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Intravenous Vitamin C (Ascorbic Acid): Information for Physicians and Patients

Dr. Paul S. Anderson – Research professor and former director of IV Services Bastyr University Oncology Research

Intravenously administered high dose ascorbic acid (HDIVC) as used in cases of patients who have cancer has considerable mythology surrounding it. The purpose of this review is not to exhaustively recap the data regarding this therapy but rather to address basic issues of safety, pharmacology and outcomes of ongoing research.

Safety:

Paramount in the decision to include a particular therapy for any condition is the safety of that treatment. The bottom line with respect to HDIVC is that in properly screened patients it is an extremely safe intervention. In a 2010 review (4) there were five reported serious adverse events in the literature. Of these one was hemolysis in a patient with G6PD deficiency (G6PD is an enzyme used in red blood cells to reduce hydrogen peroxide to water) and the balance were renal complications (in patients with preexisting renal disease or insufficiency).

All patients are pre-screened for multiple conditions prior to any HDIVC, and particular attention is paid to G6PD status, renal function and other co-morbidities. Deficient G6PD and renal insufficiency are contraindications for HDIVC.

In a review of the five cases mentioned, all could have been prevented with proper screening as recommended in current protocols.

Pharmacology:

The major concept behind HDIVC and cancer is that it is used as a pro-drug for the production of hydrogen peroxide in the extracellular space, thus potentially damaging the cancer cells (4). Is there any evidence of this potential? First, orally administered vitamin C is unable to create a plasma level high enough to create any substantial peroxide formation (1,5). Second, it has been demonstrated that HDIVC properly dosed can create the type of peroxide surge in the extracellular space required to potentially damage cancer cells (5). Finally it has been shown that some cancer cells have decreased ability to defend against the peroxide, where normal human cells can reduce the peroxide to water (1) – making HDIVC a potential anti-cancer pro-drug.

Our protocols are designed to ensure safety first. They are followed by measurement of post-HDIVC blood ascorbate levels to assure the effective peroxide forming dose for each patient.

HDIVC and Other Chemotherapeutic Agents:

A great deal of confusing information regarding the appropriate place and timing for the administration of HDIVC with other chemotherapeutic agents exists. Currently an up to date review of all available data in this arena has been completed by the author. (18) A quote from a

recent peer reviewed publication reveals the overall direction the data are pointing: “Clinical investigation of pharmacologic ascorbate should be considered as an addition to existing cancer treatments. Its mechanism of action as a pro-drug for H2O2 generation is distinct from most currently used agents. For this reason, there is potential for synergy, or at least an additive effect, in combination with other drugs. This strategy is similar to that used for treatment of many cancers, tuberculosis, serious bacterial infections, hepatitis, and HIV. Emerging data indicate that there are additive effects of ascorbate with other neoplastic agents” (11). A review of available data in 2008 summarized multiple existing cancer therapies and their effect in combination with ascorbate and found all agents either not affected or enhanced by ascorbate (9). This review had one exception which was the agent bortezomib, but later clinical data showed that even this agent had synergistic effect with HDIVC (10). More study needs to be done, but data published between late 2011 and 2012 also reveal only positive additive effects using HDIVC in combination with existing cancer treatments (7).

Ongoing Research:

Recent data in cell lines show promise using HDIVC in combination with conventional chemotherapy agents. (13) Other human data show efficacy in palliative applications and quality of life. (14, 15, 16)

Published reviews of HDIVC agree that there is limited data to support or to disprove the efficacy of this intervention in cancer patients (1,3,4,5). These authors agree that more data needs to be collected in order to verify the use of this intervention for cancer patients. In addition to many anecdotal reports regarding the positive benefits of HDIVC in cancer situations (4), two recent presentations reported a 50% positive outcome in a small sample of stage 4 cancer patients following data over a 2.5 year timeframe (6,7). A recent review of published data regarding intravenous ascorbic acid supports the above assertions as well as supporting the idea that this therapy has a role in treating the patient who has cancer (12).

While we have only preliminary outcomes data as yet regarding the success rate of HDIVC it is viewed as a safe and potentially effective treatment in a medically supervised environment. This was also supported by a Phase I-II clinical trial in patients receiving HDIVC and cytotoxic chemotherapy. (17)

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Pharmacologic Basis for Stability of High Dose Intravenous Ascorbic Acid (HDIVAA)

as used by Bastyr University Clinical Research Center (BCRC) and AMSA / AMT Clinics

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The pharmacologic stability of vitamins and minerals in parenteral solutions is reasonably well studied and published, but becomes a confusing data set when attempting to apply the available data to particular admixtures.

