AIMN review
Australasian Institute for Medical Nutrition
www.aimnutrition.org
APR 2019

Vitamin C in the treatment of viral diseases

Vitamin C has been used via various routes of administration in the treatment of viral infections since the 1930s. The typical intervention in a modern clinical setting is the use of intravenous Vitamin C (IVC) to aid in the management of influenza, shingles, glandular fever, and mosquito borne viruses like Dengue and Ross River infections. The use of intravenous Vitamin C for viral infections sits firmly in the clinical realm, with very little published formal analysis of cases and very few clinical trials. However reports of the use of intravenous Vitamin C in some viral disorders are quite spectacular, leading many physicians and researchers to call for formal clinical trials. Recent results in human clinical trials in sepsis/septic shock have also been spectacular, leading to a current surge in research interest in testing Vitamin C in sepsis. In many ways the immune response in progression of serious viral infections shares factors in common with the immune response in progression of sepsis. This has led to calls for investigations into using high dose Vitamin C for severe viral infections like Ebola, SARS, Swine Flu, Bird Flu etc. At this stage rigorous clinical studies looking at dose ranging, placebo control and route of administration in any viral infection have not been done.

Background

There is a long history of the clinical use of vitamin C, going all the way back to the 1930s and 40s. Some of the earliest attempts at using vitamin C as a therapeutic agent were with polio victims, and as the doctors administering the vitamin C tried larger and larger doses, their results improved significantly. One of the earlier doctors to consistently use higher doses of vitamin C was Dr. Frederick Klenner, following on the heels of positive research in which Jungeblut showed that the administration of ascorbic acid to monkeys infected with poliomyelitis produced a distinct reduction in the severity of the disease and enhanced their resistance to it (Jungeblut, 1939). Sabin attempted to reproduce these findings, but although he found a major lethal effect of vitamin C to polio virus in the test tube he was unable to achieve these results in vivo (Sabin, 1939). In retrospect it is apparent that in the early days there was a great variation in the size and frequency of the dose given, accordingly results were variable.

In 1949, the first of a remarkable series of case publications appeared (Klenner, 1949). Klenner described his successful treatment of poliomyelitis, as well as a variety of many other viral infections, using ascorbic acid. He gave the rationale for his treatment, his technique in detail, and his dramatic case histories. Klenner realized that the secret was in the massive doses he employed, and he tried to impart this knowledge to an unbelieving profession. In his 1952 paper, Klenner further discussed his ascorbic acid treatment of polio and comments on Sabin's and Jungeblut's earlier work (Klenner, 1952), stating: *"His results (Sabin's) were indecisive because the amount of vitamin C given was inadequate to cope with the degree of infection. Sabin's results were not as suggestive as Jungeblut's because he, Sabin, used a greater dose of virus and less Vitamin C."*

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Klenner's suggested optimal dosage rate for virus infections, calculated on the basis of a 70-kilogram (154-pound) adult, was 4.5 to 17.5 grams of ascorbic acid given every two to four hours around the clock (27 - 210 grams per day). This amount goes far beyond anything that had been previously tried. He records one successful case history after another in these papers, as well as in his 1953 report (Klenner, 1953).

Klenner's work has informed much of the megadose Vitamin C therapy that is in use today. Klenner's papers and cases are a must read for anyone wishing to gain a deeper perspective on the historical use of high dose Vitamin C and the types of cases where Vitamin C has been effectively used. An excellent overview of the cases of Klenner was published in 1988 (Smith, 1988).

Hepatitis

Further viral case presentations were published in Germany in the 1950s where there was a hepatitis outbreak in children. Vitamin C was used with great success to relieve the symptoms and reduce the duration of the disease in children (Calleja and Brooks, 1960; Kirchmair and Kirsch, 1957). Kirchmair and Kirsch stated: *"We saw a clear and substantial improvement compared to all prior treatment methods only when we gave about five-day-long daily drip infusions with 10 g ascorbic acid in 100 ml water added to 500 ml 0.9% saline solution, as well as 400 ml Isotonal ** IV"* (translated from German).

