Primary Therapies in Oncology and Chronic/Acute Infections:

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A General Note About the IVC Presentation:

- We have purposely abbreviated portions of this presentation so that more time can be given to other presenters and topics.

- We have done that knowing that most or all attendees have experience with the use of low and high dose IVC therapies clinically.

- As such our focus in this presentation is to look at updated information regarding safety concerns with IVC, dosing strategies and research and the basis for therapeutic recommendations using HDIVC in the oncology setting.

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Safety of Intravenous Ascorbate – from the conclusions in:

Pharmacologic Basis for Stability of High Dose Intravenous Ascorbic Acid (HDIVAA) as used by Bastyr University Clinical Research Center (BCRC) and Anderson Medical Specialty Associates

[This complete document is provided in the note files for this course]

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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References: Prior Slide

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. Standish L, Anderson P. “IV Therapy Experience at Bastyr Integrative Oncology Research Center.” Scientific Presentation. NOAC Meeting. Seattle, Washington. 2010.

3. Anderson P., Nadis E., Standish L. (2011, November). High Dose IV Ascorbic Acid Therapy: the Bastyr Experience. Poster session presented at the Society for Integrative Oncology, Cleveland, OH.

4. Ribeiro et al. Chemical stability study of vitamins thiamine, riboflavin, pyridoxine and ascorbic acid in parenteral nutrition for neonatal use. Nutrition Journal 2011,10:47. http://www.nutritionj.com/content/10/1/47

5. Allwood M, Kearney M. Compatibility and Stability of Additives in Parenteral Nutrition Admixtures. Nutrition Vol. 14, No. 9, 1998

6. Mühlebach S, et. al. Practical handling of AIO admixtures – Guidelines on Parenteral Nutrition, Chapter 10. GMS German Medical Science 2009, Vol. 7, ISSN 1612-3174

7. Vazquez R, et. al. Simultaneous quantification of water-soluble and fat-soluble vitamins in parenteral nutrition admixtures by HPLC-UV-MS/MS. EJHP Science 2009;15(2):28-35. © 2009 Pharma Publishing and Media Europe. All rights reserved 1781-7595 25 www.ejhp.eu

8. Schrøder AM. TOTAL PARENTERAL NUTRITION -PROBLEMS IN COMPATIBILITY AND STABILITY. EJHP Practice. Volume 14. 2008/1

9. Margolis S, Park E. Stability of Ascorbic Acid in Solutions Stored in Autosampler Vials. Clinical Chemistry 47, No. 8, 2001

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Generally what do we watch for with high dose IVC? All will be discussed in this presentation or in the protocols discussions:

- Significant dehydration
- End of life status
- G-6-PD deficiency
- Low GFR
- Admixtures to avoid on the same day (Discussed below)
  - B-Vitamins
  - Glutathione
- Admixtures to consider:
  - Any other oxidative therapies (See the presentation on IVC and Artesunate)

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IVC and Glucometer Readings:

- GLUCOMETER READINGS ARE NOT VALID WHILE A PATIENT IS ON AN IVC DRIP!

- The ascorbate is read as glucose by the glucometer and glucose values will be facetiously HIGH! – This has led to the inappropriate administration of insulin in hypoglycemic patients.

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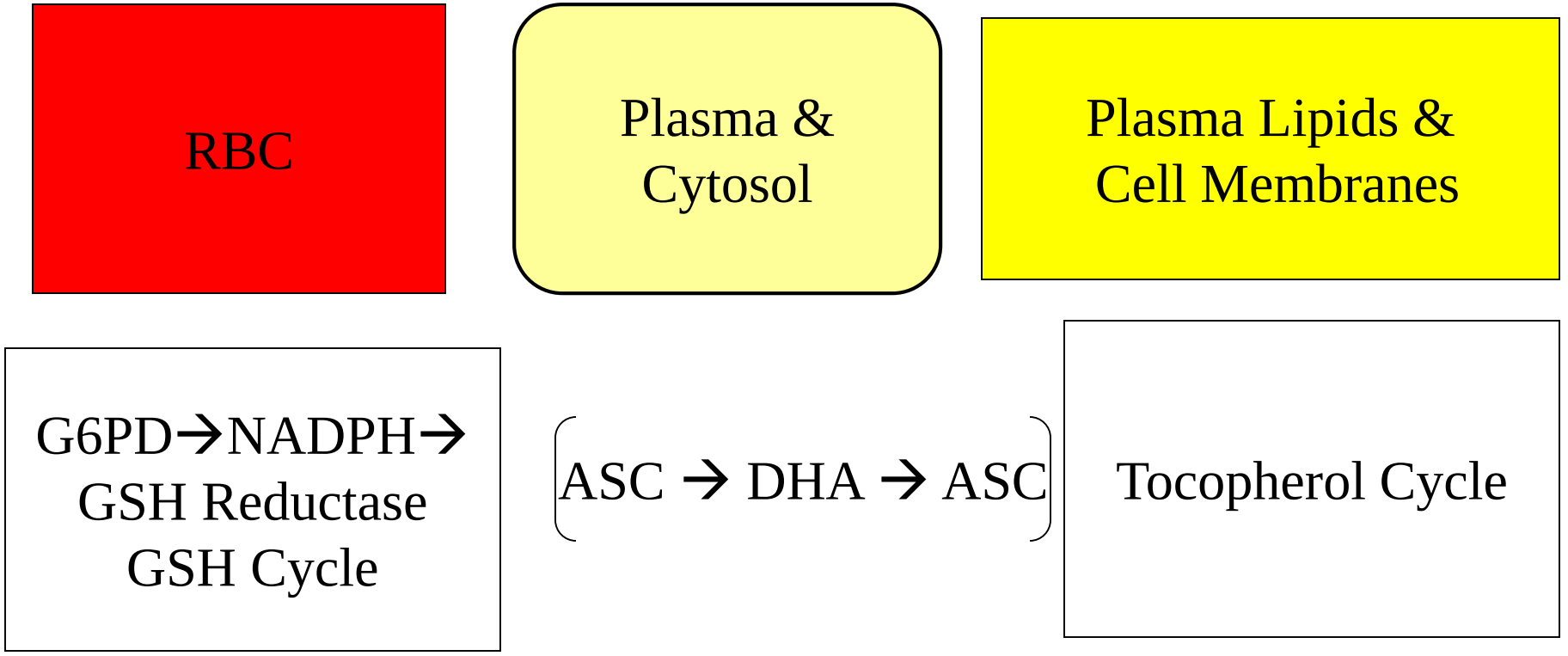
G6PD – RBC GSH – Ascorbate - Tocopherols:



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G6PD Testing

1. Qualitative ("Normal / Abnormal")

2. RBC-G6PD or Total-G6PD

3. Quantitative G6PD
    1. A calculated value using both Total and RBC G6PD – considered most sensitive at assessing borderline cases.
    2. G6PD QUANT = {G6PD Blood / RBC G6PD}
    3. Value given in Units per Trillion RBC (U/Tril RBC)

**Ultimately, all are appropriate for screening prior to HDIVC treatment.

** A Quantitative result is most sensitive.

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General Treatment Protocol for the use of Intravenous Ascorbic Acid

Causes to reassess (or more closely monitor) the patient:

- 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

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From the summary of *Intravenous Vitamin C (Ascorbic Acid): Information for Physicians and Patients*:

[This complete document is provided in the note files for this course]

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).

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References: Prior Slide

1. Verrax J and Calderon PB. The controversial place of vitamin C in cancer treatment biochemical pharmacology. 76 (2008) 1644 – 1652. PMID: 18938145.

2. Duconge J, MirandaI-Massari JR, and Gonzalez MJ, et al. Pharmacokinetics of Vitamin C. PRHSJ 2008;27(1):7-19. PMID: 18450228.

3. Ohno S, Ohno Y, and Suzuki N, et. al. High-dose Vitamin C (Ascorbic Acid) Therapy in the Treatment of Patients with Advanced Cancer. Anticancer Research 2009;29: 809-816. PMID: 19414313.

4. 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.

5. Chen Q, Espey, MG, and Sun AY, et al. Ascorbate in pharmacologic concentrations selectively generates ascorbate radical and hydrogen peroxide in extracellular fluid in vivo. Proc Natl Acad Sci U S A. 2007; 104(21):8749-54. PMID: 17502596.

6. Standish L, Anderson P. “IV Therapy Experience at Bastyr Integrative Oncology Research Center.” Scientific Presentation. NOAC Meeting. Seattle, Washington. 2010.

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

8. Fromberg, A, et.al. Ascorbate Exerts anti-proliferative effects through cell cycle inhibition and sensitizes tumor cells towards cytostatic drugs. Cancer Chemother Pharmacol, 67:1157-1166, 2011. DOI 10.1007/s00280-010-1418-6 (Springer online).

9. Verrax J and Calderon PB. The controversial place of vitamin C in cancer treatment biochemical pharmacology. 76 (2008) 1644 – 1652. PMID: 18938145.

10. Berenson JR, Yellin O, Woytowitz D, Flam MS, Cartmell A, Patel R, Duvivier H, Nassir Y, Eades B, et al. Bortezomib, ascorbic acid and melphalan (BAM) therapy for patients with newly diagnosed multiple myeloma: an effective and well-tolerated frontline regimen. Eur J Haematol. 2009;82:433–9. Downloaded from advances.nutrition.org by guest on November 15, 2011

11. Levine M, et.al. Vitamin C: A Concentration-Function Approach Yields Pharmacology and Therapeutic Discoveries. Advanced Nutrition. 2: 78–88, 2011. doi:10.3945/an.110.000109

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Regarding IV Vitamin C and potential for Oxidation:

- The Vitamin C IV's are 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.

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So – How much IVC will oxidize?

- 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.

[1] Hininger I, Waters R, Osman M, et al. Prooxidant effects of vitamin C in EDTA chelation therapy and long-term antioxidant benefits of therapy. Free Radic Biol Med 2005;38:1565-1570.

[2] Roussel AM, et.al. EDTA Chelation Therapy, without Added Vitamin C, Decreases Oxidative DNA Damage and Lipid Peroxidation. Altern Med Rev 2009;14(1):56-61

[3] Mühlhöfer A, et. al. High-dose intravenous vitamin C is not associated with an increase of pro-oxidative biomarkers. Eur J Clin Nutr. 2004 Aug;58(8):1151-8. **(Note 'High Dose' was 7.4 grams).**

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Oxidation Conclusions:

- 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 and general nutrient support.
- 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.

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Dosing of IVC:

- "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 contain support nutrients, and occasionally are given with Glutathione

- "High Dose – Oxidative" IVC
  - **<u>0.4 to 1.4 Grams per kilogram of body weight</u>**
  - 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.

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References: Prior section

[1] Hininger I, Waters R, Osman M, et al. Prooxidant effects of vitamin C in EDTA chelation therapy and long-term antioxidant benefits of therapy. Free Radic Biol Med 2005;38:1565-1570.

[2] Roussel AM, et.al. EDTA Chelation Therapy, without Added Vitamin C, Decreases Oxidative DNA Damage and Lipid Peroxidation. Altern Med Rev 2009;14(1):56-61

[3] Mühlhöfer A, et. al. High-dose intravenous vitamin C is not associated with an increase of pro-oxidative biomarkers. Eur J Clin Nutr. 2004 Aug;58(8):1151-8. (Note 'High Dose' was 7.4 grams).

