Sepsis and Acute Lung Injury

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Introduction

Sepsis syndrome is associated with diffuse microvascular injury (predominantly lung injury) which appears to be related to a wide variety of physiologically active and tissue destructive mediators. The exact cause and effect relationship between mediators and pathophysiology is becoming increasingly better understood but much remains to be elucidated. Even in those situations where biochemical mechanisms have been well worked out in animal models, it remains to be seen whether or not the findings can be transferred to humans with sepsis. The tremendous homogeneity of the sepsis syndrome population make clinical studies of this group difficult and meaning of clinical findings subject to interpretation. Increasingly, however, the availability of high quality assays and pharmacologic interventions has placed this type of research on more firm footing. In this chapter, the clinical implications of the release of bioactive lipids and free radicals of oxygen will be explored in the light of the available clinical data just now becoming available.

Role of Diffuse Membrane Damage in Sepsis and Acute Lung Injury (ALI)

The cellular damage produced by toxin and bacteriologic-induced activation of the immune system has been reviewed elsewhere [1]. Briefly, a major line of reasoning is that monocytes and macrophages recognize breaches in the immune barrier and react by producing a variety of second messengers designed to prepare the remainder of the immune system to deal with the invasion, bacteriologic or otherwise [2]. Phagocytosis is one of the fundamental mechanisms used by leukocytes, particularly macrophages and granulocytes, to destroy invading microorganisms. A principle feature of the phagocytic process involves the activation of NADPH oxidase (oxidative burst), a cell membrane associated enzyme system capable of converting molecular oxygen to superoxide anion (O_2-). Superoxide is rapidly converted to hydrogen peroxide (H_2O_2) either spontaneously or enzymatically with the participation of superoxide dismutase (SOD) with the spontaneous conversion almost

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as efficient as the enzymatic conversion. H_2O_2 is a powerful but relatively slow oxidant in biologic systems but it can damage DNA, react with sulfhydryl groups on structurally or enzymatically important proteins, and has other toxic effects. H_2O_2 is converted (detoxified) by catalase to water and oxygen or it enters in the multiple-step, iron catalyzed Fenton or Haber-Weiss reactions in which it is converted to hydroxyl radical. The hydroxyl radical is extremely reactive and in fact, is considered the most reactive free radical produced in biologic systems. Side products of this reactive species are lipid peroxides, hypochlorous acid and other highly reactive species.

The chronic infections seem in patients with chronic granulomatous disease of childhood, a genetic disorder in which the host lacks NADPH oxidase, attests to the importance of this enzyme in homeostasis and infectious disease prevention. As long as this potent oxidant activity is fairly well contained in the phagosome, little if any collateral tissue damage ensues. In the robust immune response of sepsis syndrome, it seems likely that the containment process is inadequate and that this results in damage to host tissues. The primary line of defense in the proper management of the process is a series of enzymes and free radical scavengers. SOD is important in first detoxification step of superoxide anion, conversion to hydrogen peroxide. SOD is found primarily as an intracellular enzyme although preliminary studies in patients with sepsis suggest that in this clinical condition, substantial quantities can be detected in plasma (personal communication, John Repine). Whether this is a result of cell damage, appropriate release triggered by the oxidant stress of sepsis or otherwise, the role of plasma and cellular SOD in sepsis remains to be elucidated.

Hydrogen peroxide is rapidly converted to water and oxygen by catalase, an enzyme with relatively low activity or by glutathione peroxidase, a more efficient enzyme. Glutathione peroxidase is different from catalase in other ways in that it is also active against lipid peroxides and it consumes glutathione in the catalytic process (i.e. converts glutathione (GSH) to oxidized glutathione (GSSG)) [3]. The difference in substrate specificity between catalase and GSH peroxidase is critically important. It is possible that much of the free radical attack on cell membranes results in the production of lipid peroxides rather than hydrogen peroxide. In order for the cell to recover from this injury, it must possess the ability to detoxify both types of peroxides.

Secondary defense against reactive oxygen metabolites is provided by vitamin E (α-tocopherol), β-carotene (a precursor of vitamin A), and thiols (sulfhydryl containing compounds such as methionine, cysteine and GSH). These easily oxidizable compounds provide a ready substrate for the reduction of free radicals. GSH is particularly attractive as a substrate because once oxidized to GSSG, it is easily regenerated (reduced) enzymatically through an energy consuming process by GSH reductase [3].