Our clinical research center is employing a version of a popularly used (1) HDIVAA formula for research purposes with established safety parameters (1,2). This formula is not specifically addressed in the existing pharmacologic data as to stability and administration guidelines, so this document is presented to summarize the available relevant pharmacologic data and to set a basis for safe use of our HDIVAA formula in human subjects.

The study parenteral formulations include ascorbic acid (commercially pH adjusted with sodium hydroxide and or sodium bicarbonate) concentrations from 25 to 150 grams, with additives of magnesium, calcium and potassium all in their chloride salt forms. The addition of these ions in their chloride salt forms was established during an interventional safety trial completed at BCRC (3). Further publication of this data is in progress, and formulae are available per request.

A stability study including ascorbic acid in combination with minerals and other vitamins (4) showed stability over time which was longer when refrigerated:

"Results: The results showed that the methodologies used for assessing the chemical stability of vitamins B1, B2, B6 and C in the formulation were selective, linear, precise and accurate. The vitamins could be considered stable in the formulation during the three days of study if stored at 4°C. When stored at 25°C vitamin C presented instability after 48 h.

Conclusion: The pediatric formulation containing high amount of calcium in the presence of organic phosphate, amino acids, glucose, sodium chloride, magnesium sulphate, pediatric vitamins and trace

***elements packaged in bag-type trilaminate presented a shelf life of the 72 h, when maintained under refrigeration, between 2°C and 8°C. This shelf life was measured considering the vitamins studied. Further studies are needed including all the vitamins present in this formulation*.**" **(4)**

Other data shows that vitamin degradation is accelerated in the presence of metal ions due to oxidation (5), which has a great deal of effect on parenteral ascorbic acid. This data is on par with laboratory calibration data for the measurement of ascorbate (versus dihydroascorbate) which establishes that ascorbate is stable in combination with periodic table main group ions but not polyvalent transition ions (9).

"The most significant cause of chemical instability is the oxidation of specific vitamins. The factors influencing calcium phosphate solubility include the commercial amino acid source, the calcium and phosphate salts used, temperature, magnesium concentration, and final volume. Precipitation can be avoided by organic phosphates. Trace element precipitation is most commonly caused by the formation of iron phosphate salts or copper cysteinate in cysteine-containing amino acid infusions. The least stable nutrient is ascorbic acid, which reacts with oxygen, and is catalyzed by copper ions. Oxygen originates from PN ingredients, the filling process, air remaining in the bag after filling, and oxygen permeation through the bag wall. Storage in multilayered bags with reduced gas permeability can protect residual ascorbic acid." **(5)**

This reasonable caution regarding trace mineral additives (as they are transition group elements) and ascorbate, yet not main group elements like calcium, magnesium, potassium and sodium is echoed in other parenteral guidelines (6).

Time based stability studies agree in general that ascorbate in parenteral solutions is best kept under refrigeration prior to administration if the time from preparation to administration exceeds 12 hours (6,7). This in general applies to solutions with ascorbate, and the main group elements. Addition of B-vitamins and transition metal ions can increase the oxidation of ascorbate and significantly reduce its stability (7,8). Based on available data parenteral mixtures containing ascorbate and either B-vitamins and or transition metals should be mixed and administered within the same one to four hour period, and kept in a light protected refrigerated environment (6,7,8).

Conclusions:

Based on the above review of the pharmacologic data regarding parenteral ascorbate we have established our intravenous formulations for maximum patient safety, (3) maximum stability and ascorbate conservation. Our formulations containing ascorbate (commercially pH adjusted with sodium hydroxide and or sodium bicarbonate), and the chloride salts of potassium, calcium and magnesium fit all safety and ascorbate protection parameters available in the literature as of this time.

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Pharmacology, Kinetics, Dosing and Safety of Intravenous Ascorbic Acid

Prepared as Data for Safe use of Ascorbic Acid in Human Research

As performed at Anderson Medical Specialty Associates in support of the Bastyr University Integrative Oncology Outcomes Study.