[4] Lutsenko, E A, Carcamo J M, Golde DW. Vitamin C Prevents Gene Mutation Induced by Oxidative Stress. Journal of Biological Chemistry. 277(19), May 10,2002. DOI 10.1074/jbc.M201151200 / available on line at http://www.jbc.org

[5] Vojdani, A. Namatella, G. Enhancement of Human Natural Killer Cytotoxic Activity by Vitamin C in Pure and Augmented Formulations. Journal of Nutritional and Environmental Medicine. Vol. 7, No. 3 , Pages 187-196. 1997. DOI: 10.1080/13590849762600

[6] Vollbracht C, et. al. Intravenous vitamin C administration improves quality of life in breast cancer patients during chemo-/radiotherapy and aftercare: results of a retrospective, multicentre, epidemiological cohort study in Germany. In Vivo. 2011 Nov-Dec;25(6):983-90.

[7] Yeom CH Jung GC, Song KJ. Changes of terminal cancer patients' health-related quality of life after high dose vitamin C administration. J Korean Med Sci. 2007 Feb;22(1):7-11.

[8] Mehrnoush Mirhosseini MD and Robin Fainsinger MD. Fast Facts Documents # 190 Parenteral Nutrition in Advanced Cancer Patients. http://www.eperc.mcw.edu/EPERC/FastFactsIndex/ff_190.htm. Originally published October 2007. Current version re-copy-edited in May 2009.

[9] Ali A, Njike VY, Northrup V, Sabina AB, Williams AL, Liberti LS, Perlman AI, Adelson H, Katz DL. Intravenous micronutrient therapy (Myers' Cocktail) for fibromyalgia: a placebo-controlled pilot study. J Altern Complement Med. 2009 Mar;15(3):247-57. PMID: 19250003

[10] Anderson P., Naydis E., Standish L. (2011, November). High Dose IV Ascorbic Acid Therapy: the Bastyr Experience. Poster session presented at the Society for Integrative Oncology, Cleveland, OH.

[11] Anderson P. "Intravenous Vitamin C in Naturopathic Oncology." Scientific Presentation. Oncology Association of Naturopathic Physicians. Scottsdale, Arizona. 2012.

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Pro-oxidant
Mechanism Of Action

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Where does this MOA work? The Question and Answer:

- Where does the H2O2 need to be to have a potential anti-cancer effect?

- As opposed to former thought, data presented during the past decade shown below is clear that the H2O2 surge is outside rather than inside the cell. The anti-oncologic potential effects then cascade from the H2O2 generation.

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Human pharmacokinetics data indicate that i.v. ascorbic acid (ascorbate) in pharmacologic concentrations could have an unanticipated role in cancer treatment. …

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.

Chen Q, et.al. Pharmacologic ascorbic acid concentrations selectively kill cancer cells: action as a pro-drug to deliver hydrogen peroxide to tissues.Proc Natl Acad Sci U S A. 2005 Sep 20;102(38):13604-9. Epub 2005 Sep 12.

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Chen Q, Espey, MG, and Sun AY, et al. Ascorbate in pharmacologic concentrations selectively generates ascorbate radical and hydrogen peroxide in extracellular fluid in vivo. Proc Natl Acad Sci U S A. 2007; 104(21):8749-54. PMID: 17502596.

www.pnas.orgcgidoi10.1073pnas.0702854104

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(The following three slides and images are from this paper)

Abstract:

Ascorbate (ascorbic acid, vitamin C), in pharmacologic concentrations easily achieved in humans by i.v. administration, selectively kills some cancer cells but not normal cells. We proposed that pharmacologic ascorbate is a prodrug for preferential steady-state formation of ascorbate radical ($Asc^{\bullet -}$) and H_2O_2 in the extracellular space compared with blood. Here we test this hypothesis *in vivo*. Rats were administered parenteral (i.v. or i.p.) or oral ascorbate in typical human pharmacologic doses (≈0.25–0.5 mg per gram of body weight). After i.v. injection, ascorbate baseline concentrations of 50–100 μM in blood and extracellular fluid increased to peaks of >8 mM. After i.p. injection, peaks approached 3 mM in both fluids. By gavage, the same doses produced ascorbate concentrations of <150 μM in both fluids. In blood, $Asc^{\bullet -}$ concentrations measured by EPR were undetectable with oral administration and always <50 nM with parenteral administration, even when corresponding ascorbate concentrations were >8 mM. After parenteral dosing, $Asc^{\bullet -}$ concentrations in extracellular fluid were 4- to 12-fold higher than those in blood, were as high as 250 nM, and were a function of ascorbate concentrations. By using the synthesized probe peroxyxanthone, H_2O_2 in extracellular fluid was detected only after parenteral administration of ascorbate and when $Asc^{\bullet -}$ concentrations in extracellular fluid exceeded 100 nM. The data show that pharmacologic ascorbate is a prodrug for preferential steady-state formation of $Asc^{\bullet -}$ and H_2O_2 in the extracellular space but not blood. These data provide a foundation for pursuing pharmacologic ascorbate as a prooxidant therapeutic agent in cancer and infections.

$Asc^{\bullet -}$ concentrations in extracellular fluid exceeded 100 nM. The data show that pharmacologic ascorbate is a prodrug for preferential steady-state formation of $Asc^{\bullet -}$ and H_2O_2 in the extracellular space but not blood. These data provide a foundation for pursuing pharmacologic ascorbate as a prooxidant therapeutic agent in cancer and infections.

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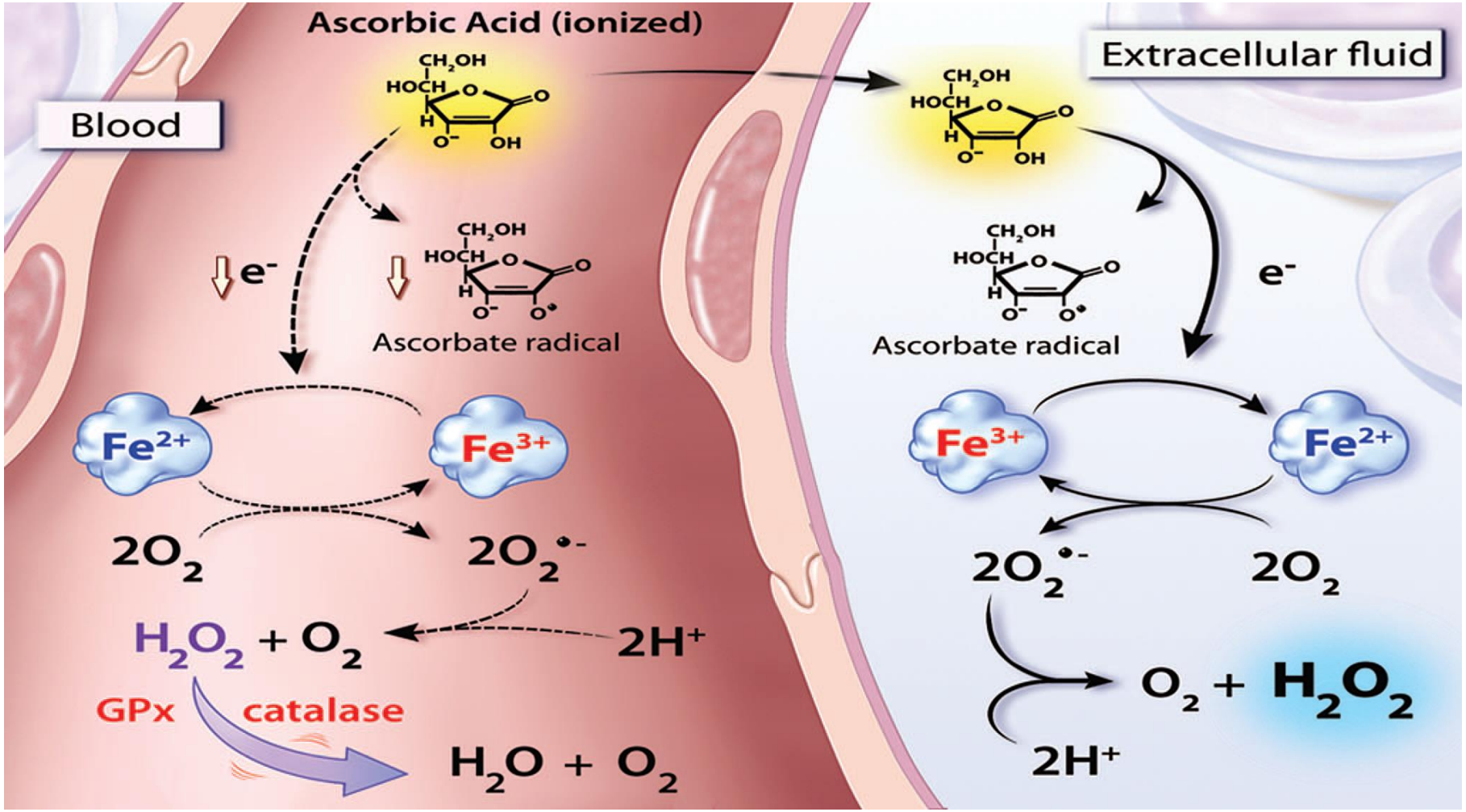
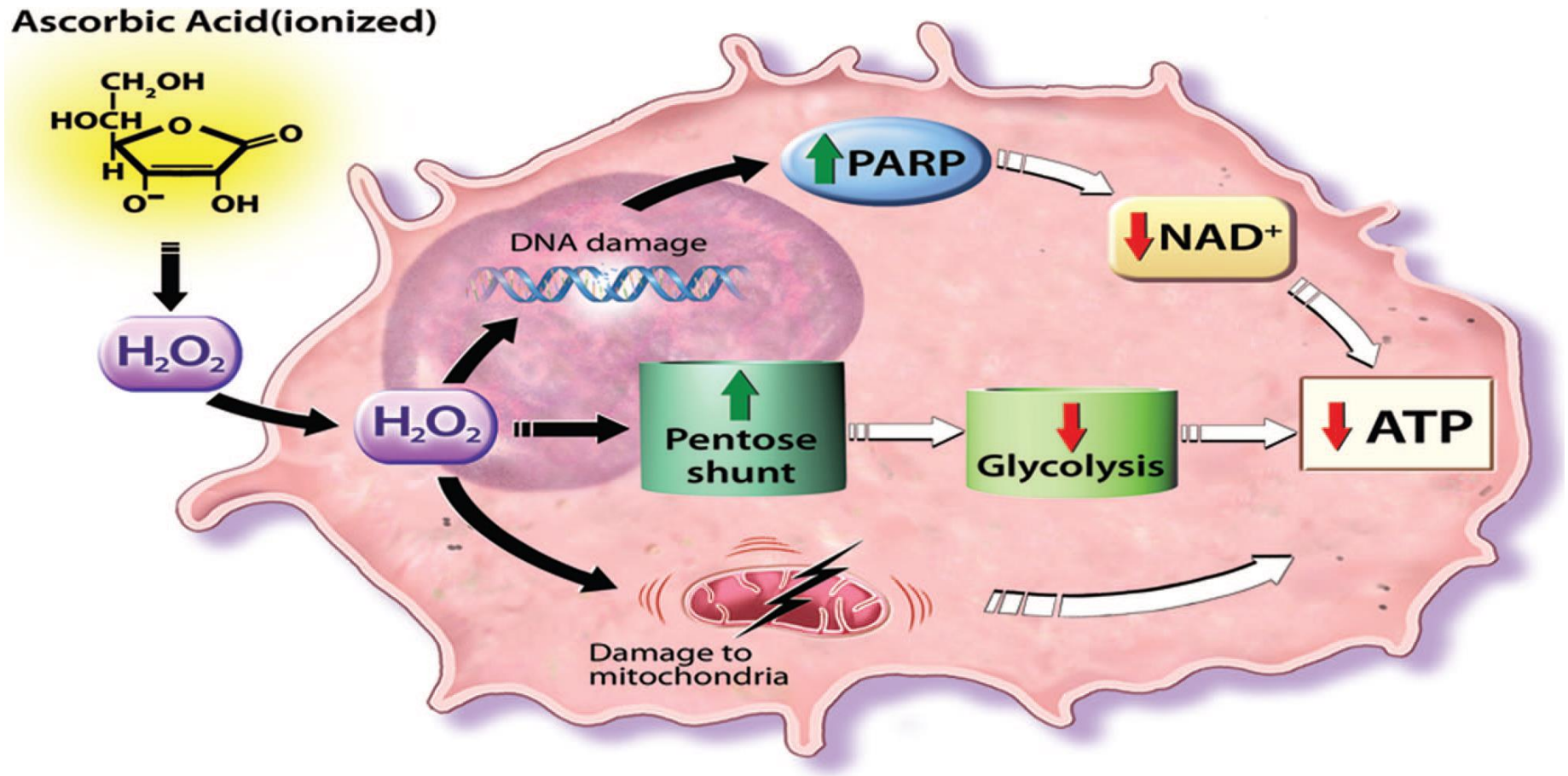