Oxidant Stress in Sepsis

Although the best known and possibly the most important oxidant stress in sepsis is oxidant burst, there are a variety of other potential sources of reactive oxygen species in this clinical syndrome. Supplemental oxygen, often required in therapy when ALI occurs, may place additional oxidant stress on the lung, drug metabolism may result in free radicals, and ischemia reperfusion injury may produce tissue injury through the production of free radicals. Free radical release may occur in the latter when hypoxanthine is converted to xanthine by xanthine oxidase. Xanthine oxidase is the form of the enzyme xanthine dehydrogenase present in ischemic tissues [4].

Relationship of Oxidant Stress to Free Radical Generation

Membrane phospholipids are the richest source of bioactive lipids in the body. During activation of inflammatory cells, phospholipases are activated resulting in the cleavage of arachidonic acid from cell membranes. Once free of the phospholipid bilayer, arachidonic acid is readily and rapidly converted to a very large variety of bioactive lipids. Through the action of 5-lipoxygenase, leukotriene B4, a potent chemoattractant, and leukotrienes C4, D4, and E4, potent bronchoconstrictors, vasoconstrictors which are also possibly important in the increased microvascular permeability associated with sepsis are released [5]. The other classic route of arachidonate metabolism is through the cyclooxygenase pathway. The major lipid mediators produced by this pathway include PGE, PGI_2, thromboxane-B_2 (TxB_2), and there are others [6]. There are still other very active lipids released as a result of cell membrane damage including platelet activation factor (PAF) [7].

The relative production of these different bioactive lipids from cell membranes is somewhat cell specific. Macrophages and platelets are the greatest source of thromboxane. There are some cell culture data suggesting that pulmonary macrophages produce more thromboxane than macrophages obtained from the peritoneum. Prostacyclin, on the other hand, is produced largely by systemic vascular bed endothelial cells. Systemic (peritoneal macrophages) are also a rich source. PAF and leukotrienes are produced by almost all cells tested to date.

Inhibition of leukotriene production in sepsis models has been of interest for several years [8]. Only recently have relatively non-toxic and potent 5-lipoxygenase inhibitors become available such that intensive testing could proceed. Such agents are currently in clinical testing for airway inflammatory changes of asthma but clinical trials in sepsis or ARDS have not been reported. Clinical studies of inhibition of the leukotriene pathway in sepsis seem rational given what we know about the adverse and long lasting effects of leukotrienes in animal models and in patients with ARDS. Recent data from patients with sepsis-induced ARDS indicate very large and sustained increases in leukotriene metabolites (Fig. 1) [5].

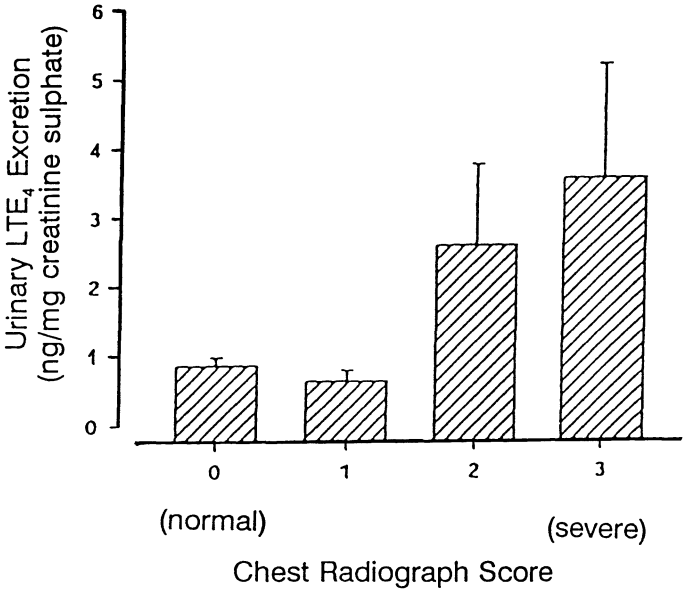

Fig. 1. Radiographic evidence of pulmonary edema and urinary LTE_4 excretion in patients with ARDS. Urinary LTE_4 excretion (ng/mg creatinine, mean ± SEM) values were compared to the chest radiograph scores obtained on the same days as the urine samples. There was a trend toward increased LTE_4 excretion on occasions where radiography revealed moderate (score = 2) and severe (score = 3) pulmonary edema. (From [5] with permission)

PGE is an anti-inflammatory prostaglandin and may be important in providing negative feedback to the inflammatory process [9]. Acting as an anti-inflammatory agent, excess quantities of this bioactive lipid are hypothesized to result in a relatively immunocompromised state in some critically ill patients and thus in these patients it may be harmful. On the other hand, the anti-inflammatory nature of the E-series prostaglandins have made them attractive in the clinical study of ARDS as potential therapy [10, 11]. It remains to be seen just how the balance between too much and too little PGE will finally settle out. This form of therapy is still under active study.

