Review

Year in review 2008: *Critical Care* - sepsis

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Abstract

The present report highlights the most important papers appearing in *Critical Care* and other major journals about severe sepsis, the systemic inflammatory response and multiorgan dysfunction over the past year. A number of these clinical and laboratory studies will have a considerable impact on the sepsis research agenda for years to come. The steroid controversy, the debate over tight glycemic control, the colloid versus crystalloid issue, the value of selective decontamination of the digestive tract, the enlarging role of biomarkers, the value of genomics and rapid diagnostic techniques have all been prominently featured in recent publications. Basic research into novel predictive assays, genetic polymorphisms, and new molecular methods to risk-stratify and to determine treatment options for sepsis have occupied much of the *Critical Care* publications relating to sepsis pathophysiology in 2008. We will attempt to briefly summarize what we consider to be the most significant contributions to the sepsis literature over the last year, and their likely ramifications in the future, for critical care clinicians, clinical investigators and basic researchers alike.

Introduction

2008 was a significant year in *Critical Care*, with a number of landmark papers being published in sepsis research in this journal and in other publications. These studies cross the spectrum from some highly promising results to some very disappointing clinical and laboratory findings reported in the literature over the past year. The year started off on a positive note with the publication of the much anticipated and frequently quoted 2008 sepsis management guidelines from the Surviving Sepsis Campaign [1]. Encouraging evidence that the adoption of the Surviving Sepsis Campaign Guidelines can achieve measurable improvements in patient outcome has already appeared [2,3]. Despite the intrinsic heterogeneity that typifies sepsis [4], standardized treatment regimens can improve outcome. Improvements in the process of care (for example, immediate resuscitation with intravenous fluids with preset physiologic goals, urgent administration of antimicrobial therapy, rapid identification and source control), and a variety of other evidence-based supportive measures, can improve survival in critically ill septic patients [1].

Two highly disappointing results were reported from large, randomized, clinical trials in 2008. The first major disappointment was the Corticus trial [5], which was expected to be a confirmatory trial from the Annane low-dose steroid study [6]. Treatment with relatively low doses of hydrocortisone (50 mg intravenously every 6 hours) followed by a tapering dose was compared with a placebo group in a multicenter randomized trial. The Corticus trial showed no overall survival benefit from the use of this seemingly logical, inexpensive treatment strategy for the relative adrenal insufficiency often accompanying septic shock. The study did find a significantly more rapid reversal in the duration of septic shock in the low-dose steroid group. This potential benefit of steroid-related shock reversal was accompanied by an increased incidence of secondary infections and secondary septic shock compared with the placebo group. The adrenocorticotrophic hormone stimulation test was used to differentiate responders from nonresponders with relative adrenal insufficiency. This finding did not distinguish patients more likely to respond to corticosteroids [5].

The German Sepsis Society clinical research group published two simultaneous clinical trials in which tight glycemic control was compared with standard glucose control, and pentastarch colloid solution was compared with crystalloid therapy for fluid resuscitation in severely septic patients (the VISEP trial) [7]. Again, the results were highly disappointing with no improvement in overall outcome of tight glycemic control with excess incidence of hypoglycemic events. These

BAL = bronchoalveolar lavage; HMGB-1 = high mobility group box 1; HMW HA = high molecular weight hyaluronan; ICU = intensive care unit; IL = interleukin; LMW HA = low molecular weight hyaluronan; NF = nuclear factor; sTREM-1 = soluble triggering receptor on myeloid cells 1; TNF = tumor necrosis factor.

negative results were recently confirmed by a large prospective clinical trial of tight glycemic control versus conventional glycemic control from Australia, New Zealand and Canada (the NICE-SUGAR Study) [8]. This study, which included over 6,000 patients, actually revealed a significantly worse outcome for those patients randomized to tight glycemic control over conventional glucose management. Tight glycemic control carries a real risk of hypoglycemic episodes and is of uncertain efficacy in a general intensive care unit (ICU) population. Likewise, the colloid treatment strategy with pentastarch in the VISEP trial demonstrated a dose-dependent worsening in renal function compared with standard crystalloid resuscitation fluids, and its use should be discouraged in the future. Whether these findings can be extended to other colloids such as gelatin and albumin remains to be demonstrated. The results are not likely to end the continuing controversy regarding colloids versus crystalloids in sepsis therapy.

The year ended with an important publication addressing a decade-long argument about the value of selective decontamination of the digestive tract versus standard care in a general ICU population. deSmet and colleagues reported a modest survival advantage in the selective decontamination of the digestive tract population (including a systemic chemoprophylaxis group and an oral chemoprophylaxis only group) versus conventional therapy in a 5,939-patient trial [9]. The 28-day mortality rate was 27.5% for the control group, 26.9% for the oral selective decontamination of the digestive tract group, and 26.6% for the systemic selective decontamination of the digestive tract group ($P < 0.05$). The oral therapy might be easier to bring into standard ICU care as this strategy could limit the concerns about selecting for multidrug-resistant bacteria and even *Clostridium difficile* infection with widespread adoption of systemic chemoprophylaxis as a general strategy in ICU patients.

Major research findings in sepsis and systemic inflammatory states reported in *Critical Care* during 2008

Many important sepsis research papers appeared in *Critical Care* during the past year. Many of these studies are association studies where various novel biomarkers, enzymes and mediators were compared with the development of severe sepsis, organ dysfunction and adverse clinical outcomes [10-19]. These new research findings are summarized in Table 1. Some of the more notable findings from basic science to clinical research studies are highlighted in the following paragraphs.