As an adjunct to our previously published guidelines as well as our ongoing use of intravenous ascorbic acid in patients with cancer I have prepared this document with appropriate references to answer common questions which are both mechanistic and practical. The purpose of this document is to organize the available peer reviewed data regarding the use, monitoring and biochemistry of intravenously administered ascorbic acid as employed in a pro-oxidative manner. All of this with the intention being to synthesize often disparate and misunderstood data as this therapy is one of many integrative oncology therapies employed in our general clinic and with study participants.

What potential mechanisms would the administration of intravenous ASC employ to create pro-oxidant effects?

"Strikingly, ascorbate may also lead to pro-oxidant effects, especially through the reduction of transition metal ions such as iron and copper… These reactions between ascorbate and transition metals are thought to be responsible for the pro-oxidant and cytotoxic properties of ascorbate observed in vitro … Ascorbate is also known to induce the release of iron bound to ferritin or haemosiderin, which could take part in the lipid peroxidation process driven by the Fenton reaction … Transition metals are not the only compounds that react with ascorbate. Indeed, quinoid compounds can be reduced by ascorbate … leading to the generation of a semiquinone radical that is readily reoxidized by molecular oxygen…" [2]

The cell paradox: Does the ASC need to enter the tumor cell?

"Extracellular but not intracellular ascorbate mediated cell death, which occurred by apoptosis and pyknosis/necrosis. Cell death was independent of metal chelators and absolutely dependent on H(2)O(2) formation. Cell death from H(2)O(2) added to cells was identical to that found when H(2)O(2) was generated by ascorbate treatment… Taken together, these data indicate that ascorbate at concentrations achieved only by i.v. administration may be a pro-drug for formation of H(2)O(2), and that blood can be a delivery system of the pro-drug to tissues. These findings give plausibility to i.v. ascorbic acid in cancer treatment, and have unexpected implications for treatment of infections where H(2)O(2) may be beneficial." [6]

If ASC is a prodrug for H2O2 production and pro-oxidant surge where does this take place?

Hoffer et.al. reported in 2008 "… doses up to 1.5 g/kg have been injected i.v. to cancer patients [4] with minimal adverse effects. This protocol achieved plasma ascorbic acid concentrations>10 mM for more than 4 h, which is largely sufficient to induce cancer cell death in vitro." [2] "The data show that pharmacologic ascorbate is a prodrug for preferential steady-state formation of Asc• and H2O2 in the extracellular space but not blood." [3] So the H2O2 surge created by ASC is primarily limited to the extracellular space which gives the H2O2 access to the cells.

What potential mechanisms can the H2O2 generated by the ASC (as well as the metabolism of the ASC itself) have in the damage and death of a cancer cell?

Pharmacologic ascorbic acid concentrations produce extracellular H2O2, which can diffuse into cells, deplete ATP in sensitive cells, and thereby cause cell death. ATP may be depleted by three mechanisms. (i) DNA damage induced by H2O2 activates PARP. Activated PARP catabolizes NAD+, thereby depleting substrate for NADH formation and consequent ATP synthesis. (ii) H2O2 is catabolized by concurrent oxidation of GSH to GSSG. To reduce GSSG back to GSH, GSH reductase utilizes NADPH, which is provided by the pentose shunt from glucose. Glucose used to reduce NADP+ to NADPH cannot be used for glycolysis or NADH production so that ATP generation is decreased. (iii) H2O2 may directly damage mitochondria, especially ATP synthase, so that ATP production falls. Some cancer cells rely primarily on glycolysis rather than on oxidative phosphorylation respiration for ATP production (the Warburg effect). Compared with oxidative phosphorylation, ATP generation by glycolysis is inefficient. In glycolysis-dependent cancer cells, decreased glycolysis may lower intracellular ATP. Cancer cells that are glycolysis-dependent may be particularly sensitive to pharmacologic ascorbic acid concentrations, compared with cells that use oxidative phosphorylation. [3]

As a note of caution watch the form of ASC being measured when reading the available literature, as the amount of plasma or ECF ASC required to create oxidation is different from the level of ascorbate radical generated:

With an infusion of 0.5 g/kg plasma ascorbate concentrations reached 8 mM with ascorbate radical concentrations reaching 250 nM (with the threshold for H2O2 production being 100 nM). "After i.v. injection, ascorbate (ASC) baseline concentrations of 50–100 micro M in blood and extracellular fluid increased to peaks of >8 mM… With i.v. administration of ascorbate, ascorbate radical (Asc•_) concentrations were as much as 12-fold greater in extracellular fluid compared to blood and approached 250 nM. Asc•_ concentrations of _100 nM in extracellular fluid were the threshold concentration for detectable production of H2O2." [3]

What is the safety profile in humans of intravenously administered ASC at levels which achieve these concentrations?