Thromboxane-B_2 is a potent bronchoconstrictor, a pulmonary vasoconstrictor, and this lipid activates platelets and causes them to aggregate. The concept of reducing the effect of thromboxane in sepsis has been tested through use of thromboxane synthetase inhibitors or by agents or by thromboxane-receptor antagonists [12].

Prostaglandin-I_2 (PGI_2) has anti-inflammatory actions as well as vaso- and bronchodilator effects which essentially oppose those of thromboxane. The balance between the two as well the relative number of receptors for each is probably important in determining the net physiologic effects of the release of these lipid mediators in sepsis. Compounding the problem is the fact that these metabolites have very short plasma and tissue half-lives making studies

of the parent/active compounds impossible. Thromboxane, for example, has a plasma half-life of approximately 30 sec under normal conditions. It is conceivable that this time could be prolonged under conditions of rapid production such as sepsis, so that the usual pathways of metabolism are overwhelmed. But for made clinical as well as animal studies of these mediators very difficult. Still, these two lipids are the most studied the time being, animal and human studies must rely on the measurements of inactive metabolites. These issues have of the arachidonic acid metabolites.

Relationship between Free Radicals and the Arachidonic Acid Cascade

Any process by which the lipid membrane of cells is perturbed has the potential for activating phospholipases and for subsequent release of arachidonic acid. Free radicals of oxygen, easily capable of lipid peroxidation through the processes described above are major contenders for this role. It is possible that an early step in the process of development of the systemic inflammatory response is the disturbance of a critical mass of endothelial (microvascular) cell membrane lipids such that local reparative and/or containment processes are overwhelmed. As key mediators such as leukotrienes, thromboxane and prostacyclin enter the general circulation host, physiology begins to be altered in a variety of ways. The manner of host response is likely dictated by the relative preponderance of each mediator in each tissue bed as well as by the timing of the appearance of these substances. For example, if prostacyclin reaches the systemic vascular bed in large quantities and is relatively unopposed by thromboxane or other vasoconstrictors, low systemic vascular resistance and shock may result. If the final result is shock, which occurs in approximately 40–60% of sepsis syndrome patients at one time or another in their illness, and if shock is sustained, additional ischemia reperfusion occurs, more oxidants are produced and the cycle is not only repeated, but amplified. If, on the other hand, PGE or anti-inflammatory cytokines are released in sufficient quantities, then the cycle of inflammation with diffuse microvessel and organ damage could be broken and homeostasis could then be restored. Further complicating the complete understanding of these effects is that the local demographics of blood flow, receptor density and other factors may also impact the net physiologic response.

The complexity of the systemic inflammatory response is such that the details of the players and their interactions will probably be worked out only in controlled basic research models. On the other hand, considering the importance of timing and mediator and organ interaction on the process, no theory of the operation of the systemic inflammatory response can be taken as fact until there is adequate testing in humans. The heterogeneous nature of human diseases underlying this process clinically dictates that a major approach to the problem must be to employ inhibitors (or augmenters in cases where

this is justified, i.e., PGE_1) of the purported mediators and observe the effect. The work to be described below with antioxidants and cyclooxygenase inhibitors is aimed directly at this process.

Relationship between Nuclear Factor kappa B, Cytokines and Inflammation

Reactive oxygen species may contribute to lung inflammation by modulating the production of inflammatory cytokines. Acute lung inflammation is distinguished by increased numbers of neutrophils within parenchyma. The exact mechanism responsible for the accumulation of neutrophils has not been fully characterized but a pervasive hypothesis is that neutrophils are recruited to the lung in response to chemotactic cytokines. Interleukin 8 (IL-8) belongs to a family of chemokines [13] and has been implemented in the pathogenesis of a wide variety of acute inflammatory conditions including ARDS [14], chronic bronchitis [15], cystic fibrosis [16], septic shock syndrome [17, 18], idiopathic pulmonary fibrosis [19], and empyema [20]. Experimental *in vitro* data, based on molecular techniques, indicate that reactive oxygen species (ROS) are involved in the regulation of the IL-8 gene. For example, exposure to hyperoxia induces IL-8 gene expression by blood monocytes [21] and oxygen scavengers block IL-8 gene expression in *ex vivo* stimulated whole blood [22].

