Cytokine Storm – A Possible Sequela to Influenza

by Dan Carter, ND

A competent immune system is usually associated with good health, but some conditions can turn the immune system component of cytokines against us. For example, the 1918-19 Spanish flu epidemic [Type A, subtype (H1N1)] caused a high number of influenza deaths. More than one-half million people died in the United States, and nearly half of the deaths were young healthy adults aged 20-40. Both the swine flu (H1N1) and bird flu (H5N1) have resulted in what has been defined as a "cytokine storm." There are no data regarding the prevalence of cytokine storm in H1N1 patients, although it is known to be the principle cause of death in patients with H5N1 infections. The high death rate associated with cytokine storms begs the question – is there an effective treatment available for this life threatening condition?

The following is a synopsis of an article published May 6, 2009:
The H1N1 flu may be dangerous for healthy young adults because it contains genetic components of the H5N1 avian influenza virus, according to U.S. researchers.
H5N1 avian influenza virus can induce a "cytokine storm," in which a patient's hyperactivated immune system causes potentially fatal damage to the lungs. David Woodland, editor in chief of Viral Immunology, says a cytokine storm occurs when the body's immune system overreacts to an intruder, such as a virus, by producing high levels of cytokines, which are signaling chemicals that help mobilize immune cells responsible for removing infectious agents from the body.
When too many cytokines are produced, they may stimulate an inflammatory response in which the accumulation of immune cells and fluid at the site of infection may prevent affected tissues and organs such as the lungs from functioning properly (acute respiratory distress syndrome, ARDS) which can lead to death.
What is known is that some H1N1 viruses have pandemic potential and that historical evidence supports the possibility that healthy young adults may be especially susceptible to more severe infection and poor outcomes due to the ability of a strong immune system to initiate a cytokine storm.
[http://www.sciencedaily.com/releases/2009/05/090505174547.htm]

Proposed mechanism of the cytokine storm

1. Influenzavirus (H5N1, H1N1, etc) enters body from an infective source
2. Epithelial cells are infected with influenzavirus, which replicates and infects other cells
3. Macrophages are attracted to the infected cells by chemotactic response and the macrophages become infected
4. Macrophage becomes activated and presents viral peptide on its surface
5. T cell binds to viral peptide and becomes activated
6. This leads to an uncontrolled energetic immune response and the release of chemoattractants plus proinflammatory cytokines from epithelial cells and macrophages and proinflammatory cytokines from the T cells

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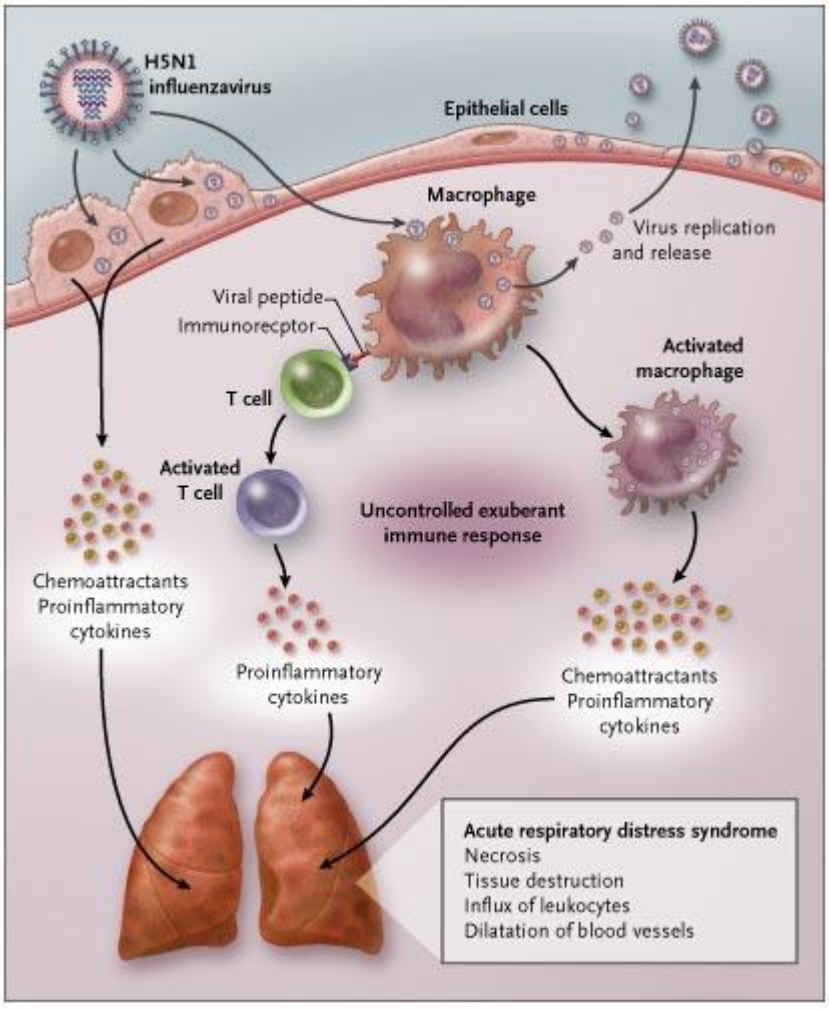
7. The cytokines migrate to the lungs and cause acute respiratory distress syndrome: necrosis, tissue destruction, influx of leukocytes, and dilation of blood vessels [Supplement to: Osterholm MT. Preparing for the Next Pandemic. N Engl J Med 2005;352(18):1839-42.]