Hoffer et.al. reported in 2008 "In the first phase I trial published this year, doses up to 1.5 g/kg have been injected i.v. to cancer patients with minimal adverse effects." [4] In 2010 Padayatty et.al. reviewed over 50,000 administrations of intravenous ASC showing an excellent safety record with the only high grade adverse events being completely preventable by proper screening. [9] The results of our own human trials

(some included in the NIH funded research into integrative oncology outcomes) initially showed an excellent safety profile in our 2010 report [7] as well as in our update in 2014 [8]. In our experience with patients ranging from One year of age to 93 years of age this excellent safety profile with no high grade adverse events has been maintained [7,8].

Have any improvements in the protocol been made through this research to make the ASC more stable and as biochemically neutral as possible while it is infused into the patient?

Yes. In the earlier days of our human research we completed an interventional trial using the original oncology patients receiving intravenous ASC to answer the question "is it possible to alter the ASC IV formula so that the oxidant capacity is preserved and patient blood chemistry (specifically electrolytes) is as unaffected as possible?" After this trial completed we had over 400 data points including pre and post IV electrolyte levels. Our changes in the base IV ASC formula proved to be as neutral to electrolyte shifts in the patient before and after the IV as possible, while maintaining a stable solution that did not degrade the oxidant potential of the ASC. [10] These formulas were presented at a scientific meeting in 2012. [7]

What practically speaking is required as to dose of the infusion to reach at least 10 mM as described above[2] for over 4 hours? (In other words 10 mM (10,000 microM)is equal to what in SI laboratory measurement?):

Ascorbic acid (ASC) conversions from SI to Traditional (lab) units: [1]

ASC converted from mg/dl to micromolar (microM) = mg/dl X 56.78

ASC converted from microM to mg/dl = microM X 0.0176

[Calculation note: The above gives micromolar (mciroM) concentrations from mg/dL. After finding micromoles convert to millimolar (mM – the units most used in the ASC studies) by multiplying microM X 0.001.]

Therefore doses to yield the following ranges in plasma should be sufficient to meet the above criteria for H2O2 production and other actions of ASC:

ASC Plasma concentrations of 300 to 400 mg/dl = ASC [17.04 - 22.7 mMol/L] exceed the 10 mM oxidative threshold originally discussed [2] and should therefore create a stead state of H2O2 production in the extracellular space for an extended period of time.

And finally: Can the assessment of plasma ASC be done without sending the plasma sample to a lab?

Yes. In a study group comparing oncology patients, diabetic non-diabetic patients (all receiving intravenous ASC) plasma levels were compared to the glucometer assessment (below) which validated this simple assessment. [5] Using a glucometer the simple reading calculation of:

[Glucometer reading post IV] – [Baseline glucometer reading] = Post IV ASC estimation

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Appendix:

Unit Conversion

0.001 mM = 1 microM = 1000 nM

Oxidative versus Non-oxidative dosing of High and Low Dose Intravenous Ascorbic Acid as used by Bastyr University Clinical Research Center (BCRC) and AMSA / AMT Clinics

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General concepts in dosing and therapeutic targeting of IVC:

- The use of Vitamin C IV's (IVC) can be seen in two major categories:
    - Those for general immune and antioxidant support
        - These IV's contain support nutrients, and occasionally are given with Glutathione
    - Those for purely oxidative purposes
        - These generally only have minerals to balance blood electrolytes, and are generally not given with glutathione or other nutrients on the same day.
- A definitive level for the threshold of oxidation in intravenously (IV) administered ascorbate is unclear.
- Two papers [1,2] indicate that lower levels than previously considered (5-10 grams IVC) may cause oxidation and another [3] disagrees.
- Although lower doses of IVC can cause transient oxidation the likelihood of use of low dose IVC as an "oxidative therapy" is small.
    - This in no way minimizes the utility of lower dose IVC strategies.
    - These lower dose IVC formulas can have more additives and can be used for quality of life enhancement [4,5,6,7] and general nutrient support [8,9].
- Truly "oxidative" IVC formulas that have a practical longer term oxidative effect in the body likely begin at 20-25 grams and above.
    - For example the "oxidative" effect of a 10 gram IVC is real, but highly transient.
    - When employing an "oxidative strategy" with IVC the dose escalation for those purposes generally starts at 25 Grams.