IL-8 is produced by monocytic phagocytes and by a wide variety of nonleukocytic cells, including lymphocytes, fibroblasts, and epithelial and endothelial cells, when stimulated with endotoxin, IL-1, or tumor necrosis factor (TNF). There is little, if any, detectable constitutive production of IL-8 or expression of IL-8 mRNA by unstimulated cells. Within 1 h of stimulation, IL-8 mRNA is expressed, reaches maximal levels by 2–3 h and gradually declines thereafter. This transcriptional activation, at least in part, involves the binding of nuclear regulatory proteins, nuclear factor kappa B (NF-κB) and nuclear factor IL-6 (NF-IL-6), to specific promoter sequences present in the promoter region of the IL-8 gene [23, 24]. Gel mobility shift analysis has indicated that the NF-IL-6-like factor constitutively binds to the region between -94 and -81, whereas an inducible factor binds to the NF-κB binding element in the region between -80 and -71 of the IL-8 gene. The combination of the NF-IL-6 and NF-κB binding elements are both essential and sufficient for IL-8 promoter activity. The nuclear translocation and binding activity of NF-κB appears to be, at least in part, modulated by alteration in the redox state of the cell [25–30]. Agents which result in cellular oxidative stress are potential activators of NF-κB which could result in transcriptional activation of genes, like IL-8, which are dependent on NF-κB regulatory elements. This mechanism may provide a possible link which relates oxidative stress and acute inflammatory lung disease.

NF-κB exists in most cells as a non-DNA binding form in the cytoplasm composed of three subunits: a DNA-binding P-50 protein, a DNA-binding

P-65 protein, and an inhibitory subunit called IκB which is bound to the P-65. IκB inhibits DNA-binding of NF-κB and appears to be responsible for the cytoplasmic localization of the complex. The release of IκB appears to trigger the activation of the NF-κB transcription factor with translocation to the nucleus and binding to the NF-κB sequence in the IL-8 gene or other responsive genes. Several lines of evidence indicate that ROS can influence the binding affinity of NF-κB following stimulation. NF-κB is directly activated by H_2O_2 treatment of cells from an inactive cytoplasmic form to an active nuclear form [25, 26]. N-acetylcysteine (NAC) can block NF-κB induction by H_2O_2. As discussed, NAC is a thiol compound which is a direct ROS scavenger and restores intracellular glutathione levels. Since, NAC blocks NF-κB activation, it is reasoned that ROS mediate the activation of NF-κB. Various other stimuli including endotoxin, TNF, and phorbol 12-myristate 13-acetate (PMA) activate NF-κB and this activation can also be blocked by prior treatment with NAC and other antioxidants including the iron chelators pyrrolidine dithiocarbamate (PDTC) [27, 28]. Further evidence of the involvement of ROS in activation of NF-κB lies in the observation that treatment of cells with TNF and PMA can both deplete intracellular GSH stores and result in release of H_2O_2 and O_2– [26]. These data appear to indicate that many different agents induce the DNA-binding form of the cytoplasmic form of NF-κB by a mechanism which involves ROS.

Clinical Studies of the Antioxidant Approach with N-Acetylcysteine and Oxothiazolidine Carboxylate

As discussed above, GSH (glutamyl-cysteinyl-glycine) is particularly important in host defense against oxidative stress. Animal studies have shown that the lung is a net importer of reduced GSH [31]. Recent data have demonstrated a relative deficiency of pulmonary GSH, as estimated by bronchoalveolar lavage, in patients with ARDS [32]. Cysteine, though not generally considered an essential amino acid and therefore not included in routine parenteral nutrition, has been considered by some to conditionally essential in the critically ill in that its availability is dependent of the efficiency of conversion from other substrates such as methionine. NAC an antioxidant that also is rapidly converted to cysteine has been an attractive candidate for study in sepsis and ARDS. Extensive preclinical testing has continued to provide support for this hypothesis [33, 34].

Given the success in preventing tissue injury with NAC in a wide variety of cell and animal models and, given the relative safety of NAC in humans treated for acetaminophen overdose, a pilot study was performed in patients with established ARDS. The pilot was designed to answer several questions: 1) is circulating red blood cell GSH decreased in patients with established ARDS?; 2) can this very large reservoir for GSH be effectively augmented by NAC?; and 3) if circulating GSH can be augmented, what are the pathophysiological effects and safety of this intervention?