As ASC Plasma concentrations rise, ECF ASC concentrations rise. ASC is then radicalized in the presence of Fe causing a peroxide surge. In catalase/GSH deficient tissues the peroxide surge creates potential cell damage.

IMAGE: © 2007 by The National Academy of Sciences of the USA



Proposed mechanism of injury in CA / Virally infected cells via high ASC concentrations.

IMAGE: © 2007 by The National Academy of Sciences of the USA

[Can we infuse enough Vitamin C to cause these concentrations?]

Recently, it has been proposed that pharmacologic concentrations of ascorbate (vitamin C) can be reached by intravenous injection. Because high doses of ascorbate have been described to possess anticancer effects, the therapeutic potential of these concentrations has been studied, both in vitro and in vivo. By using 2-h exposures, a protocol that mimics a parenteral use, we observed that pharmacologic concentrations of ascorbate killed various cancer cell lines very efficiently (EC(50) ranging from 3 to 7 mM, 170-397 mg/dL). The mechanism of cytotoxicity is based on the production of extracellular hydrogen peroxide and involves intracellular transition metals. **In agreement with what has been previously published, our in vivo results show that both intravenous and intraperitoneal administration of ascorbate induced pharmacologic concentrations (up to 20 mM, 1135 mg/dL) in blood**. In contrast, the concentrations reached orally remained physiological. According to pharmacokinetic data, parenteral administration of ascorbate decreased the growth rate of a murine hepatoma, whereas oral administration of the same dosage did not.

Verrax J, Calderon PB. Pharmacologic concentrations of ascorbate are achieved by parenteral administration and exhibit antitumoral effects. Free Radic Biol Med. 2009 Jul 1;47(1):32-40. Epub 2009 Feb 28.

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High Dose IVC compared to H_2O_2 – Biological activity:

(Or: If it is all about extracellular H_2O_2 why not just use IV H_2O_2?)

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Biochemical differences between ASC and H2O2:

One delivers H2O2 to the cell matrix – one does not.

ASC – High Dose IV:

- IV → ASC High Dose – "Pro-drug for H2O2 production"
- Plasma
  - ASC + Fe or Cu → H2O2
  - Some reduced by plasma catalase and GSH peroxidase
- ECF
  - ASC + Fe or Cu → H2O2
- Cell
  - Cytokine release / Immune stimulation PLUS:
    - Normal cell: H2O2 reduced by catalase to H2O
    - Abnormal cell: H2O2 → potential cell damage

H2O2 IV:

- IV → H2O2
- Plasma
  - H2O2 –catalase/Mn→ H2O+O2 →Plasma cytokine stimulation:
    - IL-1, IL-6, IFNa, TNF, NO
    - **ALL H2O2 is dismutated in the venous circulation in seconds**
- ECF
  - No H2O2 left But Increased Cytokine cascade → Immune stimulation
  - **No H2O2 delivered to the cells**

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References for ASC vs H2O2

- Chen Q, Espey, MG, and Sun AY, et al. Ascorbate in pharmacologic concentrations selectively generates ascorbate radical and hydrogen peroxide in extracellular fluid in vivo. Proc Natl Acad Sci U S A. 2007; 104(21):8749-54. PMID: 17502596.
- Siwale RC, et.al. The effect of intracellular antioxidant delivery (catalase) on hydrogen peroxide and proinflammatory cytokine synthesis: a new therapeutic horizon. Journal of Drug Targeting, Volume 17, Number 9 doi.org/10.3109/1061186090316132 8
- Zadeh. et.al. Regulation of ICAM/CD54 expression on human endothelial cells by hydrogen peroxide involves inducible NOS. J. Leukocyte Biology; 67: 327-334; 2000

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Ascorbate and quality of life

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Vitamin C Prevents Gene Mutation Induced by Oxidative Stress

“High intracellular concentrations of vitamin C can prevent oxidation-induced mutations in human cells.”

Lutsenko, E A, Carcamo J M, Golde DW. Vitamin C Prevents Gene Mutation Induced by Oxidative Stress. Journal of Biological Chemistry. 277(19), May 10,2002. DOI 10.1074/jbc.M201151200 / available on line at http://www.jbc.org

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Low Dose Vitamin C and NK Cell Activity:

The antitumor activity of ascorbic acid has been reported by different investigators. In this study, we determined the in vivo effects of ascorbic acid and its modified formulation (Ultra Potent-C) on human natural killer (NK) cell activity. Twenty-two healthy subjects were given either ascorbic acid or Ultra Potent-C orally at a concentration of 60 mg kg - 1. Vitamin C uptake was measured in the plasma and by peripheral blood lymphocytes (PBLs). The uptake of vitamin C by PBLs was maximized at 2-4 h and was maintained at a high level up to 24 h. At the maximal point the uptake of Ultra Potent-C was higher by 18-25% than plain ascorbic acid. In addition, PBL-NK activity was measured by a 4-h 51Cr release assay using K562 as targets. **The results demonstrated that ascorbic acid has a biphasic pattern of NK function; an early transient depression in NK activity (29%) at 1-4 h that is subsequently followed by a significant enhancement (200-400%) between 8 and 24 hours.** However, the pattern of NK activity in the Ultra Potent-C group was different from the ascorbic acid group and the early transient depression in NK activity was not observed. We conclude that ascorbic acid or its modified form is a potent immunomodulator.

Vojdani, A. Namatella, G. Enhancement of Human Natural Killer Cytotoxic Activity by Vitamin C in Pure and Augmented Formulations. Journal of Nutritional and Environmental Medicine. Vol. 7, No. 3 , Pages 187-196. 1997. DOI: 10.1080/13590849762600

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The Role of lower-dose IVC in Quality of Life (1)

Aim: The aim of the study was to evaluate under praxis conditions the safety and efficacy of intravenous (i.v.) vitamin C administration in the first postoperative year of women with breast cancer.

PATIENTS AND METHODS:
Epidemiological multicentre cohort study, … Data from 125 breast cancer patients in UICC stages IIa to IIIb were selected for the study. A total of 53 of these patients were treated with i.v. vitamin C (…7.5 g) additional to standard tumour therapy for at least 4 weeks (study group) and 72 without this additional therapy (control group).

Main outcome measures were efficacy in regard to outcome and severity of disease- or therapy-induced complaints during adjuvant chemo- and radiotherapy and aftercare.

Vollbracht C, et. al. Intravenous vitamin C administration improves quality of life in breast cancer patients during chemo-/radiotherapy and aftercare: results of a retrospective, multicentre, epidemiological cohort study in Germany. In Vivo. 2011 Nov-Dec;25(6):983-90.

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The Role of lower-dose IVC in Quality of Life (2)

RESULTS:

Comparison of control and study groups revealed that i.v. vitamin C administration resulted in a significant reduction of complaints induced by the disease and chemo-/radiotherapy, in particular of nausea, loss of appetite, fatigue, depression, sleep disorders, dizziness and haemorrhagic diathesis. After adjustment for age and baseline conditions (intensity score before adjuvant therapy, chemotherapy, radiotherapy), the overall intensity score of symptoms during adjuvant therapy and aftercare was nearly twice as high in the control group compared to the study group. No side-effects of the i.v. vitamin C administration were documented.

DISCUSSION:

Oxidative stress and vitamin C deficiency play an important role in the etiology of adverse effects of guideline-based adjuvant chemo-/radiotherapy. **Restoring antioxidative capacity by complementary i.v. vitamin C administration helps to prevent or reduce disease-, or therapy-induced complaints in breast cancer patients.**

Vollbracht C, et. al.

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Changes of Terminal Cancer Patients' Health-related Quality of Life (1)

Over the years there has been a great deal of controversy on the effect of vitamin C on cancer. To investigate the effects of vitamin C on cancer patients' health-related quality of life, we prospectively studied 39 terminal cancer patients.

All patients were given an intravenous administration of **10 g vitamin C twice with a 3-day interval and an oral intake of 4 g vitamin C daily for a week.** And then we investigated demographic data and assessed changes in patients' quality of life after administration of vitamin C.

Quality of life was assessed with EORTC QLQ-C30.

Yeom CH Jung GC, Song KJ. Changes of terminal cancer patients' health-related quality of life after high dose vitamin C administration. J Korean Med Sci. 2007 Feb;22(1):7-11.

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Changes of Terminal Cancer Patients' Health-related QOL (2)

In the global health/quality of life scale, health score improved from 36+/-18 to 55 +/- 16 after administration of vitamin C (*p=0.001).* In functional scale, the patients reported significantly higher scores for physical, role, emotional, and cognitive function after administration of vitamin C (*p<0.05).*

In symptom scale, the patients reported significantly lower scores for fatigue, nausea/vomiting, pain, and appetite loss after administration of vitamin C (*p<0.005).* The other function and symptom scales were not significantly changed after administration of vitamin C.

In terminal cancer patients, the quality of life is as important as cure.

Although there is still controversy regarding anticancer effects of vitamin C, the use of vitamin C is considered a safe and effective therapy to improve the quality of life of terminal cancer patients.

Yeom CH Jung GC, Song KJ.

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Guidelines for the Utilization of IV Vitamin C in the Supportive Care of Patients with Advanced Malignancies

Authors: Etko Klimant MD, Heather Wright ND, Hadassah Hilewitz ND

Introduction

The current literature on IV vitamin C has not shown convincing evidence of benefit for use of high dose IV vitamin C in standard supportive oncology care. There is some evidence of benefit for use of low dose IV vitamin C in the supportive care of advanced malignancies. We define low dose IVC at a dose of 3-15 g (without significant contraindications & safe for G6PD deficiency) vs. high dose IVC for doses > 15g. We present a guideline for low dose IV vitamin C for supportive care in advanced malignancies for patients on or off chemotherapy.