*** Isotonal is comprised as follows: 0.1% dextrose, 0.8% sodium chloride, 0.04% potassium chloride, 0.25% calcium chloride, 0.0005% magnesium chloride, 0.001% sodium phosphate and 0.05% sodium carbonate.*

Kirchmair and Kirsch also used rectal Vitamin C in these children which they also found to be extremely effective; even more effective than intravenous Vitamin C. Averaging both treatments, the decrease of liver swelling took 30 days without Vitamin C and 10 days with Vitamin C. Vitamin C on average also halved the number of days needed for treatment (Kirchmair and Kirsch, 1957).

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Vitamin C has been shown to reduce the incidence of post-transfusion hepatitis. A study in 1978 in Japan (Morishige and Murata, 1978) looked at the effects of Vitamin C on post-infusion hepatitis: *"Large doses, two grams or more per day, of vitamin C after whole blood transfusion were administered to 272 transfused patients. Only three cases of hepatitis (all non-B) were observed."* Also: *"The incidence of hepatitis in transfused patients was 7% for those who received little or no vitamin C and 0.2% for those who received 2 g per day or more."*

Vitamin C levels are lowered in infections (Carr and Maggini, 2017). A study on oxidative stress in children with acute hepatitis A (Popovic-Dragonjic et al., 2011) has demonstrated a significant lowering of multiple antioxidants, including Vitamin C, in hepatitis infection.

Of course not all liver injury is caused by viral infections. There is a long list of studies showing prevention of or control of inflammation in liver disorders that are not viral in origin. For example a 2013 study reviews the relationship between Vitamin C status and liver inflammation and tests the anti-inflammatory effects of Vitamin C on the liver in a mouse model (Bae et al., 2013). They showed elevated cytokines and inflammatory markers when mice were injected with concanavalin A and demonstrated that Vitamin C administration could prevent this. This is a typical finding in general for human clinical trials testing the effects of Vitamin C in severe inflammation/sepsis. Not specific to viruses, Vitamin C has been shown to control sepsis and septic shock (Marik, 2018) and is currently the focus of multiple clinical trials in sepsis/septic shock ("Vitamin C Sepsis - ClinicalTrials.gov," 2019)

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HIV/AIDS

In the 1980s Dr. Robert Cathcart used high dose vitamin C, usually intravenously, to treat AIDS patients. Many other doctors used vitamin C at the same time however Catchcart published case reviews and guidelines (Cathcart, 1984). Cathcart stated *"Preliminary clinical evidence is that massive doses of ascorbate (50-200 grams per 24 hours) can suppress the symptoms of the disease and can markedly reduce the tendency for secondary infections."* These are very large doses and are typical of the doses employed by physicians in the United States at this time; the usual practice was to titrate the dose according to the clinical response of the patient. Vitamin C in these doses or even in anything like a large dose has not been formally studied in HIV/AIDS patients. Much of the formal publication around the use of Vitamin C in HIV/AIDS has been low dose oral administration, usually as a mixed antioxidant pill.

HIV infection *in vitro* is known to respond to Vitamin C (Harakeh et al., 1990). Other antioxidants have also been shown to inhibit HIV replication (Staal et al., 1993).

A clinical trial in Tanzania looked at the effect of a multivitamin supplement and its effect on HIV disease progression and mortality in patients receiving highly active antiretroviral therapy (HAART) (Isanaka et al., 2012). *"Large randomized trials have previously shown that high-dose micronutrient supplementation can increase CD4 counts and reduce human immunodeficiency virus (HIV) disease progression and mortality among individuals not receiving highly active antiretroviral therapy (HAART)"* The Isanaka et al. trial compared a low dose vs. high dose multivitamin. The study was stopped because of increasing ALT levels in patients receiving the high dose multivitamin. *"In adults receiving HAART, use of high-dose multivitamin supplements compared with standard-dose multivitamin supplements did not result in a decrease in HIV disease progression or death but may have resulted in an increase in ALT levels."* The amount of daily Vitamin C in the high dose group in the Isanaka et al. trial was 500 mg. This is a tiny amount; the ALT response probably has nothing to do with Vitamin C.