Thirty patients who had an illness known to be associated with ARDS and who met all the following criteria were eligible for randomization (double-blind, placebo-controlled): 1) arterial blood gases revealing a PaO_2 of ≤ 70 mm Hg while they were breathing at least 40% oxygen, or a PaO_2/PAO_2 (ratio of partial pressure of arterial oxygen to partial pressure of alveolar oxygen) of ≤ 0.3 (regardless of level of PEEP); 2) bilateral diffuse infiltrates on chest radiography compatible with pulmonary edema; and 3) a pulmonary artery wedge pressure ≤ 19 mm Hg. N-acetylcysteine (Zambon Laboratories, Cadempino, Switzerland) was delivered as an IV solution with a loading dose of 150 mg/kg delivered over 30 min followed by 16 maintenance doses of 24 mg NAC/kg repeated every 4 h for a total of 17 doses. All patients received the full course of placebo or active drug. Key physiologic variables were similar at entry in the NAC and placebo groups indicating a successful randomization. The mean amount of shunting, PEEP levels, and hemodynamic variables were similar to those previously reported for ARDS patients.

The results of these pilot studies indicate that GSH as measured by red cell GSH is substantially depleted in ARDS, possibly by as much as two-thirds [33]. The rationale for measuring red cell GSH is that the vast majority of circulating GSH is in the red cell, with very little in plasma. Given that serial tissue biopsies of lung or liver are difficult and probably not justifiable at this stage of understanding of GSH metabolism in ARDS, the only substantial tissue readily available for assay is the red cell. The loading dose of NAC was clearly effective in increasing plasma cysteine levels to roughly 10 fold over entry. Levels declined during the maintenance doses to only 2 fold over entry. There was no similar change in plasma cysteine from baseline noted over the 5 day treatment period in the placebo group. Erythrocyte GSH levels increased by over 50% from entry placing these levels near normal, but this did not occur until 72 h into the treatment period.

Physiologic effects were measured including PaO_2/PAO_2 ratio which improved rapidly in both treatment groups presumably due to use of mechanical ventilation, CPAP and other clinical support measures, but there was no significant difference in the rate of improvement between groups. Chest radiographs scored for presence of pulmonary edema (0 = normal, 1 = mild, 2 = moderate, 3 = severe) using the scoring method described in previous Vanderbilt studies revealed that our patients had moderate to severe pulmonary edema at entry. By 120 h post-study entry, there was a clear improvement in the NAC treated patients both as compared to entry levels and as compared to placebo controls with further improvement over placebo patients by 120 h.

Cardiac output tended to improve rapidly after the loading dose of NAC in the treated group by approximately 30% and the placebo group was unchanged but this difference did reach statistical significance. This increase in cardiac output translated into an increase in both oxygen delivery and oxygen consumption of similar magnitude in the NAC treated patients but not

in the control group. There are now data from others suggesting a mechanism for this observation. Studies of cardiac function in models of ischemia/reperfusion indicate that oxidant injury is part of the reperfusion response which can be partially prevented or reversed by antioxidants [35].

Recently, additional pilot studies in patients with established ARDS have been conducted. Forty-six patients were randomized (double-blind, placebo-controlled) to receive either NAC (Fluimucil™, The Zambon Corporation, Cadempino, Switzerland) or oxothiazolidine carboxylate (OTC, Procysteine™, Free Radical Sciences, Cambridge, MA). The dosing regimen called for 70 mg/kg/day of NAC, 63 mg/kg/day OTC or an equal volume of placebo. The dosages for OTC and NAC are molar equivalents of each other, i.e. they provide for the same delivery of cysteine on a molar basis. Treatment was extended to 10 days total and the dosing regimen in this protocol did not provide for a loading dose. The study drugs were well tolerated and there were no adverse effects attributed to either agents. The preliminary analysis of this study confirms the presence and degree of cysteine and red cell GSH depletion in patients with ARDS. Of note is that although red cell GSH rose substantially with either treatment, some patients were still partially depleted at the end of the treatment period on day 10. This would suggest that dosing was either not maximized, that the machinery for production of red cell GSH was impaired, or that it takes more than 10 days of therapy to fully replete patients. Follow-up studies will be needed to address these issues. A large variety of physiologic responses were monitored during the total of 30 days from study entry. Favorable trends in reversal of PaO_2/FiO_2 criteria for ARDS, bilirubin levels, total white cell counts, and cardiac index were observed.

Two additional clinical studies of NAC have recently been reported. Suter el al. [36] reported a group of 61 patients with mild to moderate ALI randomized to receive NAC, 40 mg/kg/day, or placebo. The 1-month mortality was 22% in the NAC group versus 35% in the placebo group, $p = NS$. The percentage of patients requiring mechanical ventilation in the NAC group fell from 69 to 17% in three days versus a fall from 76 to 48% in the placebo group, $p = 0.01$.