The inflammatory cytokines are IL-1, IL-6 and TNF. These cytokines are associated with symptoms of infection, e.g. fever, fluid retention, swelling, malaise, headache. These inflammatory symptoms normally transition into recovery, but in the case of swine flu, other cytokines are produced, including anti-inflammatory IL-10. It appears that the heightened IL-10 signaling interferes with the natural transition from inflammation to recovery and excess inflammatory signaling becomes acute and life-threatening. The inflammatory transcription factor, NFkB is also present in excess.

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SYMPTOMS OF THE CYTOKINE STORM: ref http://www.cytokinestorm.com/

The end-stage of cytokine storm is multiple organ dysfunction syndrome (MODS). The end-stage symptoms of the bird flu, or other infection precipitating the cytokine storm may include:

- hypotension
- tachycardia
- dyspnea
- fever (temperature of >38°C or >100.4°F)
- ischemia, or insufficient tissue perfusion (especially involving the major organs)
- uncontrollable hemorrhage
- multisystem organ failure (caused primarily by hypoxia, tissue acidosis, and severe metabolism dysregulation

Oxygen free radicals, histamine, complement factor C5a, Beta-endorphin, thromboxane B2, and platelet activating factor are implicated. The major pro-inflammatory cytokines generated by the storm are TNF-alpha, IL1, IL6 and IL8. Serum TNF alpha concentrations in excess of 1 ng/mL are frequently predictive of a lethal outcome, however serum concentrations of other inflammatory cytokines involved in the pathophysiology of septic shock are usually not reliable predictors of the severity of the shock state or clinical outcome. These cytokines are released by macrophages following activation by bacterial endotoxins.

The role of NF-kappaB

J Immunol. 2009 Oct 15;183(8):5180-9. Epub 2009 Sep 28.

Essential impact of NF-kappaB signaling on the H5N1 influenza A virus-induced transcriptome.

Schmolke M, Viemann D, Roth J, Ludwig S.

Systemic infections of humans and birds with highly pathogenic avian influenza A viruses of the H5N1 subtype are characterized by inner bleedings and a massive overproduction of cytokines known as cytokine storm. Growing evidence supports the role of endothelial cells in these processes. The aim of this study was to elucidate determinants of this strong response in endothelial cells with a focus on the transcription factor NF-kappaB. This factor is known as a major regulator of inflammatory response; however, its role in influenza virus replication and virus-induced immune responses is controversially discussed. By global mRNA profiling of infected cells in the presence or absence of a dominant negative mutant of IkappaB kinase 2 that specifically blocks the pathway, we could show that almost all H5N1 virus-induced genes depend on functional NF-kappaB signaling. In particular, activation of NF-kappaB is a bottleneck for the expression of IFN-beta and thus influences the expression of IFN-dependent genes indirectly in the primary innate immune response against H5N1 influenza

virus. Control experiments with a low pathogenic influenza strain revealed a much weaker and less NF-kappaB-dependent host cell response.
J Immunol. 2003 Jun 15;170(12):6224-33.

Activation of NF-kappa B in virus-infected macrophages is dependent on mitochondrial oxidative stress and intracellular calcium: downstream involvement of the kinases TGF-beta-activated kinase 1, mitogen-activated kinase/extracellular signal-regulated kinase kinase 1, and I kappa B kinase.
Mogensen TH, Melchjorsen J, Höllsberg P, Paludan SR.