A review of supplement interactions with antiretrovirals was published in 2017 (Jalloh et al., 2017). There is some concern in the literature that Vitamin C (and other antioxidants) may interfere with antiretroviral therapy. Jalloh et al. refer to a pharmacokinetic study comparing Indinavir alone (IDV, Crixivan) to oral Indinavir + 1g oral Vitamin C which found that the addition of Vitamin C significantly lowered the plasma concentration of Indinavir (Slain et al., 2005), lowering the peak plasma concentration by approximately 20%. However Slain et al. point out that the clinical relevance of this is unknown. It is not known if this occurs systematically or with other antiretrovirals. The mechanism of interaction is presumed to

be induction of cytochrome isoenzymes such as CYP3A, but it is not clear at all that there is any clinical relevance to this. Indinavir is a first generation antiretroviral and was most popular in the late 1990s. Indinavir use had significant issues with toxicity and its use fell out of favour (Boyd, 2007).

Outside this there is currently no evidence to say that Vitamin C interferes with current medication regimes in HIV treatment.

A 2016 study examined the effects of Vitamin C against HIV (Hayash, 2016): *"Previous reports demonstrated the antiviral activity of AA against a broad spectrum of RNA and DNA viruses including polio virus, herpes virus, HIV-1 in-vivo and in-vitro."* Hayash also looked at the concomitant use of Vitamin C with highly active antiretroviral therapy (HAART) and found the combination to be very beneficial: *"Significantly increased HAART adherence is demonstrated during periods of AA usage compared to when the patients were not consuming AA. Due to the potential impact this simple, inexpensive intervention may have on HIV-positive patients, we believe a large community-based clinical trial is indicated."*

Herpes/Shingles/PHN

Vitamin C has been used clinically in acute viral infections; one such infection where Vitamin C has been used extensively is as an aid in the management of shingles/herpes/post herpetic neuralgia (PHN). A case report in 2006 using IV Vitamin C 2.5 g daily (Chen et al., 2006) and further cases and a study published using IV Vitamin C doses from 7.5 grams – 15 grams in the early 2010s (Schencking et al., 2012, 2010) highlight the successful use of intravenous vitamin C to significantly reduce pain in patients with shingles outbreaks. Intravenous Vitamin C 7.5 g also significantly reduced lesions and improved general fatigue and concentration (Schencking et al., 2012).

A case published in 2011 (Byun and Jeon, 2011) is typical of reports and describes a patient who did not respond to conventional therapy but had an immediate reduction in pain when administered Vitamin C. *"On the third day after right SGB (stellate ganglion block), the pain did not decrease in intensity. But 30 minutes after SGB, 4 g of vitamin C administered intravenously sequentially reduced the constant aching pain from a VAS (Visual Analogue Scale) of 5 to 2, which was maintained for about 12 hours. However, there was no intermittent shooting pain after the administration of the vitamin C on the third day. On the fourth day, right SGB and sequential intravenous injection of 4 g of vitamin C was done just like before. Immediately after the administration of the vitamin C, she rated her pain intensity from a VAS of 4 to 1, which was maintained for about 12 hours. On the fifth day, intravenous injection of 4 g of vitamin C was done without SGB. Immediately after the administration of the vitamin C, she rated her pain intensity from a VAS of 4 to 0. Since then, her pain intensity has been maintained at a VAS of 0-1."*

A 2012 letter reviewing the use of Vitamin C therapy in post herpetic neuralgia (PHN) points out that Vitamin C levels are lowered in these patients, that Vitamin C acts by modulating serum levels of cytokine IL-6 and IL-8, and that Vitamin C attenuates spontaneous pain in patients with PHN (Kapoor, 2012).

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Kim et al. conducted a clinical trial looking at the effects of IVC on acute pain and its effects on preventing PHN (Kim et al., 2016). Their treatment period was 5 days. Patients got 5 g IVC or saline on days 1, 3 and 5 as well as standard treatments. *"PHN occurred in 14 patients (31.1%) in the vitamin C treatment group and 24 patients (57.1%) in the control group."* After 8 weeks pain was also significantly lower in the Vitamin C group. A 2018 study tested the effects of Vitamin C or a prophylactic oral antiviral agent vs. control on herpes simplex epithelial keratitis (HSK) (Kim et al., 2018). Each Vitamin C group patient was given a 1,000 mg tablet twice a day. *"The recurrence rates were lower in the prophylactic oral antiviral agent group (16 / 48 eyes, 33.3% vs. 49 / 101 eyes, 48.5%) and the ascorbic acid treatment group (13 / 48 eyes, 27.1% vs. 81 / 101 eyes, 70.3%) compared with the groups without medications."*