Jepsen et al. [37] studied a group of 66 ICU patients with ARDS randomizing to either NAC (150 mg/kg/load and 20 mg/kg/h for six days) or placebo. No differences were detected in PaO_2/FiO_2, chest radiograph, compliance or mortality over the 7 day study period. NAC did appear to impact the coagulation system as measured by serial platelet counts, fibrinogen and antithrombin III.

Clinical Studies of Cyclooxygenase Inhibition with Ibuprofen

Animals studies conducted over the past 25 years have supported the potential of cyclooxygenase inhibitors in the treatment of sepsis syndrome. In later years, the role of thromboxane and prostacyclin production has been eluci-

dated in the acute alterations in pulmonary function seen following endotoxemia [38]. Snapper and colleagues [39], working with the chronically instrumented sheep model, demonstrated that pretreatment with the cyclooxygenase inhibitor meclofenamate blocked the early pulmonary hypertension and fall in dynamic compliance and lung volume seen after endotoxin infusion. Treatment with ibuprofen, even after established endotoxin-induced lung dysfunction in sheep, results in improved lung mechanics and pulmonary hemodynamics [40], suggesting that prostanoid production is persistent and continues to alter lung function.

Based on these and other data, a double-blind, randomized, placebo-controlled pilot study of the effect of ibuprofen (800 mg per rectum every 4 h for 12 h) in 30 patients with sepsis syndrome was undertaken [36]. Patients with

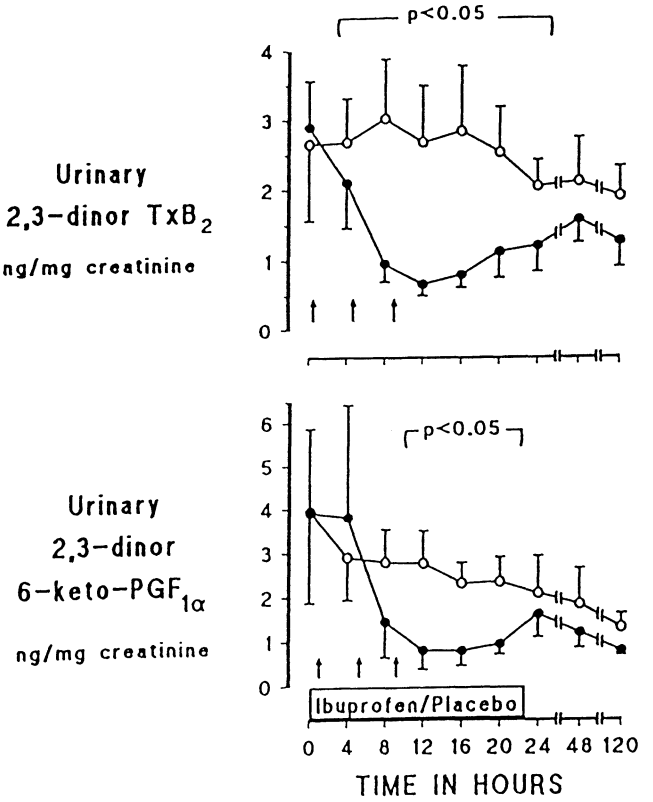

Fig. 2. Urinary concentrations of systemic eicosanoids in patients with sepsis syndrome. Urinary concentrations of 2,3-dinor-thromboxane-B_2 and 2,3-dinor-6-keto-$PGE_{1\alpha}$ normalized to urinary creatinine concentration. The arrows indicate the timing of the three doses of ibuprofen (800 mg) or placebo; p values refer to comparisons of ibuprofen group with placebo group for time-matched treatment periods. Open circles = placebo (n=8); closed circles = ibuprofen (n=9). (From [38] with permission)

abnormal vital signs including fever with at least one organ system failure secondary to sepsis were enrolled. Ibuprofen-treated patients experienced a significant decrease in heart rate, body temperature, peak airway pressure and minute ventilation. The ibuprofen-treated group experienced a significant decrease in urinary 2,3-dinor-6-keto-$PGF_{1\alpha}$ and 2,3-dinor-thromboxane B_2, whereas levels in the placebo-treated patients remained high for at least 120 h (Fig. 1). There was a positive correlation between the thromboxane metabolite and peak airway and pulmonary artery pressures, and an inverse correlation between the prostacyclin metabolite and mean systemic blood pressure. There also appeared to be a trend toward an increase in blood pressure especially for those patients in shock at study entry (Fig. 2) and more rapid resolution of pulmonary changes in ARDS blood gas criteria (Fig. 3). The findings in this study were consistent with the hypothesis that both constrictor and dilator prostaglandins contribute to the pathophysiology in septic patients.

