-patient with simultaneous scurvy and Wernicke's encephalopathy (100%, 48 y)	• IV vitamin C in banana bag (1)	–	The patient's recovery over a several day period showed the benefits of vitamin replacement, though longer periods of replacement may be required
Weitzel and Moon, 2019, US[20]	Case report	1 In-patient with scurvy secondary to eosinophilic esophagitis (100%, 31 y)	• Vitamin C (1)	Resolution of scurvy	"Intravenous vitamin C can be used as treatment for scurvy in those patients that cannot tolerate oral vitamin C."
Indication 4: Methemoglobinemia					
Anderson *et al.*, 2004, US[21]	Case report	2 In-patients who developed methemoglobinemia after undergoing aortic reconstruction (0%, range 57-73 y)	• Ascorbic acid (2)	–	In methemoglobinemia, treatment with methylene blue and adjuvants like dextrose and ascorbic acid should be started promptly
Faust *et al*., 2018, US[22]	Case report	1 Pregnant in-patient with methemoglobinemia concern after exposure to "large" quantity of prilocaine during teeth extraction (0%, 35 y)	• Ascorbic acid (1)	–	Due to concerns about teratogenicity with methylene blue, ascorbic acid was effective treatment, despite delayed onset
Kotwal *et al.*, 2015, US[23]	–	1 In-patient with hemolytic anemia and methemoglobinemia due to underlying glucose-6-phosphate-dehydrogenase deficiency (100%, 43 y)	• Ascorbic acid with red blood cell transfusion and IV fluids (1)	Improvement of anemia, resolution of leukocytosis	Ascorbic acid should be used to treat methemoglobinemia in patients with glucose-6-phosphate-dehydrogenase deficiency
Makkar *et al.*, 2018, US[58]	Case report	1 In-patient with relapsed chronic lymphocytic leukemia and rasburicase-induced methemoglobinemia (100%, 61 y)	• Vitamin C (1)	–	It is important to check a patient's glucose-6-phosphate-dehydrogenase status before treating methemoglobinemia with methylene blue in order to avoid life-threatening hemolysis.

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Reeves *et al.*, 2016, US[24]	Case report	1 In-patient with recent diagnosis of multiple myeloma and renal insufficiency (100%, 46 y)	• Ascorbic acid (1)	Oxygen saturation values and symptoms	Ascorbic acid was used to treat methemoglobinemia due to the concern of the patient having glucose-6-phosphate-dehydrogenase deficiency; methemoglobinemia was resolved without worsening renal function
Indication 5: Acute respiratory distress syndrome (ARDS)					
Ali *et al.*, 2018, US[25]	–	1 In-patient presenting with a case of adenovirus-induced ARDS (100%, 62 y)	• IV Vitamin C (1)	–	IV vitamin C is potentially an effective adjunct therapy for ARDS
Indication 5: Epstein-Barr virus (EBV)					
Mikirova and Hunninghake, 2014, US[26]	–	218 Out-patients with EBV who had received a diagnosis of chronic fatigue syndromes, nononucleosis, fatigue, or EBV infection (gender and age not specified)	• IV Vitamin C (218)	EBV antibodies before and after vitamin C therapy, vitamin C levels, vitamin D levels	The study showed a reduction in EBV antibodies during IV vitamin C therapy, consistent with literature observations
Indication 6: Neutrophil locomotory dysfunction due to serious trauma					
Maderazo *et al.*, 1991, US[27]	Prospective, placebo-controlled, double-blind, randomized block	46 In-patients with serious blunt trauma (78%, range 14-62 y) 87 normal controls (25%, range 21-63 y)	• 5% dextrose in water or saline placebo (18) • Alpha-tocopherol / ascorbic acid (14) • Alpha-tocopherol (9) • Ascorbic acid (5)	Neutrophil (PMN) locomotion, serum and leukocyte levels of ascorbic acid and alpha-tocopherol	The use of antioxidant replacement therapy in patients with blunt trauma causes a significant improvement in PMN locomotory abnormality

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 7: Reduce acute lung injury caused by SARS-Cov-2					
Kashiouris and Davis, 2020, US[62]	Randomized, parallel assignment, quadruple masked clinical trial	In-patients >18 y with a positive diagnosis of SARS-Cov-2 (based on positive test) and hypoxemia Estimated enrollment: 200	• Placebo: standard of care, dextrose 5% water • Intervention: ascorbic acid	Number of ventilator-free days	*Ongoing, estimated completion date 2021*

Abbreviations: "–", not mentioned; APACHE, Acute Physiology and Chronic Health Evaluation; CT, computed tomography; ICU, intensive care unit; IV, intravenous; LOS, length of stay; QOL, quality of life; RECIST, response evaluation criteria in solid tumors; RCT, randomized controlled trial; SOFA, Sequential Organ Failure Assessment.

[a]As defined by authors.

Appendix 3. Survey instrument

Welcome. We want to understand your clinical use of compounded sodium ascorbate. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly,
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	o	o	o
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you prescribe or administer sodium ascorbate to your patients?