Reference Guide for Low Dose IV VITAMIN C (IVC) In the Supportive Care of Oncology Patients

Rationale

- At low doses Vitamin C acts as an antioxidant, whereas at pharmacological concentrations achieved only by IV doses exceeding 15g, (at extracellular concentrations higher than 10 mmol/L), vitamin C is a pro-oxidant, by producing hydrogen peroxide. i
- Improved Quality of Life (QOL) has been a finding in other studies of terminal cancer patients receiving low dose IVC in coordination with standard treatment.ii, iii, iv, v
- Several human studies have indicated plasma vitamin C deficiency in a higher percentage of patients with malignancy, those status post surgery, and in the chronically ill. IVC may improve biomarkers related to health and quality of life in these populations. vi, vii
- As vitamin C is rapidly excreted through the renal system. IVC could be given prior to chemotherapy or after chemotherapy at the discretion of the oncologist depending on clearance. viii, ix, x
- Literature supports the use of IVC administration several times weekly. xi, xii
- Parenteral application of vitamin C has anti-depressant-like effects. xiii, xiv, xv

Key Points

- For this guideline, low dose IV vitamin C is considered to be 15g or less.
- May be given 60 minutes prior to chemotherapy to allow for renal clearance of Vitamin C or may be given after chemotherapy with observance of chemotherapy clearance times, generally 48-72 hours after chemotherapy
- Can be administered through port
- Patients should be encouraged to drink fluids during infusion
- The osmolarity of infused solutions should be kept as close to physiologic as possible

Indications

- Reduce oxidative stress while considering the half-life and goals of anti-neoplastic treatment
- Replete plasma antioxidant status
- Enhance wound healing
- Support integrity of connective tissue
- Support mood

Contraindications

- Uncontrolled serum glucose >300 mg / dl
- Renal insufficiency – at the physician's discretion: Creatinine ≥ 2.0 mg / dL (IVC excreted renally)
- Hypercalcemia – at the physician's discretion, to be monitored
- Iron overload/ Hemochromatosis: Ferritin > 500 ng / ml (IVC increased iron absorption)
- Wilson's disease (Increased copper absorption)

Possible Side Effects

- Dehydration (not probable with low dose IVC) & thirst
- Increased urinary excretion
- Mild nausea (not probable with low dose IVC)
- Mild dizziness (not probable with low dose IVC)
- Finger stick glucose monitoring may be falsely elevated for 1-2 hours after IVC administration

Cancer Treatment Centers of America

Infusion

Vitamin C (500mg/mL Ascorbic Acid) Dosage in grams:	Osmolarity (mOsm/L - Half Normal Saline - HNS)	Infusion time
3g = 6 mL	290 (In 250 ml HNS)	60 min
6g = 12 mL	419 (In 250 ml HNS)	90 min
10g = 20 mL	378 (In 500 ml HNS)	120 min
15g = 30 mL	482 (In 500 ml HNS)	120 min

Conclusion

The use of IVC in supportive care for patients with advanced malignancies is controversial. According to the literature there may be clinical benefit from low dose IV vitamin C in supportive care of patients with advanced malignancies. Our guideline for low dose IV vitamin C is a step towards evidence-based practice of integrative oncology. Further studies looking at Low dose versus High dose IV vitamin C in supportive care of cancer patients are warranted.

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Infusion

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Guidelines for the Utilization of IV Vitamin C in the Supportive Care of Patients with Advanced Malignancies: SIO Poster Presentation, 2012

Authors: Eiko Klimant MD, Heather Wright ND, Hadassah Hilewitz ND

Conclusion:

- The use of IVC in supportive care for patients with advanced malignancies is controversial.
- According to the literature there may be clinical benefit from low dose IV vitamin C in supportive care of patients with advanced malignancies.
- Our guideline for low dose IV vitamin C is a step towards evidence-based practice of integrative oncology.
- Further studies looking at Low dose versus High dose IV vitamin C in supportive care of cancer patients are warranted.

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PDQ Integrative, Alternative, and Complementary Therapies Editorial Board

- **Studies of vitamin C alone**Intravenous (IV) vitamin C was studied in patients with breast cancer who were treated with adjuvant chemotherapy and radiation therapy. The study found that patients who received IV vitamin C had better quality of life and fewer side effects than those who did not.
- A study of IV vitamin C and high doses of vitamin C taken by mouth was done in patients with cancer that could not be cured. Vitamin C was shown to be a safe and effective therapy to improve quality of life in these patients, including physical, mental, and emotional functions, symptoms of fatigue, nauseaand vomiting, pain, and appetite loss.
- Vitamin C has been shown to be safe when given to healthy volunteers and cancer patients at doses up to 1.5 g/kg, while screening out patients with certain risk factors who should avoid vitamin C. Studies have also shown that Vitamin C levels in the blood are higher when taken by IV than when taken by mouth, and last for more than 4 hours.

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Guidelines for the Utilization of IV Vitamin C in the Supportive Care of Patients with Advanced Malignancies: SIO Poster Presentation, 2012 Authors: Eiko Klimant MD, Heather Wright ND, Hadassah Hilewitz ND

i Padyatty SJ, Sun H, Wang Y, Riordan HD, Hewitt SM, Katz A, Wesley RA, Levine M: Vitamin C Pharmacokinetics: Implications for Oral and Intravenous Use. Annals of Internal Medicine; 2004; 140; 533-573.

iiCameron E, Pauling L: Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer. Proc Natl Acad Sci USA 1976; 73:3685-3689.

iii Murata A, Morishige F, Yamaguchi H; Prolongation of survival times of terminal cancer patients by administration of large doses of ascorbate; Int J Vitam Nutr Res Suppl; 1982; 23:103-113.

Iv Yeom CH, Jung GC, Song KJ: Changes of terminal cancer patients' health related quality of life after high dose vitamin C administration. J Korean Med Sci 2007; 22:7-11.

v Vollbracht C, Schneider B, Van Leendert, Weiss G, Auerbach L, Beuth J; Intravenous Vitamin C Administration Improves Quality of Life in Breast. Cancer Patients during Chemo-/Radiotherapy and Aftercare: Results of a Retrospective, Multicentre Epidemiological Cohort Study in Germany. In Vivo 25: 983-990 (2011).

vi Ichim TE, Minev B, Braciak T, Luna B, Hunninghake R, Mikirova NA, Jackson JA, Gonzalez MJ, Miranda-Massari JR, Alexandrescu DT, Dasanu CA, Bogin V, Ancans J, Stevens RB, Markosian B, Koropatnick J, Chen CS, Riordan NH; Intravenous ascorbic acid to prevent and treat cancer-associated sepsis? J Transl Med. 2011 Mar 4;9:25.

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vii Mayland CR, Bennett MI, Allan K; Vitamin C deficiency in cancer patients; Palliative Medicine 2005;19:17-20.

viii Hoffer LJ, Levine M, Assouline S, Melnychuk D, Padayatty SJ, Rosadiuk K, Rousseau C, Robitaille L, Miller WH Jr. Phase I clinical trial of i.v. ascorbic acid in advanced malignancy. Ann Oncol. 2008 Nov;19(11):1969-74.

ix Friedman GJ, Sherry S, Ralli EP; The mechanism of the excretion of vitamin C by the human kidney at low and normal plasma levels of ascorbic acid; J Clin Inves. 1940;19:685-689.

x Kallner A, Hartmann D, Hornig D. Steady-state turnover and body pool of ascorbic acid in man. Am J Clin Nutr. 1979;32:530-539. xiYeom CH, Jung GC, Song KJ: Changes of terminal cancer patients' health related quality of life after high dose vitamin C administration. J Korean Med Sci 2007; 22:7-11.

xii Ichim et. al. Journal of Translational Medicine. 2011, 9:25. [http://www.translational-medicine.com/content/9/1/25]. xiiiGalecki P, Szemraj J, Bienkiewicz M, Florkowski A, Galecka E; Lipid peroxidation and antioxidant protection in patients during acute depressive episodes and in remission after fluoxetine treatment. Pharmacological Reports. 2009. (61) 436-447.

xiv Khanzode SD, Dakhale GN, Khanzode SS, Saoji A, Palasodkar R. Oxidative damage and major depression: the potential antioxidant action of selective serotonin re-uptake inhibitors. Redox Rep. 2003; 8(6):365-70. xvBinfaré RW, Rosa AO, Lobato KR, Santos AR, Rodrigues AL. Ascorbic acid administration produces an antidepressant-like effect: evidence for the involvement of monoaminergic neurotransmission. Prog Neuropsychopharmacol Biol Psychiatry. 2009. Apr 30;33(3): 530-40.

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IV Vitamin C and other additives

- B-Vitamins and IVC:
- Glutathione and IVC:
- Electrolytes and IVC:

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Should we separate B-Vitamins from High-dose / oxidative IVC?

The bottom line is that while B-Vitamins and other antioxidants are needed during cancer therapy, they may decrease the oxidative effect of HDIVC if concurrently administered.

Ochi M, Hetherington J, Lamson D. The Concern about B-Vitamins with Intravenous Ascorbate for Malignancy; Altern Med Rev 2011;16(Supp):1S-5S

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Glutathione and IVC for Oxidation on the same day:

Two popular complementary, alternative, and integrative medicine therapies, high-dose intravenous ascorbic acid (AA) and intravenous glutathione (GSH), are often coadministered to cancer patients with unclear efficacy and drug-drug interaction. Treatment in mouse pancreatic cancer xenografts showed that intraperitoneal AA at 4g/kg daily reduced tumor volume by 42%. Addition of intraperitoneal GSH inhibited the AA-induced tumor volume reduction. 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**.

Chen P, Stone J, Sullivan G, Drisko JA, Chen Q. Anti-cancer effect of pharmacologic ascorbate and its interaction with supplementary parenteral glutathione in preclinical cancer models. Free Radic Biol Med. 2011 May 30. PMID: 21672627

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All this data is contained in a document
We have placed that in the documents section of your handout

Ascorbate safety, electrolytes and formula optimization:

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Interventional Study: HDIVC and Electrolyte Shifts

In an interventional study associated with BIORC and AMSA we attempted to answer the questions regarding electrolyte shifts and HDIVC administration.

Anderson P., Naydis E., Standish L. (2011, November). *High Dose IV Ascorbic Acid Therapy: the Bastyr Experience*. Poster session presented at the Society for Integrative Oncology, Cleveland, OH.

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Electrolyte shift Concerns with HDIVC:

- Hypocalcemia
- Hypokalemia
- Hypernatremia
- Hypochloremia

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High Dose IVC and Electrolyte changes data:

Baseline:

- Na (N=135-145)
  - Mean = 140
- Cl (N=98-111)
  - Mean = 102
- Ca (N=8.5-10.5)
  - Mean = 9.1
- K (N=3.5-5.4)
  - Mean = 4.1

Directly post IVC:

- Na
  - Mean = 147.3 **(HIGH)**
- Cl
  - Mean = 90.25 **(LOW)**
- Ca
  - Mean = 8.4 **(LOW)**
- K
  - Mean = 4.58 **(Normal)**

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Study Conclusions

- After informed consent, and a number of interventions to discover an improved formula:
  - We altered the constituents of the HDIVC formulae to negate most of these electrolyte shifts.
  - We ran a crossover group once the new formulae were in place. The crossover group returned to the original imbalances, and these resolved when we crossed the patients back to the new formula.
- Those study validated formulae are included in the pdf document.