The success of this pilot study using a limited course of ibuprofen in sepsis syndrome has led to the constitution of a multicenter working group supported by the Lung Division of the National Institutes of Health, National Heart Lung and Blood Institute. Seven clinical centers in North America are coordinating their efforts to determine if IV ibuprofen, 10 mg/kg (maximum 800 mg)/6 h for 8 doses, delivered early in the course of sepsis syndrome has an impact on the mortality and organ failure of this major clinical process (Fig. 4 and Table 1).

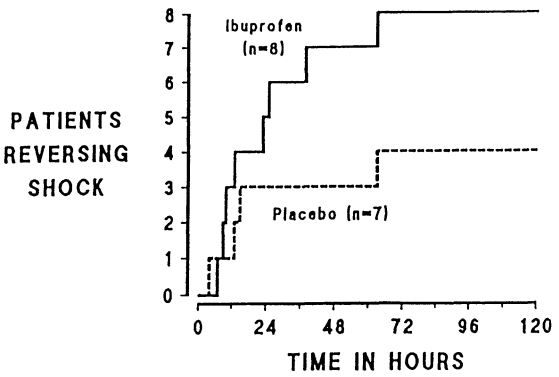

Fig. 3. Reversal trend in shock. The shock reversal trends in ibuprofen-treated patients (n=8) versus placebo-treated patients (n=7) who had septic shock diagnosed within 24 h of study entry are shown. Shock was present if systolic blood pressure was persistently less than 90 mm Hg after at least 500 mL volume resuscitation. Reversal was defined to have occurred when the systolic blood pressure was above 90 mm Hg in the absence of pressor therapy. The differences were not statistically significant (p=0.12). (From [38] with permission)

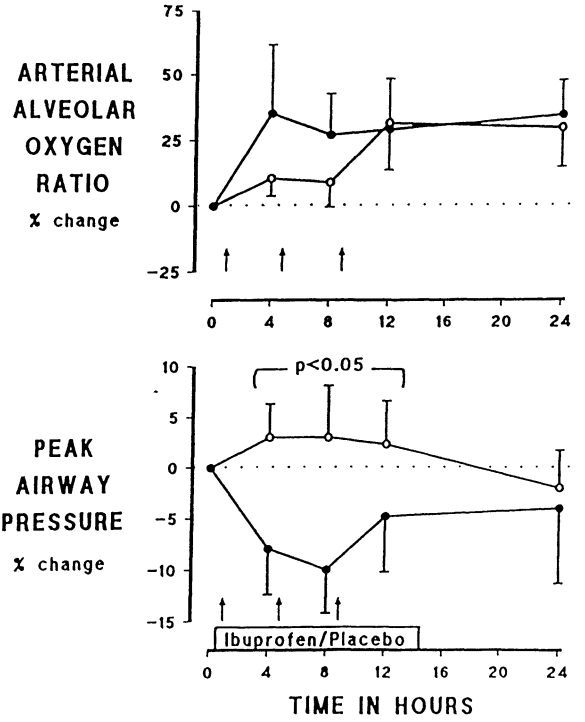

Fig. 4. Effect of cyclooxygenase inhibition on oxygenation and airway pressure. Effect of ibuprofen on arterial to alveolar PO_2 ratio (PaO_2/PAO_2) and peak airway pressure (for those patients requiring mechanical ventilation; PEEP has been subtracted) expressed as percent change from study entry. The arrows indicate the timing of the three doses of ibuprofen (800 mg) or placebo; p values refer to comparisons of ibuprofen group with placebo group for time-matched treatment periods. (Top) open circles = placebo (n=14); closed circles = ibuprofen (n=16). (Bottom) open circles = placebo (n=10); closed circles = ibuprofen (n=12)

Conclusion

Sepsis and ARDS, with their attendant high morbidity and mortality, remain difficult management problems and continue to constitute a major drain on health care resources. There is now a firm foundation to the understanding of the systemic inflammatory response which has markedly improved the climate for the conduct of clinical studies. The ability to accurately measure mediators or their metabolites and to block these mediators in a somewhat selective fashion (e.g. ibuprofen vs methylprednisolone) has also improved the outlook for progress in this area. Specifically, a large body of data derived from animal models suggest that therapies aimed at preventing unrestrained production of arachidonic acid metabolites and augmenting host antioxidant defenses are rational approaches for clinical trials in patients

Table 1. Entry data for patients entered into the study of ibuprofen in sepsis syndrome[a]. (From [38] with permission)