Efficient clearance of virus infections depends on the nature of the host response raised by the infected organism. A proinflammatory cell-mediated immune response is important for elimination of many viruses, including herpesviruses. Macrophages are intimately involved in generation of a proinflammatory response, the initiation of which involves activation of the transcription factor NF-kappaB. However, the mechanisms of HSV-induced NF-kappaB activation are poorly understood. In this study we demonstrate that activation of NF-kappaB by HSV in macrophages is dependent on a functional viral genome and proceeds through a mechanism involving the cellular IkappaB kinase, as well as the upstream kinases TGF-beta-activated kinase 1, mitogen-activated kinase/extracellular signal-regulated kinase kinase 1, and possibly NF-kappaB-inducing kinase. Furthermore, we show that HSV triggers NF-kappaB activation by a signaling pathway involving oxidative stress in mitochondria and intracellular calcium, because specific inhibition of mitochondria-derived reactive oxygen intermediates, as well as mitochondrial calcium channels, prevented NF-kappaB activation. Together, these results point to mitochondria as cellular checkpoints able to initiate NF-kappaB activation after virus infection and also show that the cellular NF-kappaB-regulating kinases IkappaB kinase, TGF-beta-activated kinase 1, mitogen-activated kinase/extracellular signal-regulated kinase kinase 1, and possibly NF-kappaB-inducing kinase, are essential components in the HSV-induced signaling pathway.
J Immunol. 2004 Feb 15;172(4):2522-9.

Involvement of reactive oxygen species in Toll-like receptor 4-dependent activation of NF-kappa B.
Asehnoune K, Strassheim D, Mitra S, Kim JY, Abraham E.

Although oxidative stress has been thought to play a general role in the activation of NF-kappaB, the involvement of reactive oxygen species (ROS) in facilitating nuclear translocation of NF-kappaB in neutrophils has not been described. In addition, the mechanisms by which ROS modulate the transcriptional activity of NF-kappaB in response to Toll-like receptor 4 (TLR4)-dependent signaling are not well characterized. To examine these issues, oxidant-dependent signaling events downstream of TLR4 were investigated in neutrophils stimulated with LPS. Pretreatment of neutrophils with the antioxidants N-acetylcysteine or alpha-tocopherol prevented LPS-induced nuclear translocation of NF-kappaB. Antioxidant treatment of LPS-stimulated neutrophils also inhibited the production of proinflammatory cytokines (TNF-alpha, macrophage inflammatory protein-2, and IL-1beta), as well as activation of the kinases IkappaB kinase alpha, IkappaB

> kinase beta, p38, Akt, and extracellular receptor-activated kinases 1 and 2. The decrease in cytoplasmic levels of IkappaBalpha produced by exposure of neutrophils to LPS was prevented by N-acetylcysteine or alpha-tocopherol. Activation of IL-1R-associated kinase-1 (IRAK-1) and IRAK-4 in response to LPS stimulation was inhibited by antioxidants. These results demonstrate that proximal events in TLR4 signaling, at or antecedent to IRAK-1 and IRAK-4 activation, are oxidant dependent and indicate that ROS can modulate NF-kappaB-dependent transcription through their involvement in early TLR4-mediated cellular responses.

Cytokine Storm & Vitamin D relationship

http://www.medicalnewstoday.com/articles/154759.php

The Possible Roles Of Solar Ultraviolet-B Radiation And Vitamin D In Reducing Case-Fatality Rates From The 1918-1919 Influenza Pandemic In EU

Article Date: 22 Jun 2009 - 1:00 PDT

An estimated 675,000 Americans died from the A/H1N1 pandemic influenza in the United States in 1918-1919. Many of these deaths were from ensuing bacterial pneumonia rather than directly from the viral infection. The United States Public Health Service conducted surveys in twelve cities and rural areas of the country in late 1918 to early 1919 to determine the case-fatality rate in each city or area. Case-fatality rates varied from 0.78 deaths/100 cases in San Antonio, Texas to 3.14 deaths/100 cases in New London, Connecticut. The strong variation with location suggested that solar ultraviolet-B (UVB) irradiance, through production of vitamin D, reduced the risk of death following infection by this pandemic influenza.

To investigate this possibility, the case-fatality rate data were compared statistically with solar UVB doses in July and January. Strong correlations with UVB doses were found for both indices.

There are two mechanisms whereby vitamin D can reduce the risk of death once the pandemic influenza virus infection took hold: reduced production of proinflammatory cytokines and reduced risk of bacterial pneumonia. The hormonal metabolite of vitamin D, 1,25-dihydroxyvitamin D, reduces the production of cytokines from T-helper 1 type (proinflammatory). 1,25-dihydroxyvitamin D also induces the production of human cathelicidin, LL-37, which has both antimicrobial and antiendotoxin properties. LL-37 has been found effective in reducing the risk of several types of bacteria, and is also thought to reduce the risk of respiratory viral infections including seasonal influenza.