* PDF - 4 Ascorbate and Electrolytes with Formulas

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High Dose IVC and Electrolyte changes data
New Formula

Baseline:

- Na (N=135-145)
  - Mean = 140
- Cl (N=98-111)
  - Mean = 102
- Ca (N=8.5-10.5)
  - Mean = 9.1
- K (N=3.5-5.4)
  - Mean = 4.1

Directly post IVC:

- Na
  - Mean = 144.93 **(Normal)**
- Cl
  - Mean = 94.59 **(LOW)**
- Ca
  - Mean = 8.64 **(Normal)**
- K
  - Mean = 4.70 **(Normal)**

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High Dose IVC and Electrolyte changes data
New Formula

Na /Cl Ratio

- **Ideal: (140/104) = 1.35 = range 36**
- **Old Formula: (146/90)**
  - **Range = 56 – Likely increases cardioactive side effects.**
- **New Formula: (145/94)**
  - **New formula diminishes the ratio after IV by 14%**

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BIORC – AMSA

IV Therapy Guidelines and Treatment Possibilities

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BIORC /AMSA – IV Therapy Intervention Plan and Flow

Goals: Quality of Life Improvement – Oncologic Therapy Augmentation – Improved Survival

PATIENT INTAKE:

- DX –STAGE/GRADE
- QOL METRICS
- MARKERS-IMAGING-PE-OTHER METRICS
- PATIENT AND PHYSICIAN GOALS CLARIFIED
- REFERRAL TO IV SERVICE

IV INTAKE:

- PARQ Discussion
- Labs including G6PD / CBC / Chem-23 / HbA1C
- Other Labs considered: NKCF / CTC / Clotting Studies / Baseline Tumor Markers / etc

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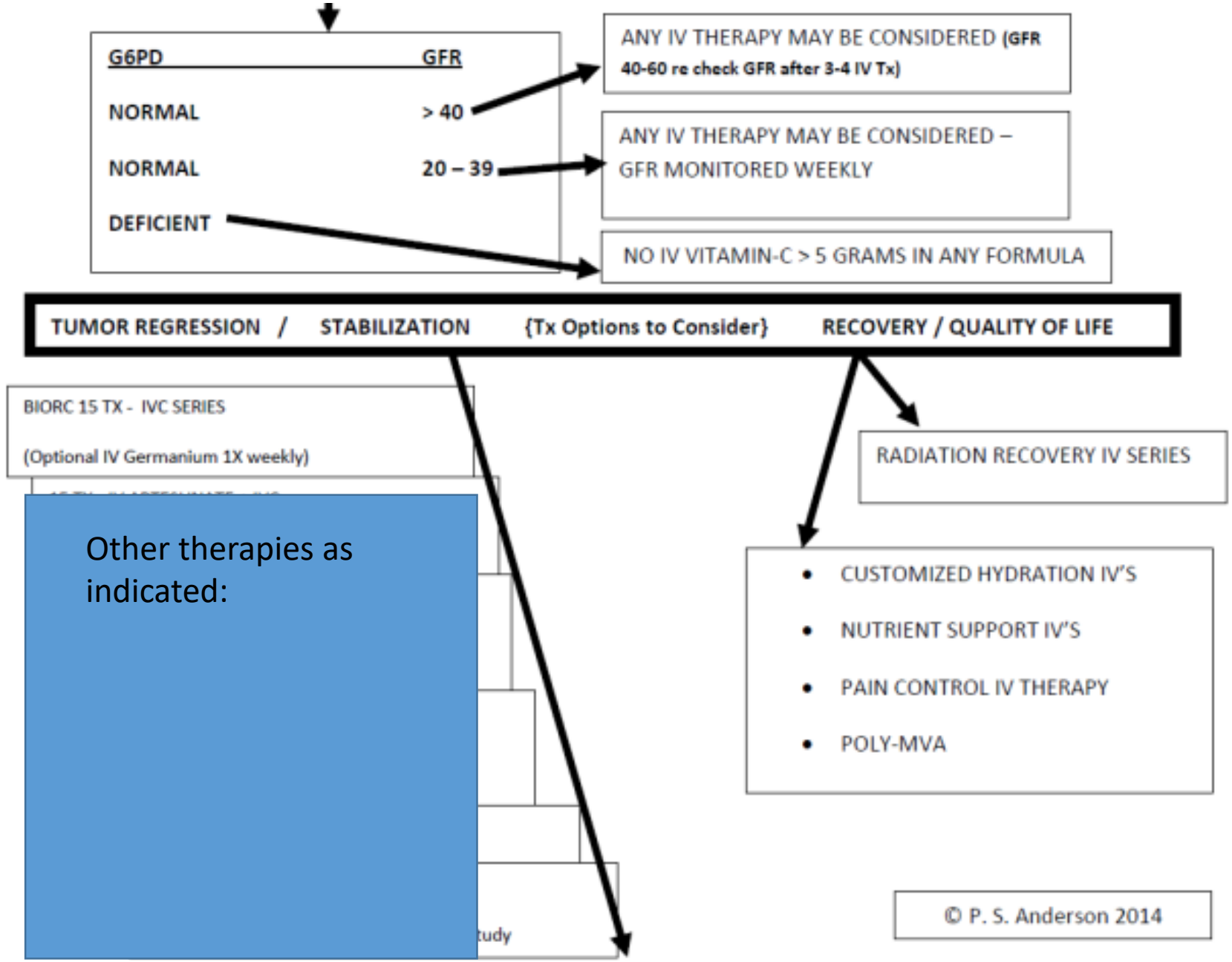
G6PD
GFR
NORMAL
> 40
NORMAL
20 – 39
DEFICIENT
ANY IV THERAPY MAY BE CONSIDERED (GFR 40-60 re check GFR after 3-4 IV Tx)
ANY IV THERAPY MAY BE CONSIDERED – GFR MONITORED WEEKLY
NO IV VITAMIN-C > 5 GRAMS IN ANY FORMULA
TUMOR REGRESSION / STABILIZATION {Tx Options to Consider} RECOVERY / QUALITY OF LIFE
BIORC 15 TX - IVC SERIES
(Optional IV Germanium 1X weekly)
Other therapies as indicated:
RADIATION RECOVERY IV SERIES
CUSTOMIZED HYDRATION IV'S
NUTRIENT SUPPORT IV'S
PAIN CONTROL IV THERAPY
POLY-MVA
© P. S. Anderson 2014

General Treatment Protocol for the use of Intravenous Ascorbic Acid

- 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.

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General Treatment Protocol for the use of Intravenous Ascorbic Acid

- 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.

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General Treatment Protocol for the use of Intravenous Ascorbic Acid

- 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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Any ways other than sending the plasma or serum to the lab to check post-tx levels?

- Based on data provided by Ma, Sullivan et. al. the following is the accepted protocol for determining a post IV blood ascorbate level. The currently accepted goal in oxidative therapy is 350 – 400 mg/dL (20-23 mM) as measured post IV by standard lab HPLC techniques.
- Based on the data cited the following simple calculation can be made using a finger stick glucose meter with two readings: a baseline value prior to the IV and a post IV finger stick value taken after the IV has been discontinued up to 15 minutes post IV. The calculation provides an accurate representation of the mg/dl level of blood ascorbate above 50 mg/dL.

Ma Y, Sullivan G, Schrick E, et.al. A Convenient Method for Measuring Blood Ascorbate Concentrations in Patients Receiving High-Dose Intravenous Ascorbate. Journal of the American College of Nutrition. Volume 32, Issue 3, pages 187-193. 2013 DOI:10.1080/07315724.2013.791167

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Simple Calculation:

<u>POST IV</u> FINGER STICK READING: _____

<u>PRE IV</u> FINGER STICK READING: [-] _____

==========

ESTIMATION OF BLOOD ASCORBATE: _____ mg/dL

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What if the GFR is low / LFT's are high?

- Generally the IV's are well tolerated with low GFR and / or high LFT's

- Only way to tell is a therapeutic trial:
  - Patient has baseline labs
  - Patient has 1-3 IV Tx
  - Labs are re-run (never draw electrolytes or kidney labs within 24 hours of HDIVC).
  - If labs are stable or improved Tx progresses with predetermined monitoring
  - If labs worsen then a clinical decision is made as to risk-benefit of Tx and monitoring frequency required to keep the Tx safe.

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Why 15 IVC Treatments Before Re-assessment?

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Based on a retrospective analysis of the first three years outcomes with the BIORC-AMSA patient group we found:

- Using the above criteria for response if the patient had completed:
  - 12-15 or more IVC Tx:
    - A clear assessment of the effect of the IVC on their baseline criteria could be made.
    - If disease and other criteria are stable or improving at this point then they are good candidates for continuation. If not then another strategy should be considered.
  - Less than 12 IVC Tx:
    - Not enough treatment time or effort had elapsed to make a determination regarding the efficacy of treatment.

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What if it works?

What does IVC long term look like?

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Is the response positive or negative?

- If one is a "responder"
  - i.e. positive response in any of the following areas: QOL, Tumor regression, Stable disease, marker regression or stabilization etc
    - Then it is worth continuing IVC: Decrease from 2-3X a week to 1X a week for 4-8 weeks.
  - Non-responders it is not worth it, but rather trying another IV agent or an add on to the IVC.
- After that (if still positive response when assessed again) then **spread the IV frequency out** to every two weeks for a month then every three weeks and so on **until you find a length of interval which loses the positive response** and then keep maintenance at whatever interval maintained the positive response.

- This is usually somewhere between every 2 to 6 weeks. Average is 3-4 weeks.

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Ascorbate and oncologic therapies – compatibility, cautions and synergy

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Table 1 – Influence of vitamin C on the efficacy of different chemotherapeutic drugs.

Treatment	Influence of vitamin C	Reference
5-Fluorouracil	↑[a]	[30]
	↑[b]	[72]
Bleomycin	↑[a]	[30]
Doxorubicin	↑[a]	[70]
Paclitaxel	↑[a]	[70]
Cisplatin	↑[a]	[70]
	↑[a]	[74]
Cyclophosphamide	↑[b]	[72]
Procarbazin	↑[b]	[72]
Asparaginase	↑[b]	[72]
Vinblastine	↑[b]	[72]
Adriamycin	↑[b]	[72]
Gemcitabin	↑[b]	[73]
Vincristin	↑[a]	[67]
	↑[a]	[68]
X-rays	↑[a]	[30]
	↑[b]	[76]
Trisenox	↑[a]	[75]
	↑[a]	[69]
	↑[c]	[71]
	↓[d]	[79]
Methotrexate	↓[a]	[30]
TRAIL ligand	↓[d]	[78]
Bortezomib	↓[a]	[77]

[a] In vitro results.
[b] In vivo results in combination with menadione.
[c] In vivo results.
[d] In vitro results in cells loaded with ascorbic acid.

The current published review:

Verrax J and Calderon PB. The controversial place of vitamin C in cancer treatment biochemical pharmacology. 76 (2008) 1644 – 1652. PMID: 18938145.

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Parenteral Ascorbic Acid - Use in integrative Oncology; Dosing, timing and compatibility with allopathic therapies.