Dosing guidelines for IVC based on therapeutic target:

- "Low Dose" IVC
    - **<u>0.07 to 0.14 Grams per kilogram of body weight</u>**
    - Quality of Life in cancer and other illnesses
    - General immune and antioxidant support

- These IV's often contain support nutrients, and occasionally are given with Glutathione

- "High Dose – Oxidative" IVC [12,13,14]
  - **0.4 to 1.5 Grams per kilogram of body weight**
  - Those for purely oxidative purposes
    - These generally only have minerals to balance blood electrolytes [10,11] such as magnesium, calcium and potassium in their chloride salt forms and are generally not given with glutathione or other nutrients / antioxidants on the same day.

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General Treatment Protocol for the use of Intravenous Ascorbic Acid

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General Schedule:

- Treatment Frequency:
    - IV # 1- 15: one to three times weekly
    - Based on our internal data review regarding assessment of efficacy our protocol the data showed an inability to assess positive or negative response until 12 to 15 IVC treatments were achieved.
- Intake Visit:
    - Informed Consent
    - Pre-Testing: CBC + Reticulocyte count, CMP aka Chem 14 (ALB/T.Prot/BUN/CRE/AlkPhos Glucose/T.Bili/K/Ca/Cl/CO2/Na/ALT/AST) , G6PD; (And – per situation - NK Activity, CTC, Tumor Markers, Imaging)
    - If Calcium or Potassium are hypo or hyper consider IVC formula alteration to compensate.
- Criteria for assessment of performance of IVC:
    - At intake clinical decisions should be made regarding metrics to be used as measurement of regression, stabilization or progression of disease.
        - This can include any positive findings present at the outset of therapy, including but not limited to:
            - Tumor markers
            - PET-CT
            - Other Imaging

        - Physical Exam Findings
        - Patient signs and symptoms directly attributed to the cancer
    - This assessment can also include general quality of life metrics as partial or entire criteria.
- IV #1: PARQ Conference, then IVC 25 Grams
- IV #2: IVC 50 Grams
- IV #3: IVC 75 Grams, Then post IV (drawn directly after IV) Serum / Plasma ASC level
    - If ASC level = > 350 - 400 mg/dL: continue 75 gram IVC
    - If ASC level < 350 - 400 mg/dL: increase to 100 gram IVC and re test ASC level
    - NOTE:
        - Some centers use a glucometer to estimate ascorbate concentrations
        - Some centers do not run ascorbate levels and arbitrarily set the treatment dose at 25 to 100 grams.
- IV #4 forward = 75 grams or higher (per testing).
    - After 3 – 6 IVC doses Re check BMP (electrolytes, BUN-CRE, GFR, Gluc) + Bilirubin (Or order a Chem-23) and CBC + Reticulocyte count, drawn **before the IV.**
    - If needed re-check LFT's etc.
    - If Na, K, Ca altered: consider oral or IV addition. Check GFR. If BMP altered re-check in 3-4 Tx.
- At Tx 12-15:
    - Re test NK Fct, Markers etc
    - Consider second round of IVC 2X weekly or Maintenance at 1 Tx weekly.

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Causes to clear further treatment with IV services Chief or Fellow:

- Electrolyte change from baseline to frank hypo or hyper state
- Muscle spasm / Cardiac rhythm disturbance during IV
- Anemia coupled with:
    - Increased Bilirubin and/or Increased reticulocytes [Need to rule out hemolysis]

- Suppressed RDW (<13) or WBC below 2.0 [Need to consider marrow suppression]

- GFR decrease of greater than 10 points OR below 40

High Dose IV Vitamin C (HDIVC) in Marginal Kidney Function

HDIVC in cases of marginal GFR:

HDIVC is a transient kidney stress. In the presence of other therapies like chemotherapy and dehydration this can be additive in stressfulness to the kidney function. That said during the many years and tens of thousands of HDIVC administrations I have ordered the frequency of oxalosis or GFR decrease has been nonexistent. There are two reported cases in the literature [1] but those were in people we would have never infused with HDIVC due to poor GFR prior to treatment.