   - o Yes
   - o No

3. Do you prescribe or administer sodium ascorbate by any of the following dosage forms and/or routes of administration? (check all that apply)

   - o Intramuscular injection
   - o Intravenous injection
   - o None of the above

4. I prescribe or administer sodium ascorbate for the following conditions or diseases: (check all that apply)

   - o Advanced colorectal cancer
   - o Adjuvant for cancer patients on chemotherapy
   - o Cold and flu
   - o Immune boost
   - o Vitamin deficiency or scurvy
   - o Other (please explain) _____

5. I use compounded sodium ascorbate because: (check all that apply)

    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain) _____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing sodium ascorbate.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded sodium ascorbate at your practice?

    - o Yes
    - o No
    - o I'm not sure

7. I obtain compounded sodium ascorbate from the following: (check all that apply)

    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____

8. What is your practice setting? (check all that apply)

    - o Physician office/private practice
    - o Outpatient clinic
    - o Hospital/health system
    - o Academic medical center
    - o Emergency room
    - o Operating room
    - o Other (please describe) _____

9. What degree do you hold? (check all that apply)

    - o Doctor of Medicine (MD)
    - o Doctor of Osteopathic Medicine (DO)
    - o Doctor of Medicine in Dentistry (DMD/DDS)
    - o Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - o Naturopathic Doctor (ND)
    - o Nurse Practitioner (NP)
    - o Physician Assistant (PA)
    - o Other (please describe) _____

Appendix 4. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Allergy/Immunology	American Academy of Allergy, Asthma, and Immunology (AAAI)	Declined – survey not approved
Anesthesia	American Society of Regional Anesthesia and Pain Medicine (ASRA)	Declined – failed to respond
	Society for Ambulatory Anesthesia (SAMBA)	Declined – failed to respond
	Society for Neuroscience in Anesthesiology and Critical Care	Declined – failed to respond
Critical Care	Critical Care Societies Collaborative	Declined – failed to respond
Dentistry & Oral Medicine	Academy of General Dentistry (AGD)	Declined – provided interview referrals
	American Dental Association (ADA)	Declined – failed to respond
Dermatology	American Academy of Dermatology (AAD)	Agreed
	American Osteopathic College of Dermatology (AOCD)	Declined – not interested
Endocrinology	The Endocrine Society (ENDO)	Agreed
	Pediatric Endocrine Society	Agreed
Gastroenterology	American Gastroenterological Association (AGA)	Declined – failed to respond
	Obesity Medicine Association (OMA)	Declined – did not have anyone to contribute to research
Hematology	American Society of Hematology (ASH)	Declined – does not distribute surveys
Infectious Disease	American Academy of HIV Medicine (AAHIVM)	Declined – failed to respond
Medicine	American Medical Association (AMA)	Declined – failed to respond

Naturopathy	American Association of Naturopathic Physicians (AANP)	Agreed
	The Oncology Association of Naturopathic Physicians (OncANP)	Agreed
Nephrology	American College of Clinical Pharmacists: Nephrology Practice Network	Agreed
	American Society of Nephrology	Declined – provided interview referrals
Nutrition	American Society for Parenteral and Enteral Nutrition (ASPEN)	Declined – provided interview referrals
Obstetrics and Gynecology	American Gynecological and Obstetrical Society (AGOS)	Declined – failed to respond
	Nurse Practitioners in Women's Health	Agreed
Ophthalmology	American Academy of Ophthalmology (AAO)	Agreed
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Declined – survey not approved
Pain Management	American Academy of Pain Medicine (AAPM)	Declined – survey not approved
	American Academy of Physical Medicine and Rehabilitation	Declined – failed to respond
Pediatrics and Neonatology	American Academy of Pediatrics (AAP)	Agreed
Primary Care	American College of Physicians (ACP)	Declined – failed to respond
Psychiatry	American Academy of Clinical Psychiatrists	Declined – failed to respond
	American Association for Geriatric Psychiatry	Declined – failed to respond
Rheumatology	American College of Rheumatology (ACR)	Agreed

Surgery	Ambulatory Surgery Center Association (ASCA)	Agreed
	American Academy of Orthopaedic Surgeons (AAOS)	Declined – no interest in participation from members
	American Association of Hip and Knee Surgeons (AAHKS)	Declined – only send surveys from members
	American College of Surgeons (ACS)	Agreed
	American Society for Metabolic and Bariatric Surgery (AMBS)	Declined – only send surveys from members
	The Association of Bone and Joint Surgeons	Declined – failed to respond
	Physician Assistants in Orthopaedic Surgery	Declined – failed to respond
	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	Declined – failed to respond
	Society of Gynecologic Surgeons (SGS)	Declined – policy limits number of surveys per year and do not have a method to identify if any of the SGS members are using ipamorelin
Toxicology	American Academy of Environmental Medicine (AAEM)	Declined – failed to respond
Urology	Sexual Medicine Society of North America (SMSNA)	Agreed

[a]Associations that declined in Year 1 were not contacted in Year 2.