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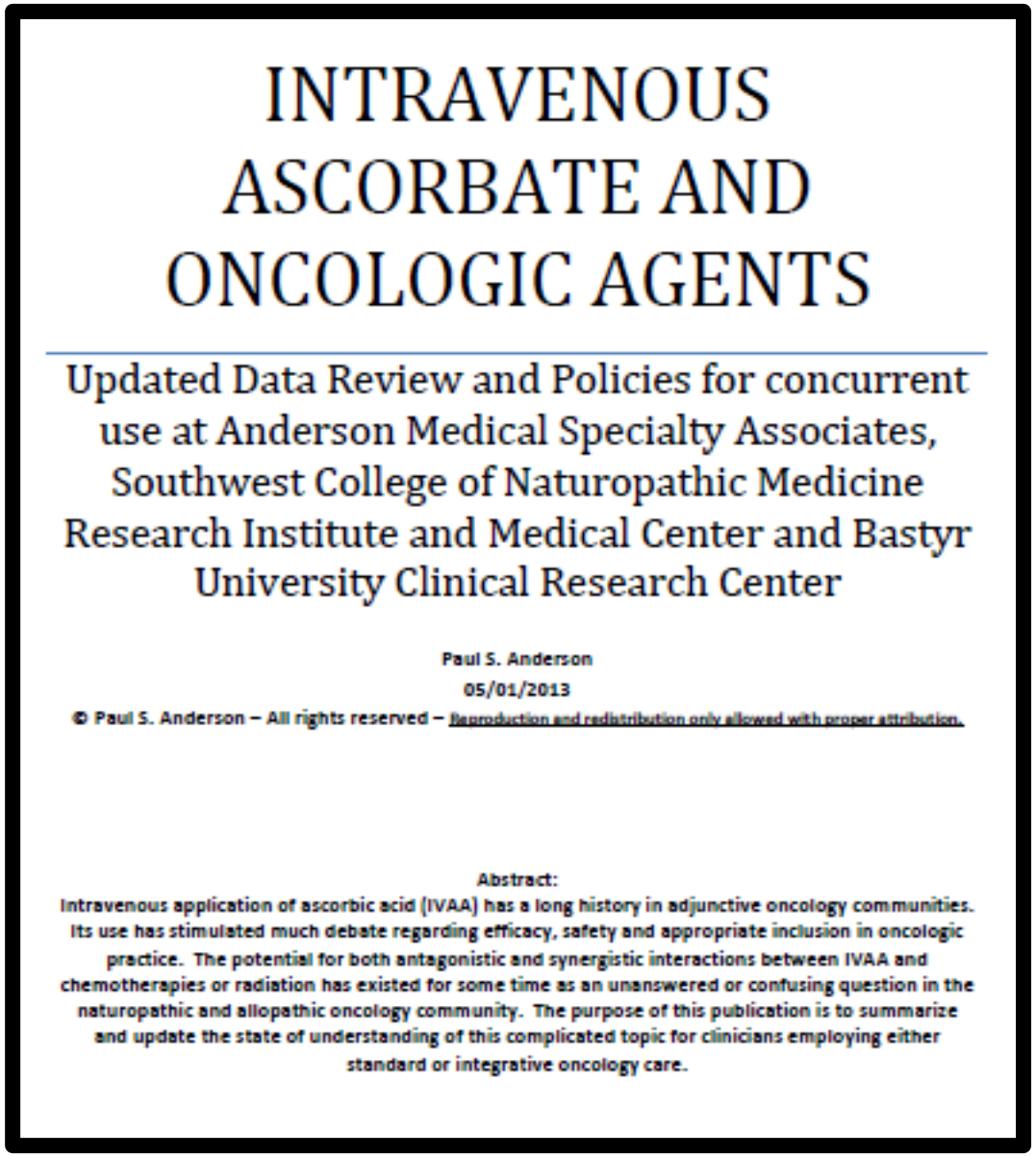
We have included this PDF in the note packet for this course.

- Ascorbate and Oncologic Agents: Compatibility and interactions →



INTRAVENOUS ASCORBATE AND ONCOLOGIC AGENTS

Updated Data Review and Policies for concurrent use at Anderson Medical Specialty Associates, Southwest College of Naturopathic Medicine Research Institute and Medical Center and Bastyr University Clinical Research Center

Paul S. Anderson

05/01/2013

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Abstract:
Intravenous application of ascorbic acid (IVAA) has a long history in adjunctive oncology communities. Its use has stimulated much debate regarding efficacy, safety and appropriate inclusion in oncologic practice. The potential for both antagonistic and synergistic interactions between IVAA and chemotherapies or radiation has existed for some time as an unanswered or confusing question in the naturopathic and allopathic oncology community. The purpose of this publication is to summarize and update the state of understanding of this complicated topic for clinicians employing either standard or integrative oncology care.

Ascorbate and infectious disease

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Effect of high dose vitamin C on Epstein-Barr viral infection

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F

ACDE Nina A. Mikirova
A Ronald Hunninghake

Bio-Communication Research Institute, Riordan Clinic, Wichita, KS, U.S.A.

Conclusions:

The clinical study of ascorbic acid and EBV infection showed the reduction in EBV EA IgG and EBV VCA IgM antibody levels over time during IVC therapy that is consistent with observations from the literature that millimolar levels of ascorbate hinder viral infection and replication *in vitro*.

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Intravenous Vitamin C and Septic Shock

An Introduction to the work of Paul Marik, MD, and Alpha A. Fowler, MD, in the use of IV Vitamin C for Septic Shock and Sepsis

Consensus Definitions for Sepsis and Septic Shock

- Bacterial sepsis refers to symptomatic bacteremia, with or without organ dysfunction
- Sepsis is commonly defined as the presence of infection in conjunction with the systemic inflammatory response syndrome (SIRS)
  - Severe sepsis, as sepsis complicated by organ dysfunction
  - Septic shock, as a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone
    - Septic shock is identified using the clinical criteria of hypotension requiring vasopressor therapy to maintain mean blood pressure of 65 mm Hg or greater and having a serum lactate level >2 mmol/L after adequate fluid resuscitation

JAMA. 2016 Feb 23;315(8):775-87. doi: 10.1001/jama.2016.0289.
PMID: 26903336

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Treatment goals for septic shock

- Initiate adequate antibiotic therapy (proper dosage and spectrum) as early as possible
- Resuscitate the patient using supportive measures to correct hypoxia, hypotension, and decreased tissue oxygenation (hypoperfusion)
- Identify the source of infection, and treat with antimicrobial therapy, surgery, or both (source control)
- Maintain sufficient organ system function, guided by cardiovascular monitoring, and interrupt the progression to multiple organ dysfunction syndrome (MODS)

From the website: http://emedicine.medscape.com/article/168402-treatment. Accessed May 11, 2017.

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Sepsis mortality is high

- Patients with severe sepsis requiring intensive care unit (ICU) admission have very high rates of ICU and hospital mortality, with estimates ranging from 18 to 50%.[1,2]
- A large observational cohort study in the United States found an overall hospital mortality rate of 28%.[3] In a multicenter European cohort study, the ICU mortality was 27% and the overall hospital mortality was 36%.
- What these studies point out is that treatment of septic shock is both difficult and in many cases, ineffective at preventing mortality due to shock and MODS.

[1] PMID: 15312201, [2] PMID: 12700374, [3] PMID: 11445675

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How Does IV Vitamin C Help in Septic Shock?

- Preclinical studies show that high-dose vitamin C can prevent or restore microcirculatory flow impairment by inhibiting activation of nicotinamide adenine dinucleotide phosphate-oxidase and inducible nitric oxide synthase
- It also enhances tetrahydrobiopterin, preventing uncoupling of oxidative phosphorylation, and decreasing the formation of superoxide and peroxynitrite, and by directly scavenging superoxide
- Vitamin C can additionally restore vascular responsiveness to vasoconstrictors, preserve endothelial barrier by maintaining cyclic guanylate phosphatase and occludin phosphorylation and preventing apoptosis
- Finally, high-dose vitamin C can augment antibacterial defense

Crit Care. 2014 Aug 6;18(4):460. doi: 10.1186/s13054-014-0460-x. PMID: 25185110

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Development of the “Marik Protocol”

- It started in January, 2016, when Dr Paul Marik was supervising the intensive care unit at Sentara Norfolk General Hospital. A 48-year-old female came in with a severe case of sepsis. "Her kidneys were failing. Her lungs weren't working. She was going to die," Marik said. "In a situation like this, you need start thinking out of the box."
- Marik had recently read a study by researchers at Virginia Commonwealth University in Richmond. Dr Alpha A. Fowler and his colleagues had shown some moderate success in treating people who had sepsis with intravenous vitamin C.

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A Hypothesis Tested

- Marik decided to use IV ascorbate with the woman.
- He added in a low dose of corticosteroids, which are used to treat sepsis

[Annane D. The rold of ACCTH and corticosteroids for sepsis and septic shock: an update. Front Endocrinol (Lausanne). 2016 Jun 20;7:70. PMID: 27379022]

- He also included thiamine.

[Manzanares W, Hardy G.Thiamine supplementation in the critically ill. Curr Opin Clin Nutr Metab Care. 2011 Nov;14(6):610-7. PMID: 21912244]

- His severely ill patient received this treatment according to his instructions

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An unexpected positive outcome

- "I was expecting the next morning when I came to work she would be dead," Marik said."But when I walked in the next morning, I got the shock of my life." The patient was progressing on the road to recovery.
- Marik tried this treatment with the next two sepsis patients he encountered, and was likewise surprised. He started treating most of his sepsis patients with the vitamin and steroid infusion.
- After treating 50 patients, he decided to write up his results. As Marik described in *Chest*, only four of those 47 patients died in the hospital, and all the deaths were from their underlying diseases, not from sepsis. For comparison, he reviewed 47 patients the hospital had treated before he tried the vitamin C infusion and found that 19 had died in hospital

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Continued treatment success

- Normally, the new treatment would be tested simultaneously with a placebo or standard treatment. But the results were so astounding, Marik decided that he would treat all his sepsis patients with the vitamin C infusion. As of March 2017, he had treated about 150 patients, and only one died of sepsis

Marik PE, Khangoora V, Rivera R, et al. Hydrocortisone, Vitamin C and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. Chest. 2016 Dec 6. pii. S0012-3693(16)62564-3. PMID: 27940189

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Dr Paul Merik's Septic Shock Protocol

- **Vitamin C:** 1.5 g IV q 6 hourly for 4 days or until discharge from the ICU. Vitamin C is provided by the manufacturer as a 50 ml vial at a concentration of 500mg/ml. Three (3) ml of vitamin C will be placed in a 100ml bag of either dextrose 5% in water (D5W) or normal saline and infused over 60 minutes
- **Hydrocortisone:** 50mg IV push q 6 hourly for 6 days or until discharge from the ICU. Taper is not required. Optional dosing strategy: Hydrocortisone 50 mg bolus, followed by a 24-hour continuous infusion of 200 mg for 4 days
- **Thiamine:** 200mg IV q 12 hourly for 4 days or until discharge from the ICU. Intravenous thiamine (200 mg) was placed in a piggyback in 50 ml of either D5W or normal saline and administered as a 15-minute infusion

Protocol source: From the website: http://www.evms.edu/about_evms/administrative_offices/marketing_communications/publications/issue_9_4/sepsis.php#medical-professional. Accessed May 12, 2017.