Mosquito viruses

Cases have been published where high dose intravenous vitamin C has been used as part of the treatment for Chikungunya infection. A 2015 case report highlights the use of intravenous vitamin C over 2 days (Gonzalez et al., 2015): *"The patient was treated with high doses of intravenous vitamin C (100g/day) for a duration of two days. In relation to lab parameters before treatment, the only abnormality was an extremely large increase in C-reactive protein/CRP (26.9 mg/L). This CRP measure after treatment was reduced to 15.8 mg/L. The symptoms of pain, fever, and rash resolved after the infusions without any side effects. The symptoms improved substantially in 24 hours and were absent the next day."*

A review of Chikungunya infection cases where high dose intravenous vitamin C was used in combination with other therapies has been published by Marcial-Vega et al (Marcial-Vega et al., 2015). Forty-two (42/56=75%) of the patients received 25-30 grams of vitamin C. Seven, 6, 5 and 3 patients received 30 grams, 20 grams, 50 grams and 40 grams respectively: *"Our protocol has shown that the use of intravenous hydrogen peroxide and ascorbic acid is safe and strongly associated with a more than 61% post-infusion reduction of pain in patients affected with Chikungunya virus*

related arthralgias." "These results are consistent with previous in-vitro research which has shown that ascorbic acid inactivates the polio, herpes, vaccinia, tobacco mosaic, bacteriophage, entero, influenza and rabies viruses." "They are also consistent with previous clinical research showing ascorbic acid can resolve polio, Its associated flaccid paralysis, acute hepatitis, viral encephalitis, measles (simple and complicated), mumps (simple and complicated), chickenpox, influenza and rabies in guinea pigs."

Many infected patients treated with intravenous Vitamin C in Australia present with symptomatic Dengue or Ross River virus infections. Despite this there are no formal published cases in these conditions. However these are the viral conditions where physicians are reporting good results with IVC therapy. The usual IVC doses employed are 15 – 30 grams per dose for 3-5 days, titrated depending on the clinical response of the patient. It is high time that the use of IVC in these conditions is studied, or at the very least case reviews are undertaken.

Another mosquito vector virus that has come to prominent attention recently is Zika. A review of the use of Vitamin C in Zika virus infection was published in 2016 (Dettman, 2016). Further to this it would appear that the Zika epidemic is waning, certainly the panic is over (https://www.facebook.com/nmiroff, n.d.) . Reporting of Zika infection is mandatory in the USA. In 2016 in US states 5,168 symptomatic Zika virus disease cases were reported and in US territories 36,512 symptomatic Zika virus disease cases were reported. In 2019 (up until the end of March) zero cases have been reported in either US states or territories ("Zika Virus case counts," 2014). This does not mean Zika risk is over; Zika has definitely mutated since the 2015-2016 epidemics however there is still a potential risk for the foetus in infected pregnant women (Vouga et al., 2018; "Zika and Pregnancy," 2014).

Zika and Dengue are both flaviviruses. It appears that prior Dengue infection protects against symptomatic Zika infection (Gordon et al., 2019).

Epstein-Barr virus

Most case information about the use of vitamin C in viral diseases remains unpublished. Since Klenner's publications of cases from the 1950s to the 1970s, very few cases involving Vitamin C use in viral infections have seen the light of day, despite many thousands of doses given by many hundreds of doctors worldwide for infections such as HIV, Epstein-Barr virus/glandular fever, Dengue, Ross River, Barmah forest, Chikungunya etc. However there is still some significant published material in these cases to use as a basis for clinical evidence and to inform the direction for clinical research. An analysis of data from patients treated with high dose IVC for glandular fever at the Riordan Clinic was published in 2014 (Mikirova and Hunninghake, 2014): *"Our data provide evidence that high dose intravenous vitamin C therapy has a positive effect on disease duration and reduction of viral antibody levels. Plasma levels of ascorbic acid and vitamin D were correlated with levels of antibodies to EBV. We found an inverse correlation between EBV VCA (Viral Capsid Antigen) IgM and vitamin C in plasma in patients with mononucleosis and CFS meaning that patients with high levels of vitamin C tended to have lower levels of antigens in the acute state of disease."*

High dose Vitamin C, usually intravenously, is used by many physicians as an aid to the treatment of Glandular Fever. Contemporary cases and typical treatment protocols remain unpublished. However applications of Vitamin C, particularly in the acute stages of infection, have been reported to resolve symptoms rapidly and reduce or prevent abnormal liver enzyme levels.