Treatment Suggestions - Cytokine storms associated with ARDS have been treated by forcing progression of the inflammatory process into its recovery phase with anti-inflammatory treatments

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Pharmaceutical treatments
The treatment to prevent or stop the autoimmune reaction (cytokine storm) is commercially available by prescription, but is not currently being recommended by the World Health Organization to treat these patients. [http://www.cytokinestorm.com/]
ACE inhibitors and Angiotensin II Receptor Blockers (ARBs) have proven to be beneficial in treating the cytokine storm.
Corticosteroids are used to combat the cytokines storm, but they are prescribed in the second phase of the disease to avoid further lung damage. Corticosteroids should not be used as an antipyretic agent, and obviously not an anti-viral agent.
Methylprednisolone in the form of pulse therapy is effective. Detail protocol can be found in the Hospital Authority Guideline (www.ha.org.hk).

Nutritional treatments

IV Nutritional Treatments – Perform G6PD test prior to administration (consider benefit/risk if not performed). It is advised that the first IV administered contain one-half dose ascorbic acid; if this is well tolerated, the second IV may be administered at full dose.
Magnesium chloride, 200 mg/mL, 5 mL
Calcium chloride, 100 mg/mL, 10 mL
DMSO, 99%, 5 mL (optional)
Ascorbic acid, 500 mg/mL, 100 mL
Sodium bicarbonate, 8.4%, 25 mL
Sterile water, 500 mL

Oral Nutritional Treatments

Antioxidants have been shown to significantly reduce pro-inflammatory cytokine release and membrane lipid peroxidation: e.g. ascorbic acid, N-acetylcysteine, taurine, phytic acid and lipoic acid. [Spreafico A, et al. Antioxidants inhibit SAA formation and pro-inflammatory cytokine release in a human cell model of alkaptonuria. Rheumatology (Oxford). 2013 Sep;52(9):1667-73. PMID 23704321], [Lin YC, Lai YS, Chou TC. The protective effect of alpha-lipoic acid in lipopolysaccharide-induced acute lung injury is mediated by heme oxygenase-1. Evid Based Complement Alternat Med. 2013:2013:590363. PMID 23573137], [Deng C, et al. Alpha-lipoic acid reduces infarct size and preserves cardiac function in rat myocardial ischemia/reperfusion injury through activation of PI3K/Akt/Nrf2 pathway. PLoS One. 2013:8(3):e58371. PMID 23505496], [Shaik_Dasthaqirisaheb YB, et al. Role of vitamins D, E, and C in immunity and inflammation. J Biol Regul Homeost Agents. 2013 Apr-Jun;27(2):291-5. PMID

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23830380], [Kim Y, et al. Vitamin C is an essential factor on the anti-viral immune responses through the production of interferon-alpha-beta at the initial stage of influenza A virus (H2N2) infection. Immune Netw. 2013 Apr:13(2):70-4. PMID 23700397]

Curcumin is a potent inhibitor of NFkB
[Siddiqui AM, Cui X, Wu R, Dong W, Zhou M, Hu M, Simms HH, Wang P. The anti-inflammatory effect of curcumin in an experimental model of sepsis is mediated by up-regulation of peroxisome proliferator-activated receptor-gamma. Crit Care Med. 2006 Jul;34(7):1874-82. PMID 16715036]

Omega-3 fatty acid EPA is converted by COX-2 into an anti-inflammatory prostaglandin. [Siger P, Shapiro H. Enteral omega-3 in acute respiratory distress syndrome. Curr Opin Clin Nutr Metab Care. 2009 Mar;12(2):123-8. PMID 19202383]

Vitamin D3: If patient is not taking a vitamin D supplement, give 50,000 IU daily for two weeks. For preventive measure during the winter months an adult dose of 4,000 IU daily is recommended. Blood levels of vitamin D should be monitored to determine the optimal dosing schedule; blood concentrations of 80 ng/ml (25-OH cholecalciferol) have been suggested as a level at which maximal calcium absorption takes place (note: the measurement of calcium absorption is standardized, whereas there are no tests to determine the direct effect of vitamin D levels on immune function). [Heaney, RP. Functional indices of vitamin D statues and ramification of vitamin D deficiency. Am J Clin Nutr. 2004 Dec;80(6 suppl):1706S-9S. PMID15585791]

Dan Carter, ND, graduated from National College of Naturopathic Medicine (NCNM) and completed a 2-year family practice residency. He was appointed to a full-time faculty position in 1997 and served as a core faculty member through 2003. He has been in private practice in Bozeman, Montana since 2004 and is currently offering expert consulting services focusing on cardiovascular disease, metabolic syndrome, hormone restoration and IV nutrient therapies. Dan has been an ACAM member since 2007 and has been a speaker at past ACAM conferences.