Renal function and G6PD based screening:

The standard screening I set for the BIORC research study was as follows:

eGFR	IV Rx. [2]	Frequency of re-testing
>60	*Standard [2]	every 4-6 weeks
40-60	*Standard [2]	every week until proven stable
21-40	*Modified	36-48 hrs post every IV until proven stable
<20	Hydration or QOL formulas only	

Assessment of dose adjustment in altered eGFR:

The only way to assess dose effect in the patient with eGRF <40 is a therapeutic trial. Below is our standard protocol which has proven safety and efficacy in over 1000 cases:

1. Patient has baseline labs drawn (or patient on active therapy has an eGFR slip below 40).

2. Patient has 1-3 IV infusions at the lowest end of the body weight dose (Range is 0.4 to 1.5 grams / kilogram body weight [3,4,5]) these infusions are dosed at 0.4 grams per kilogram.
3. Labs are re-run (never draw electrolytes or kidney labs within 24 hours of HDIVC).
4. If labs are stable or improved IV infusions progress with predetermined monitoring
5. If labs worsen then a clinical decision is made as to risk-benefit of infusion and monitoring frequency required to keep the therapy safe.

References:

1. Padayatty SJ, Sun AY, and Chen Q, et al. (2010) Vitamin C: Intravenous Use by Complementary and Alternative Medicine Practitioners and Adverse Effects. PLoS ONE 5(7): e11414:1-8. PMID: 20628650.

2. Anderson P. “Intravenous Vitamin C in Naturopathic Oncology.” Scientific Presentation. Oncology Association of Naturopathic Physicians. Scottsdale, Arizona. 2012.

3. Chen, et.al. Ascorbate in pharmacologic concentrations selectively generates ascorbate radical and hydrogen peroxide in extracellular fluid in vivo .www.pnas.org doi:10.1073:pnas.0702854104 PNAS, May 22, 2007. vol. 104. no. 21; 8749–8754

4. Hoffer L, LevineM, Assouline S, Melnychuk D, Paddayatty S, Rosadiuk K, et al. Phase I clinical trial of i.v. ascorbic acid in advanced malignancy. Ann Oncol 2008.

5. Verrax J, Calderon PB. The controversial place of vitamin C in cancer treatment. Biochemical Pharmacology 76 (2008) 1644–1652

*Note: “Standard” HDIVC therapy for adults is the 25, 50, 75 gram escalation as published in reference 2 above. Modified can be 10, 15, 15, etc… as decided by the practitioner. All formulas assume the IVC is balanced with the chloride salts of Mg/K/Ca as described in that same presentation

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Separating Intravenous Ascorbic Acid [IV Ascorbate] and Glutathione on the same Day in Oxidative Therapies. Rationale and limitations of clinical timing.

While non-oxidant doses of intravenous vitamin c (IVC) and glutathione (GSH) are synergistic in support of the ReDox cascade between physiological compartments (Cytosol-Cell Membrane-Plasma-Plasma Lipids)* it was previously theorized that an oxidant therapy such as high dose IVC (HDIVC) may be defeated by addition of GSH in proximity. Chen et. al proved this in an animal model. [Quote below]

This has led to the common separation of GSH from HDIVC on the same day.

In reality due to the kinetics of HDIVC and IV GSH there is some question regarding the time required between IV GSH and high dose IVC (or most oxidative therapies**).

To shorten this discussion the following clinical points are helpful:

If giving IV GSH prior to or following HDIVC a separation of "a day" is a common recommendation. A consideration for people needing IV GSH and HDIVC within a 24 hour period would be that HDIVC distributes through and stays in Plasma much longer than IV GSH – so if one "must" administer GSH and HDIVC within a 24 hour period administration of the GSH should be done prior to (and not after) HDIVC to minimize crossover.

Generally a separation of 24 or more hours of any antioxidant IV (GSH, Nutrient IV followed by GSH etc.) allows plenty of time to have both the oxidative and anti-oxidative therapies work to maximum.

In cancer specifically as noted in the paper below survival was improved with BOTH HDIVC and GSH separately (but not when used together in proximity) my general use in cancer is to have "oxidant" days of therapy and "antioxidant" days to maximize both effects and my experience is similar to the animal data of Chen et. al – people survive longer and have better quality of life with a balance.