Influenza and other respiratory infections

There is a significant body of work now about Vitamin C and its effects on immunity and some on viruses in respiratory infections. A review of drug therapies in Avian Influenza has highlighted the potential and typical use of Vitamin C in serious Influenza infections (Yuan, 2013). In this review Yuan states that *"effective inhibition of viral replication and apparent symptom alleviation usually requires over 5mM of VC (plasma concentration)"* Also Yuan comments that oral Vitamin C is inadequate because these levels cannot be obtained.

A mouse study by Li et al. looked at Vitamin C levels and pathology in influenza infected mice. The gulo-/- mice used cannot make Vitamin C. The mice were split into two groups; prior to infection one group got Vitamin C and one group did not (Li et al., 2006). They found that the lung is more susceptible to Vitamin C deficiency than the liver. *"At d 7 after infection, vitamin C–deficient mice had significantly greater lung pathology compared with vitamin C–adequate mice."*

Several authors have called for the use of high dose Vitamin C in influenza, in particular in relation to highly pathogenic strains such a avian flu. Ely (Ely, 2007) reviewed the potential use of Vitamin C in Avian flu: *"Now, we consider a person who is malnourished but not in extremely poor health, although his resistance to many diseases is rather marginal. Such a person can still survive a mild infection of flu if the amount of flu virus is not exceeding his ability to: (i) provide sufficient white blood cells for defense; and (ii) stimulate interferon production to go into adjacent cells, preventing the virus from reproducing in them."* Ely follows on the heels of a long history of use of Vitamin C in infections, including influenza and other viral infections, and cites previous reviews on the material by Linus Pauling.

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Carr et al. have recently undertaken an extensive review of the role of Vitamin C in immune response (Carr and Maggini, 2017). They document numerous functions of Vitamin C and conclude that: *"Vitamin C deficiency results in impaired immunity and higher susceptibility to infections. In turn, infections significantly impact on vitamin C levels due to enhanced inflammation and metabolic requirements. Furthermore, supplementation with vitamin C appears to be able to both prevent and treat respiratory and systemic infections."*

Some other specific studies and reviews related to respiratory infections include:

- Effects of a nutrient mixture on infectious properties of the highly pathogenic strain of avian influenza virus A/H5N1 (Deryabin et al., 2008, p. 1). The nutrient mixture contained lysine, proline, ascorbic acid, green tea extract, N-acetyl cysteine, selenium and other micro nutrients, and the mixture was applied to virus infected cultured cells. *"(the nutrient mixture) demonstrated high antiviral activity evident even at prolonged periods after infection. NM antiviral properties were comparable to those of conventional drugs (amantadine and oseltamivir); however, NM had the advantage of affecting viral replication at the late stages of the infection process."*
- Combined inhalational and oral supplementation of ascorbic acid may prevent influenza pandemic emergency: A hypothesis (Banerjee and Kaul, 2010)
- [Pharmacologic ascorbate treatment of influenza in vivo] (Cheng et al., 2014). The study investigated the effects of C against Influenza A/CA/7/09 (H1N12009) in mice. *"Mice infected with influenza virus and treated with pharmacologic ascorbate had higher survival and less weight loss, and had lung viral titers reduced by as much as 10 to 100-fold compared to the controls. Pathologic study of the lungs showed that the treated animals had little inflammation (bronchiolitis, perivasculitis, alveolitis, and vasculitis) compared to the controls.IL-1, IL-6, and IFN-alpha lung levels were lower in the treated animals compared to the controls."*
- Vitamin C and Infections (Hemilä, 2017). *"Three controlled trials found that vitamin C prevented pneumonia. Two controlled trials found a treatment benefit of vitamin C for pneumonia patients."*
- Intravenous vitamin C as adjunctive therapy for enterovirus/rhinovirus induced acute respiratory distress syndrome (Fowler Iii et al., 2017). This is a report of a case of high dose intravenous Vitamin C administration in a patient with virus induced Acute Respiratory Distress Syndrome (ARDS). High-dose intravenous vitamin C (200 mg/kg per 24 h) was initiated on ECMO (Extracorporeal membrane oxygenation) day 1 with the total daily vitamin C dosage divided equally into four doses and infused every 6 h. *"Infusing high dose intravenous vitamin C into this patient with virus-induced ARDS was associated with rapid resolution of lung injury with no evidence of post-ARDS fibroproliferative sequelae. Intravenous vitamin C as a treatment for ARDS may open a new era of therapy for ARDS from many causes."*
- Extra Dose of Vitamin C Based on a Daily Supplementation Shortens the Common Cold: A Meta-Analysis of 9 Randomized Controlled Trials (Ran et al., 2018)
- Efficacy of vitamin C for the prevention and treatment of upper respiratory tract infection. A meta-analysis in children (Vorilhon et al., 2019). *"…vitamin C intake reduced the duration of URTI. Considering the frequency of URTI, the inappropriate prescription of antibiotics, and the safe nature of vitamin C, its supplementation is justified, especially in children under 6 years of age and those who present a high frequency of URTI."*