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Pathophysiology of sepsis & septic shock (1) Vitamin C blocks or reverses these reactions

- Endothelial dysfunction is initiated by increased concentrations of ROS produced by inducible enzymes
- ROS are also produced by xanthine oxidase, lipoxygenase and cyclooxygenase, and during oxidation of catecholamines
- Unopposed ROS oxidize tetrahydrobiopterin (BH_4) the cofactor of eNOS (endothelial nitric oxide synthase), and thereby reduce eNOS activity, the enzyme producing endothelial nitric oxide (eNO). eNO triggers vasodilation by stimulating soluble guanylcyclase and increasing cyclic guanosine monophosphate in smooth muscle cells

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Pathophysiology of sepsis & septic shock (2) Vitamin C blocks or reverses these reactions

- eNO also inhibits platelet aggregation and adhesion of activated platelets and leukocytes. For this reason eNO is crucial for patency of the microcirculation and its depletion impedes organ perfusion and oxygenation
- Without BH_4, eNOS becomes uncoupled, producing superoxide (O_2^-) rather than nitric oxide (NO)
- O_2^- and NO produce peroxynitrite, the most damaging ROS

Oudemans-van Straaten HM, Spoelstra-de Man AM, de Waard MC. Vitamin C revisited. Crit Care. 2014 Aug 6;18(4):460. PMID: 25185110

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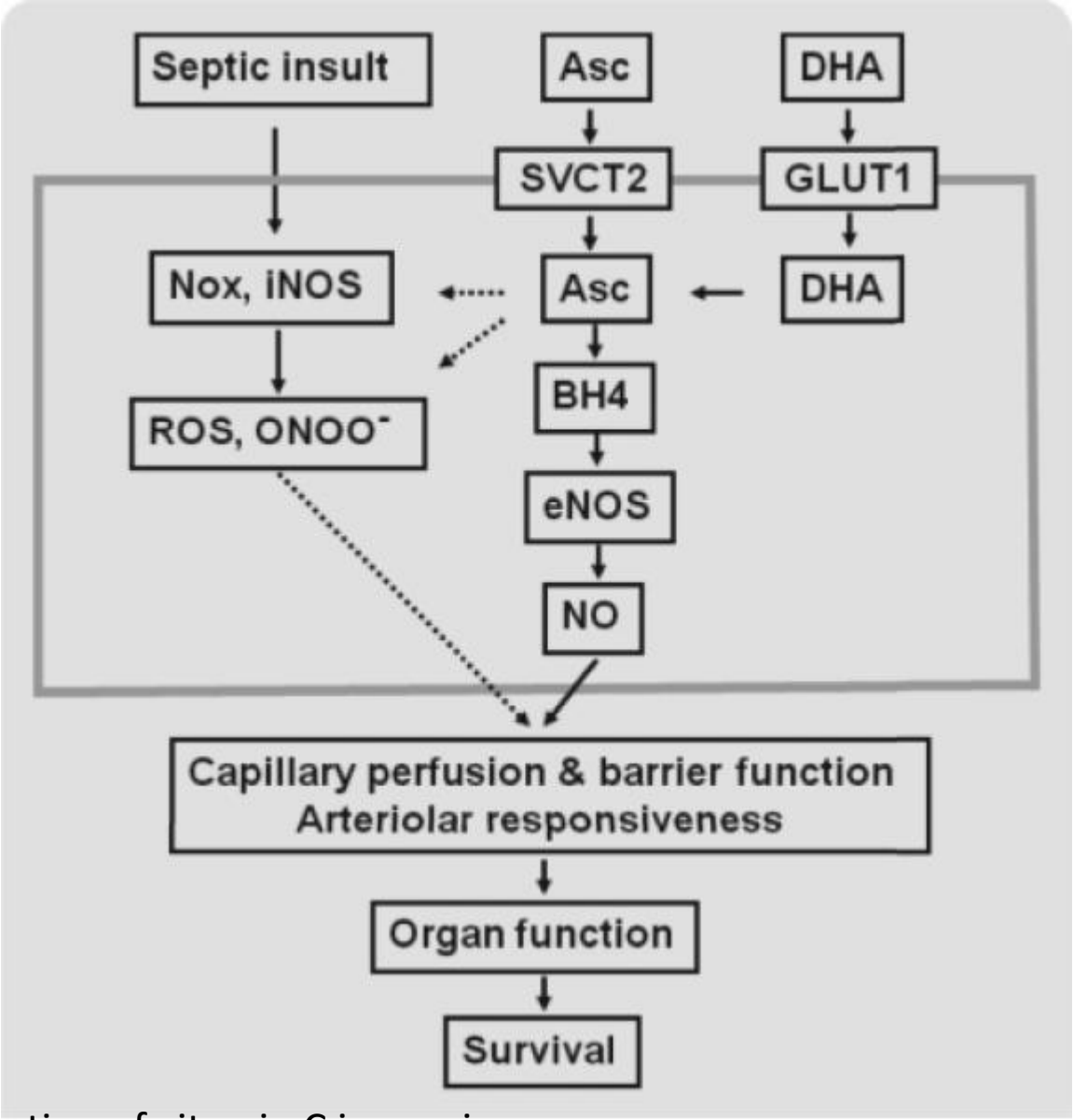

Wilson, J. Mechanism of action of vitamin C in sepsis:
Ascorbate modulates redox sinaling in endothelium. Biofactors.
2009 Jan-Feb; 35 (1): PMID: 19319840

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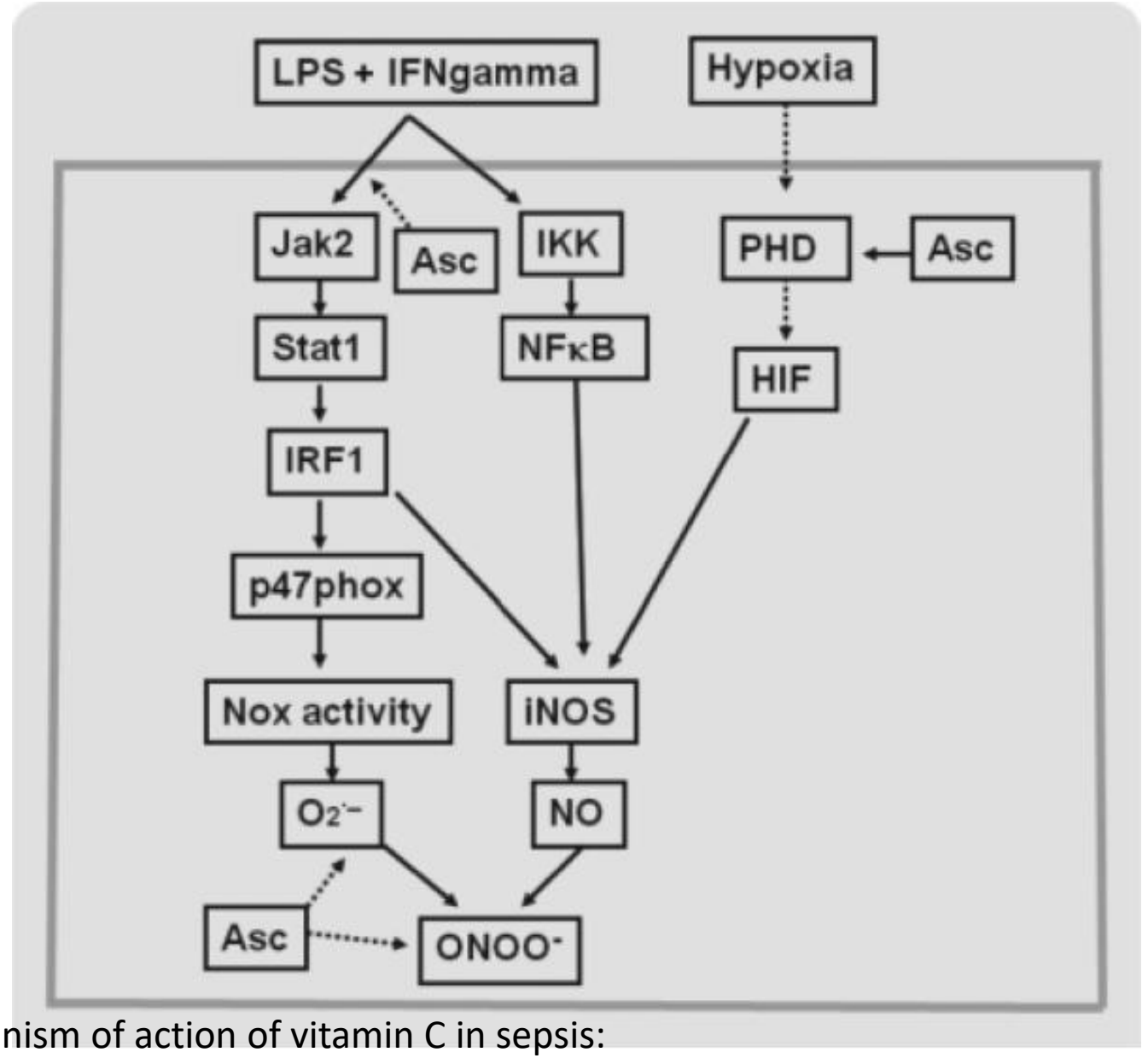

Wilson, J. Mechanism of action of vitamin C in sepsis:
Ascorbate modulates redox sinaling in endothelium. Biofactors.
2009 Jan-Feb; 35 (1): PMID: 19319840

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Sepsis causes increased consumption of thiamine and Vitamin C

- Vitamin C levels always fall during sepsis, at times dropping below the level of detection. Vitamin C deficiency correlates with multiorgan failure and death [Wilson JX. Mechanism of action of vitamin C in sepsis: ascorbate modulates redox signaling in endothelium. Biofactors. 2009 Jan-Feb;35(1):5-13. PMID: 19319840]
- Thiamine deficiency is common in sepsis, occurring in about one-third of patients. Different studies have shown that critical illness in adults and children is accompanied by absolute or relative thiamine depletion, which is associated with an almost 50% increase in mortality [Manzanares W, Hardy G.Thiamine supplementation in the critically ill. Curr Opin Clin Nutr Metab Care. 2011 Nov;14(6):610-7. PMID: 21912244]

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Rationale for vitamin C infusion

- Sepsis increases the risk of death and disability, but treatment consists only of supportive therapies because no specific therapy has been available
- Severe sepsis is characterized by ascorbate (reduced vitamin C) depletion, excessive protein nitration in microvascular endothelial cells, and microvascular dysfunction composed of refractive vasodilation, endothelial barrier dysfunction, and disseminated intravascular coagulation
- Parenteral administration of ascorbate prevents or reverses these pathological changes and so decreases hypotension, edema, multiorgan failure, and death in animal models of sepsis

Wilson JX. Evaluation of vitamin C for adjuvant sepsis therapy. Antioxid Redox Signal. 2013 Dec 10;(19)17:2129-40. PMID: 23682970

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The use of IV vitamin C is mandatory

- Only parenterally administered vitamin C can achieve sufficient blood concentrations to combat oxidative stress
- There is no evidence that parenteral vitamin C exerts prooxidant effects in humans while it is resident in circulation. Theoretical concerns in relation to competitive interactions between vitamin C and glucose cellular uptake are probably only relevant for oxidised vitamin C (dehydroascorbate)

Lehr HA, et al. Consensus meeting on “Relevance of parenteral vitamin C in acute endothelial dependent pathophysiological conditions (EDPC)”. Eur J Med Res. 2006 Dec 14;11(12):516-26. PMID: 17182364

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Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis (1)

- **BACKGROUND:** Parenterally administered ascorbic acid modulates sepsis-induced inflammation and coagulation in experimental animal models. The objective of this randomized, double-blind, placebo-controlled, phase I trial was to determine the safety of intravenously infused ascorbic acid in patients with severe sepsis.
- **METHODS:** Twenty-four patients with severe sepsis in the medical intensive care unit were randomized 1:1:1 to receive intravenous infusions every six hours for four days of ascorbic acid: Lo-AscA (50 mg/kg/24 h, n = 8), or Hi-AscA (200 mg/kg/24 h, n = 8), or Placebo (5% dextrose/water, n = 8). The primary end points were ascorbic acid safety and tolerability, assessed as treatment-related adverse-event frequency and severity. Patients were monitored for worsened arterial hypotension, tachycardia, hypernatremia, and nausea or vomiting. In addition Sequential Organ Failure Assessment (SOFA) scores and plasma levels of ascorbic acid, C-reactive protein, procalcitonin, and thrombomodulin were monitored.