If considering infectious and other non-cancer cases where alterations of oxidative and anti-oxidative therapies may be considered I personally observe the same separation of a day between each therapy type.

*Redox Biology – a review of four systematic review papers –
https://www.consultdranderson.com/redox-biology/

**Oxidative therapies may include HDIVC, Artesunate, H_2O_2, Ozone etc.

Quote from Abstract: Chen, Ping & Stone, Jennifer & Sullivan, Garrett & Drisko, Jeanne & Chen, Qi. Anti-Cancer Effect of Pharmacologic Ascorbate and Its Interaction with Supplementary Parenteral Glutathione in Preclinical Cancer Models. Free Radical Biology and Medicine 51(3):681-7 · May 2011.DOI: 10.1016/j.freeradbiomed.2011.05.031

"Although all treatments (AA, GSH, and AA+GSH) improved survival rate, AA+GSH inhibited the cytotoxic effect of AA alone and failed to provide further survival benefit. These data confirm the pro-oxidative anti-cancer mechanism of pharmacologic AA and suggest that AA and GSH administered together provide no additional benefit compared with AA alone. There is an antagonism between ascorbate and glutathione in treating cancer, and therefore iv AA and iv GSH should not be coadministered to cancer patients on the same day."

Safety of Intravenous and Oral Ascorbic Acid in Pregnancy

Prepared as Data for Safe use of Ascorbic Acid in Human Research

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Much conjecture and mythology surrounds the use of vitamin C during pregnancy. A review of clinical use and safety as well as the limited data regarding this topic leads to a different safety profile for vitamin C in pregnancy than often reported.

Of anecdotal note is the statement by the author “I have observed no ill effects in pregnant patients receiving IVC at 5 to 50 gram doses in all three trimesters in my private practice patients.” [1] Case reports by Klenner (using oral and injectable doses of 4 to 15 grams) report the same safety. This quote comes from a 1971 paper: [2]

> “Observations made on over 300 consecutive obstetrical cases using supplemental ascorbic acid, by mouth, convinced me that failure to use this agent in sufficient amounts in pregnancy borders on malpractice. The lowest amount of ascorbic acid used was 4 grams and the highest amount 15 grams each day. (Remember the rat-no stress manufactures equivalent "C" up to 4 grams and with stress up to 15.2 grams). Requirements were roughly 4 grams first trimester, 6 grams second trimester and 10 grams third trimester. Approximately 20 percent required 15 grams, each day, during last trimester. Eighty percent of this series received a booster injection of 10 grams, intravenously, on admission to the hospital. Hemoglobin levels were much easier to maintain. Leg cramps were less than three percent and always was (sic) associated with "getting out" of Vitamin C tablets.”

Additionally in an observational study Javert [3] showed less spontaneous abortion (SAB) in humans with higher plasma ascorbate.

The often quoted caution "vitamin c as abortifacient' info emanates from the Rat study by Ovcharov [4] seemingly showing altered Corpus leuteum function with increased Rat ascorbate levels - however Vobecky et. al [5] seemed to discount a causal relationship between vitamin C and potential for SAB.

Of course in pregnancy the clinician should be much more conservative with all therapies, considering risks and benefits carefully. Appropriate patient education and informed consent is crucial. With the inability to do interventional studies on pregnant women you would have to consider the FDA "pregnancy risk classification" in respect to the use of vitamin C. Based on

the data available vitamin C would be considered pregnancy class "B". This class is considered safe to use if the patient and clinician believe the benefits to exceed any theoretical risks.

From the FDA: [6] “Animal studies have revealed no evidence of harm to the fetus, however, there are no adequate and well-controlled studies in pregnant women. OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.”

Cautions and contraindications commonly listed in lay and professional publications typically list the implausible basic science data [5] and ignore the higher grade human data. Therefore it is plausible to assume that such cautions or contraindications are based on erroneous data or incomplete data. In summary the use of vitamin C in pregnancy based upon available data is a safe intervention. As with all interventions in pregnancy it should be considered with regard to all risks and benefits before implementation.