Anitiviral mechanisms

Numerous studies have been done highlighting various effects of Vitamin C on immune response, normalisation of disrupted immune response, and specifically on viral replication and inhibition. However, there is still a lot to learn and understand about how Vitamin C influences viral infections. Already cited, a review by Carr et al. (Carr and Maggini, 2017) gives a good overview of much of the research to date behind the antiviral effects of Vitamin C. Vitamin C is involved in multiple immune functions, including; chemotaxis, phagocytosis and generation of reactive oxygen species involved in pathogen destruction, apoptosis and clearance of spent neutrophils, proliferation of B- and T-cells, production of interferon, neutrophil blastogenesis and many more. Current research is looking at the gene modifying effects of Vitamin C, including epigenetic effects on functions of the immune system.

One area gaining research traction is the idea of Vitamin C in high doses as a pro-oxidant. This is a common theory found in cancer research, the idea is that low doses of Vitamin C act as an antioxidant but high doses have a damaging effect, or pro-oxidant effect on cancer cells. Similar ideas are to be found in literature associating Vitamin C with ant-viral effects. In cancer research the pro-oxidant theories of Vitamin C action have been demonstrated and consistently replicated *in vitro*, but as yet have not been proven *in vivo* in humans. In general, *in vivo* conditions are very different to *in vitro* or cell culture environments. Spectacular and repeatable results seen with Vitamin C and cancer cell killing in cell culture studies are not seen in living patients. It is likely the case with treating real patients with viral infections that like in cancer, Vitamin C is participating in multiple mechanisms in virus control; immune response, genetic response and direct actions on various viruses.

Some more published mechanisms and discussions include:

- Antiviral effects of ascorbic and dehydroascorbic acids *in vitro* (Furuya et al., 2008). *"In the present study, ascorbic acid weakly inhibited the multiplication of viruses of three different families: herpes simplex virus type 1 (HSV-1), influenza virus type A and poliovirus type 1. Dehydroascorbic acid, an oxidized form of ascorbic acid and hence without reducing ability, showed much stronger antiviral activity than ascorbic acid, indicating that the antiviral activity of ascorbic acid is due to factors other than an antioxidant mechanism."* The authors note that the addition of iron (Fe+++) strongly enhanced the activity of ascorbic acid.
- Antiviral effects of dehydroascorbic acid (Uozaki et al., 2010). *"These results indicate that the reagent inhibits HSV-1 multiplication after the completion of viral DNA replication, probably at the step of the envelopment of viral nucleocapsids at the Golgi apparatus of infected cells."*
- p53 Serves as a Host Antiviral Factor That Enhances Innate and Adaptive Immune Responses to Influenza A Virus (Munoz-Fontela et al., 2011). *"Several direct target genes of the p53 tumor suppressor have been identified within*

pathways involved in viral sensing, cytokine production, and inflammation, suggesting a potential role of p53 in antiviral immunity." P53 is not just a tumour suppressor gene. This is important in relation to Vitamin C, because in cancer research Vitamin C has been shown to enhance P53 activity. *In vivo* antitumor activity is enhanced by the presence of p53 (Kim et al., 2012, p. 53).