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Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis (2)

- **RESULTS:** Mean plasma ascorbic acid levels at entry for the entire cohort were 17.9 ± 2.4 µM (normal range 50-70 µM). Ascorbic acid infusion rapidly and significantly increased plasma ascorbic acid levels. No adverse safety events were observed in ascorbic acid-infused patients. Patients receiving ascorbic acid exhibited prompt reductions in SOFA scores while placebo patients exhibited no such reduction. Ascorbic acid significantly reduced the proinflammatory biomarkers C-reactive protein and procalcitonin. Unlike placebo patients, thrombomodulin in ascorbic acid infused patients exhibited no significant rise, suggesting attenuation of vascular endothelial injury.
- **CONCLUSIONS:**Intravenous ascorbic acid infusion was safe and well tolerated in this study and may positively impact the extent of multiple organ failure and biomarkers of inflammation and endothelial injury.

Fowler AA, et al. Phase 1 safety trial of intravenous ascorbic acid in patients with severe sepsis. J Transl Med. 2014 Jan 31;12:32. PMID: 24484547

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Clinical Trial

- Professor Fowler and his colleague Professor Ramesh Natarajan hypothesise that endoplasmic reticulum stress, autophagy (an intracellular degradation system), histone citrullination (which controls gene expression) and NFkB activation could all play key roles in the molecular pathways that stimulate NETosis. Therefore, modulation of these pathways could be the reason the team saw attenuated NETosis in subjects treated with ascorbic acid.
- Furthermore, ascorbic acid increases the synthesis and activity of ion pumps and channels located on the alveolar surface, restoring normal water movement.
- **Ascorbic acid as a human treatment**
  The team from Virginia Commonwealth University have also used ascorbic acid as an interventional drug to treat sepsis-induced lung injury, conducting trials on humans suffering from acute respiratory failure. Twenty-four patients with severe sepsis were given intravenous infusions of ascorbic acid every six hours for four days. Overall, not only did the results show that ascorbic acid had no adverse safety issues, it also significantly reduced proinflammatory biomarkers, supporting Professor Fowler's earlier work.
- However, further research is needed before ascorbic acid can be approved as a legitimate treatment for sepsis-induced lung injury. Therefore, Professor Fowler is currently conducting a larger-scale Phase II proof of concept trial, in collaboration with four medical centres (Virginia Commonwealth University, The Cleveland Clinic, The Medical College of Wisconsin and The University of Kentucky).
- The aim of this trial is to determine whether intravenous ascorbic acid will decrease multiple organ failure of sepsis and reduce inflammation and coagulation, indicated by reduced levels of pro-inflammatory biomarkers associated with this condition.
- Professor Fowler's innovative research has provided much evidence to show that ascorbic acid can be an effective drug to mitigate the effects of sepsis-induced lung injury, saving tens of thousands of lives.

- Vitamin C – breathing new life into septic acute lung injury therapy? AB. Fowler III etal.Oregon State University

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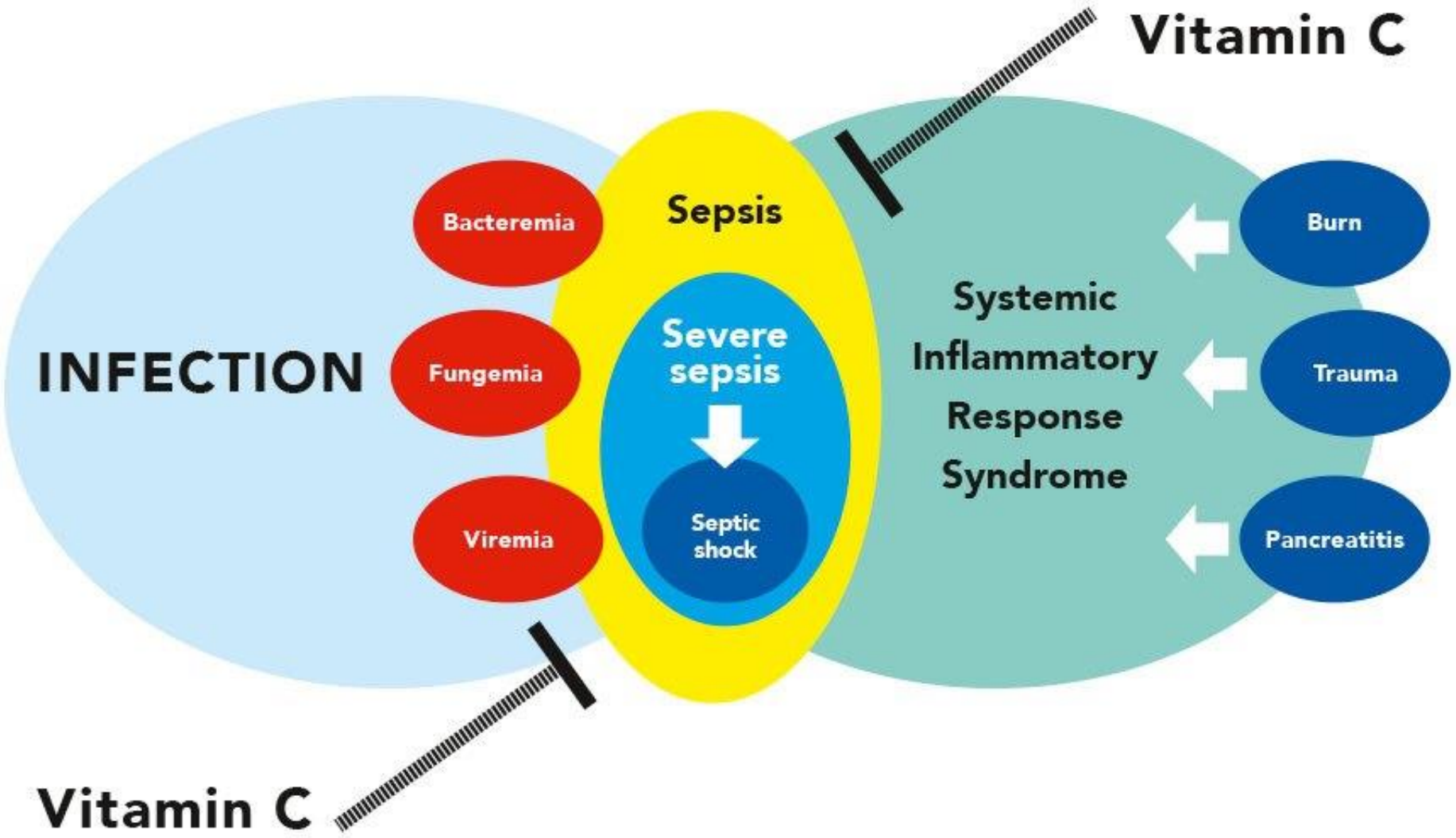
Fowler, A.B etal 8.2017



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Comments regarding Fowler's study

- Lo-AscA (50 mg/kg/24 h), the low dose cohort
  - For a 70 kg (154.3 lb) person the daily dose is 3500 mg
  - Infusions were administered every 6 hours, or 4 times/day
  - Each infusion contained 875 mg ascorbic acid
- Hi-AscA (200 mg/kg/24 h), the high dose cohort
  - For a 70 kg person the daily dose is 14,000 mg (14 g)
  - Infusions were administered every 6 hours
  - Each infusion contained 3500 mg ascorbic acid
- Fowler's doses are conservative; could higher doses be more effective in sepsis?
- Integrative physicians in the U.S. routinely increment vitamin C doses to 50 grams for acute viral infections

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Septic shock & Vitamin C (1)

- Septic shock is characterized by refractory hypotension and is normally managed by fluid resuscitation and administration of the catecholamine vasopressor norepinephrine. Vasopressin can also be administered to raise mean arterial pressure and decrease the norepinephrine dose
- Endogenous norepinephrine and vasopressin are synthesised by two copper-containing enzymes, dopamine β-hydroxylase for norepinephrine and peptidylglycine α-amidating monooxygenase, for vasopressin
- Both enzymes require ascorbate as a cofactor for optimal activity. Patients with severe sepsis show hypovitaminosis C. and pre-clinical and clinical studies indicate that administration of high-dose ascorbate decreases the levels of pro-inflammatory biomarkers, attenuates organ dysfunction and improves haemodynamic parameters.

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Septic shock & Vitamin C (2)

- Pre-clinical and clinical studies indicate that administration of high-dose ascorbate decreases the levels of pro-inflammatory biomarkers, attenuates organ dysfunction and improves haemodynamic parameters
- Vitamin C improves endogenous vasopressor synthesis and thus ameliorates the requirement for exogenously administered vasopressors

Carr AC, Shaw GM, Fowler AA, Natarajan R. Ascorbate-dependent vasopressor synthesis: a rationale for vitamin C administration in severe sepsis and septic shock? Crit Care. 2015 Nov 27;19:418. PMID: 26612352

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Mitochondrial resuscitation

- Mitochondrial dysfunction occurs early in sepsis and has an important role in MODS development. MODS severity and recovery of mitochondrial function are associated with survival
- Recent clinical and experimental investigations suggest that mitochondrion-targeted therapy for sepsis and septic shock will help reduce MODS severity and mortality
- Supplementation with micronutrients identified as potential metabolic resuscitators could be beneficial [coenzyme Q10 (CoQ10), cytochrome oxidase (CytOx), L-carnitine, melatonin, selenium, zinc]

Leite HP, de Lima LF. Metabolic resuscitation in sepsis: a necessary step beyond the hemodynamic? J Thorac Dis 2016 Jul;8(7):E552-7. PMID: 27501325

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Intravenous Vitamin C Administered as Adjunctive Therapy for Recurrent Acute Respiratory Distress Syndrome

- Amit Bharara, Catherine Grossman, Daniel Grinnan, Aamer Syed, Bernard Fisher, Christine DeWilde, Ramesh Natarajan, and Alpha A. (Berry) Fowler *

- **Abstract**
- This case report summarizes the first use of intravenous vitamin C employed as an adjunctive interventional agent in the therapy of *recurrent* acute respiratory distress syndrome (ARDS). The two episodes of ARDS occurred in a young female patient with Cronkhite-Canada syndrome, a rare, sporadically occurring, noninherited disorder that is characterized by extensive gastrointestinal polyposis and malabsorption. Prior to the episodes of sepsis, the patient was receiving nutrition via chronic hyperalimentation administered through a long-standing central venous catheter. The patient became recurrently septic with Gram positive cocci which led to two instances of ARDS. This report describes the broad-based general critical care of a septic patient with acute respiratory failure that includes fluid resuscitation, broad-spectrum antibiotics, and vasopressor support. Intravenous vitamin C infused at 50 mg per kilogram body weight every 6 hours for 96 hours was incorporated as an adjunctive agent in the care of this patient. Vitamin C when used as a parenteral agent in high doses acts “pleiotropically” to attenuate proinflammatory mediator expression, to improve alveolar fluid clearance, and to act as an antioxidant.

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