References:

1. Anderson PS. Personal Communication regarding the use of intravenous ascorbic acid in pregnant patients. PS Anderson 2013 Seattle Washington
2. Klenner FR. Observations On the Dose and Administration of Ascorbic Acid When Employed Beyond the Range Of A Vitamin In Human Pathology. Journal of Applied Nutrition Vol. 23, No's 3 & 4, Winter 1971
3. Javert CT, Stander HJ (1943). "Plasma Vitamin C and Prothrombin Concentration in Pregnancy and in Threatened, Spontaneous, and Habitual Abortion". Surgery, Gynecology, and Obstetrics 76: 115–122.
4. Ovcharov R, Todorov S (1974). "[The effect of vitamin C on the estrus cycle and embryogenesis of rats]" (in Bulgarian). Akusherstvo I Ginekologiia 13 (3): 191–5. PMID 4467736.
5. Vobecky JS, Vobecky J, Shapcott D, Cloutier D, Lafond R, Blanchard R (1976). "Vitamins C and E in spontaneous abortion". International Journal for Vitamin and Nutrition Research 46 (3): 291–6. PMID 988001.
6. http://www.drugs.com/pregnancy-categories.html. Accessed 01-01-2014.

G6PD

BEST KIND OF TEST?

ANSWER: G6PD testing is complex but the basics are as follows:

If you have a negative test of any of the three kinds you are free to proceed with oxidative therapies.

The three test modalities are:

1. Qualitative ("Normal / Abnormal")

2. RBC-G6PD or Total-G6PD

3. Quantitative G6PD [i.e. Lab Corp code – 001917]

* A "Quant" G6PD is a calculated value using both Total and RBC G6PD – considered most sensitive at assessing borderline cases. G6PD QUANT = {G6PD Blood / RBC G6PD} Value given in Units per Trillion RBC (U/Tril RBC)

If you have a positive test however the most sensitive (as there are many false positives in #1&2 above) you are best to use the Quantitative G6PD to find out if it is a "true" positive. If the "Quant" (#3) is low then you truly cannot proceed with oxidative therapies. As a note if it is a low result occasionally that can be functional (post chemo or radiation, nutrient deficient etc) so we will often run 2-4 weeks of IV Nutrients with glutathione and re check the Quant – sometimes we see the Quant rise to normal. If it is still low it is likely a true genetic issue and they just have to avoid oxidation.

Best reference for the sensitivity of G6PD testing from which I derived this guideline is Am. J. Trop. Med. Hyg.,91(4), 2014, pp. 854–861

TRANSIENT CHANGES IN G6PD DURING TREATMENT?

QUESTION: I have a patient with a low G6PD quantative test. Is it really a genetic deficiency or can I treat them?

ANSWER: Basically there are two options:

1- it is a true deficiency and you find this out on repeat testing.

2- it is transient (which is common) and after treatment with antioxidants, on retesting it is normal. Bottom Line for now: you can't use oxidative therapies while it is low.

QUESTION: I have a pancreatic cancer patient with mets to the liver who is going for blood transfusions every 2-3 weeks RE a suspected GI bleed – 3 transfusions so far. G6PD was tested initially and was WNL.

We are doing IV Vit C and IV ALA, Mistletoe, as well as several oral therapies. The patient feels much stronger the day following an IV Vitamin C treatment. Are there any concerns with the patient potentially receiving G6PD deficient blood during transfusion – RE safety of IV Vit C? Does G6PD need to be re-tested on the transfused blood prior to administering it to the patient or once it has been administered? Any advice RE timing of IVC after a transfusion? Any other concerns?

ANSWER: Very good question with a few aspects. First, on the whole, G6PD is synthesized mainly in hepatocytes. In this regard a transfusion will not affect the levels or activity of G6PD in the body. We see many people through transfusion and other blood products, and in practice do not see that change G6PD. Second, G6PD and G6PD activity DO change with other treatments on a temporary basis. For example we do see G6PD "drop" after chemo on some occasions. This said, the person is not actually G6PD deficient but having a transient decrease in hepatic G6PD synthesis (which is affected by things like insulin availability, corticoids and a host of cytokines which can be temporarily slowed down by therapies like chemo. In these patients, both the data on G6PD "repair and stimulation" as well as my experience show that a short time (2-4 weeks) of ReDox stabilizing nutrients will bring these transiently depressed G6PD levels back. Low dose IVC or oral ascorbate, mixed tocopherols or tocotrienols and ALA for 2-4 weeks are sufficient.

(Note that this does not work for genetically deficient G6PD patients).

So, while other factors may alter G6PD status temporarily in a person with initially normal G6PD, as a single intervention, blood products do not generally create such a situation on their own.