- Vitamin C Is an Essential Factor on the Anti-viral Immune Responses through the Production of Interferon-α/β at the Initial Stage of Influenza A Virus (H3N2) Infection (Kim et al., 2013). This was a mouse study that again used mice that cannot make Vitamin C. *"Viral titers in the lung of vitamin C-insufficient Gulo (-/-) mice were definitely increased but production of anti-viral cytokine, interferon (IFN)-α/β, was decreased. On the contrary, the infiltration of inflammatory cells into the lung and production of pro-inflammatory cytokines, tumor necrosis factor (TNF)-α and interleukin (IL)-α/β, were increased in the lung." "Vitamin C shows in vivo anti-viral immune responses at the early time of infection, especially against influenza virus, through increased production of IFN-α/β."*
- A new mechanism of vitamin C effects on A/FM/1/47(H1N1) virus-induced pneumonia in restraint-stressed mice (Cai et al., 2015). *"Results showed that restraint stress significantly increased the mortality and the severity of pneumonia in mice caused by A/FM/1/47(H1N1) virus infection, which was attenuated by oral administration of vitamin C (125 and 250 mg/kg). Moreover, vitamin C administration significantly decreased expression of susceptibility genes, including mitochondrial antiviral signaling (MAVS) and interferon regulatory factor 3 (IRF3), and increased expression of NF-κB. These work in conjunction to induce type I interferons (IFNs) and elicit innate antiviral response".* The authors found that the above was also related to inhibition of excess CORT (corticosterone) synthesis by regulating steroid hydroxylating enzymes in adrenal gland, which reduces susceptibility to the infection.
- Vitamin C increases viral mimicry induced by 5-aza-2'-deoxycytidine (Liu et al., 2016). The study found parallels between epigenetic effects of Vitamin C in cancer and effects in immune response. When Vitamin C is combined with DNA methyltransferase inhibitors (DNMTis): *"These effects are associated with enhanced immune signals including increased expression of bidirectionally transcribed endogenous retrovirus (ERV) transcripts, increased cytosolic dsRNA, and activation of an IFN (interferon)-inducing cellular response. This synergistic effect is likely the result of both passive DNA demethylation by DNMTi and active conversion of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) by ten-eleven translocation (TET) enzymes at LTR regions of ERVs, because vitamin C acts as a cofactor for TET proteins."*

Ebola

The Ebola scare from 2014 is over, however this does not mean it will not return. Consideration should be given to high dose IVC as a potentially life saving aid in the management of infection. For a comprehensive review of the use of Vitamin C in Ebola infection, please see (Dettman, 2014). The basic idea here is that the survivors of Ebola infection are the ones who have mounted an adequate, timely and effective host defense. Approximately half of all infected patients in the last

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African outbreak died from the overwhelming consequences of the Ebola infection before they could mount a host response. The take home message? Vitamin C is known to impact viral infections. Vitamin C buys time, decreases the severity of the pathology and gives the infected person more of a chance to mount an innate response. High dose Vitamin C, in severe infection, could literally be lifesaving.

What is missing?

More clinical trials need to be done. Success has been reported with high dose Vitamin C usage in glandular fever, various mosquito borne infections like Dengue fever, Chikungunya, Ross River fever etc., shingles, various other herpes infections and respiratory infections. Clinical trials using Vitamin C in the management of sepsis have been successful, many other similar trials are recruiting or running. Dose ranging needs to be done in this area to best understand the effects and limitations of high dose Vitamin C and its place in the management of sepsis. Severe sepsis and severe acute viral infections share some similar immune response features, there is no reason to doubt that there should be some impact of Vitamin C in severe viral infections. Large studies looking at dose ranging, length of treatment and short term and long-term outcomes for the use of Vitamin C in a variety of serious viral infections have not been done. The use of high dose Vitamin C in serious infections such a bird flu and Ebola have not been investigated. Given the pedigree of Vitamin C in viral infections, it would seem it is time to investigate the effect of high dose Vitamin C in the field. Vitamin C is largely non-toxic, major precautions include assessing renal function and glucose 6 phosphate dehydrogenase (G6PD) deficiency prior to treatment. For the vase majority of patients these issues do not exist, are not clinically relevant, o can be managed.

A last case

Persistent parvovirus B19 viremia with chronic arthralgia treated with ascorbic acid: a case report (Lallement et al., 2015). The patient was given oral acid ascorbic at 10 grams per day for 10 days. *"We report the case of a 54-year-old Caucasian woman with chronic arthralgia due to persistent parvovirus B19 viremia. High doses of ascorbic acid treatment were initiated due to the failure of conventional analgesic therapy. Clinical benefit was observed with a simultaneous loss of biological parvovirus B19 viremia."*

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