	Placebo (n=14)	Ibuprofen (n=16)
Age, yr	54.3±3.9	53.8±3.6
Vital signs		
Temperature, °F	100.5±0.5	100.5±0.5
Heart rate, beats/min	108±6	112±5
Respiratory measurements		
Respiratory rate, breaths/min	21±3	17±2
PaO_2/PAO_2	0.36±0.05	0.35±0.03
Mechanical ventilation, n (%)	11 (79)	13 (81)
FiO_2	0.60±0.07	0.60±0.05
Minute ventilation, L/min	13.4±1.6	13.9±1.1
Total thoracic compliance, mL/cm H_2O	52±7	47±7
Pulmonary edema score[b]	0.9±0.3	1.4±0.3
Cardiovascular function		
Patients with pulmonary artery catheter, n (%)	7 (50)	9 (56)
Cardiac output, L/min	6.49±0.67	6.13±0.89
Paw, mm Hg	18±2	12±2[c]
Systemic blood pressure, mm Hg	86±4	87±4
Ppa, mm Hg	30±2	26±4
SVR, dyne·cm·s^{-5}	909±152	1084±195
PVR, dyne·cm·s^{-5}	152±27	245±107
Renal and hepatic function		
Serum creatinine, mg/dL	1.2±0.1	1.6±0.3
Patients with creatinine >4, n (%)	0 (0)	1 (6)
Creatinine clearance, mL/min	72±14	62±15
Bilirubin, mg/dL	2.8±0.8	2.0±0.6
Patients with bilirubin >4, n (%)	4 (29)	2 (13)
SGPT, IU/L	41±17	46±7
Other data		
WBC, thousands/mm^3	15±2	15±2
Platelet count, thousands/mm^3	219±47	301±55
Positive cultures, n (%)	12/14 (86)	14/16 (88)
Gramnegative, n	9	9
Positive blood cultures, n (%)	7/14 (50)	4/16 (25)
Gram-negative	3	1
Sepsis onset to treatment, h	7.2±0.7	7.6±0.6

[a] Data are shown as mean±SEM.
[b] 0=normal; 1=mild; 2=moderate; 3=severe.
[c] Indicates $p<0.05$ ibuprofen group versus placebo.

with either sepsis or ALI. Large scale clinical trials in these areas are ongoing and, if these interventions prove effective, patients with sepsis and ALI will have a better prognosis and Science will have gotten one step closer toward a better understanding of the basic biologic processes underlying these closely related syndromes.

Specific Conclusions

1. Though there is Level II data available for the use of antioxidants, specifically N-acetylcysteine, in acute lung injury, the studies have demonstrated conflicting results with one study showing benefit and a second study unable to demonstrate benefit. Routine therapy with N-acetylcysteine cannot be recommended at this time and remains experimental (Fig. 5).
2. Level II data exist supporting the use of ibuprofen in sepsis syndrome. The study was a pilot study and the number of patients too small to permit a recommendation regarding routine clinical use. This therapy should be considered experimental.

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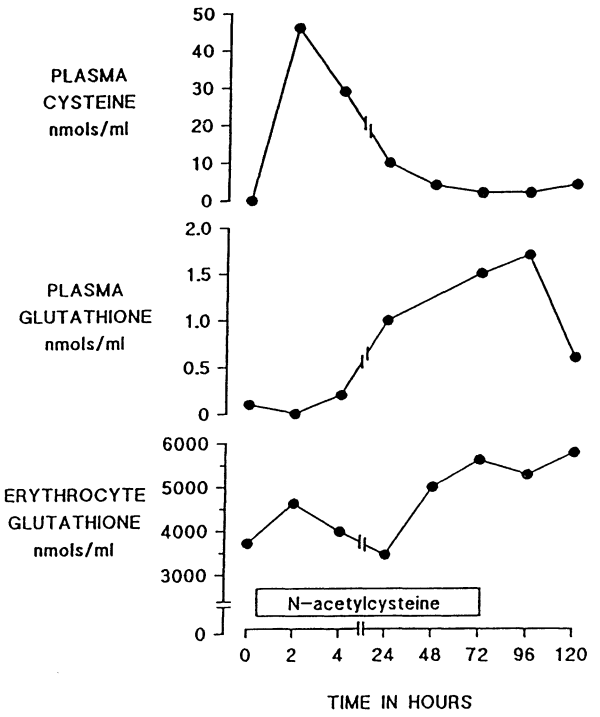

Fig. 5. Effect of N-acetylcysteine in a patient with ARDS. Therapy consisted of an IV loading dose of 150 mg/kg followed by 24 mg/kg every 4 h for 72 h. The loading dose had a profound and immediate effect on plasma cysteine while the plasma and red cell glutathione levels did not increase until approximately 24 h of therapy. (From [33] with permission)

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