Biomarkers for the diagnosis and risk stratification of multiorgan failure and sepsis

Soluble triggering receptor on myeloid cells 1

Soluble triggering receptor on myeloid cells 1 (sTREM-1) is a member of the immunoglobulin superfamily that is up-regulated on the surface of neutrophils, monocytes and macrophages in the presence of extracellular bacteria and fungi. Early studies by Gibot and colleagues demonstrated a diagnostic sensitivity of 98% and a specificity of 90% for detecting pneumonia by the measurement of sTREM-1 from mini-bronchoalveolar lavage (mini-BAL) fluids [20].

Huh and colleagues examined the diagnostic role of sTREM-1 in BAL fluid in 80 patients with bilateral lung infiltrates [10]. The authors compared BAL sTREM-1 with the clinical pneumonia infection severity score and the BAL neutrophil percentage in three patient groups: extracellular bacterial and fungal infection; pneumonia due to atypical intracellular bacteria, mycobacteria or viruses; and noninfectious illnesses. The levels of sTREM-1 were statistically significantly greater in the extracellular bacteria and fungal group (521.2 ± 94.7 pg/ml) compared with the viral/mycobacterial/atypical pathogen group (92.9 ± 20 pg/ml) and the non-infected group (92.8 ± 10.7 pg/ml). At a cutoff level of 184 pg/ml, sTREM-1 had a sensitivity of 86% and 90% specificity. While a clinical pneumonia infection severity score of 6 or greater and a BAL neutrophil percentage of 60% were statistically greater in the infected groups versus the non-infected group, sTREM-1 had the highest area under the receiver operating characteristic curve at 0.91 and was the only remaining variable statistically significant on multiple logistic regression analysis [10].

The findings in Huh and colleagues' study are in agreement with those of Richeldi and colleagues, where sTREM-1 differentiated community-acquired pneumonia from tuberculosis and interstitial lung disease [21]. Individual studies by Horonenko and colleagues and by Anand and colleagues did not show the same diagnostic accuracy with sTREM-1 as the Huh and colleagues study [22,23] – both of these studies demonstrated false positive s-TREM levels in the setting of pulmonary hemorrhage. The allowance of patients with prior antibiotic administration in Anand and colleagues' study may have contributed to the discordant results. Future studies of sTREM-1 will need to be performed with a standardized assay and procedure for the BAL collection, and must examine the effect of antibiotic therapy on sTREM-1 levels.

Eosinopenia

A surprising simple measure to differentiate infection from noninfectious inflammation by eosinophil counts has resurfaced recently [11]. This is not a new idea but is appealing in its simplicity and availability [24]. The mechanism underlying eosinopenia is thought to be chemotactic factors, which draw the eosinophils to the site of infection [25].

Abidi and colleagues examined the value of eosinopenia in differentiating sepsis from noninfectious systemic inflammatory response syndrome in 198 medical ICU patients [11]. Patients without infection had a median eosinophil count of 109 cells/mm^3 (interquartile range = 102 to 121), compared with 13 cells/mm^3 (interquartile range = 8 to 28) in those with

Table 1

Selected biomarker studies and disease association studies in *Critical Care* (2008)

Molecule	Reference	Number studied	Patient type or animal model	Main findings
sTREM	Huh and colleagues [10]	80	VAP patients	sTREM in BAL fluid was highest in bacterial infection patients, high in viral/mycobacterial pneumonia patients and low in noninfected patients
Eosinopenia	Abidi and colleagues [11]	198	Sepsis patients	Low eosinophil levels discriminate infection from noninfectious inflammation and are comparable with PCT and CRP as predictors
Gelsolin	Wang and colleagues [12]	91	Surgical patients	Gelsolin is an actin scavenger, and reduced levels of gelsolin are associated with worsening sepsis
Kerbs von Lungren 6	Nathani and colleagues [13]	42	ARDS and at-risk patients	Kerbs von Lungren 6 is an alveolar type 2 cell marker associated with increased risk of ARDS
Copeptin	Seligman and colleagues [14]	71	VAP patients	Copeptin is a derivative of preproAVP and a strong predictor of mortality in VAP
Protein disulfide isomerase	Zhou and colleagues [15]	30	CLP or LPS-treated rats	PDI suppresses TNF gene expression in septic states; reduced PDI upregulates TNF
Bim and *Bid* gene expression	Weber and colleagues [16]	37	Septic patients	*Bim* and *Bid* proapoptotic genes are strongly upregulated in sepsis and lymphocyte depletion
Endothelin-1	Trachsel and colleagues [17]	28	LPS-treated pigs	Endothelin-1 levels correlate with pulmonary hypertension and responsiveness to inhaled nitric oxide
Reactive oxygen species	Martins and colleagues [18]	41	Septic patients	ROS are upregulated in myeloid cells and are correlated with adverse outcome
Akt and ERK1/2	Li and colleagues [19]	77	C57/BL6 mice	Akt and ERK1/2 mediate in part pulmonary injury/fibrosis from high tidal volume ventilation

Akt, serine/threonine kinase B; ARDS, acute respiratory distress syndrome; AVP, arginine vasopressin; BAL, bronchoalveolar lavage; CLP, cecal ligation and puncture; CRP, C-reactive protein; ERK1/2, extracellular signal regulated kinase 1/2b; LPS, lipopolysaccharide; PCT, procalcitonin; PDI, protein disulfide isomerase; ROS, reactive oxygen species; sTREM, soluble triggering receptor expressed on myeloid cells; VAP, ventilator-associated pneumonia.

infection ($P<0.001$). An eosinophil cutoff value <50 cells/mm^3 provided a sensitivity of 80%, a specificity of 91%, a likelihood ratio of 9.12, and an area under the receiver operating characteristic curve of 0.89. This was superior to C-reactive protein at a cutoff value of 70. By way of comparison, a meta-analysis by Tang and colleagues of the ability of procalcitonin to diagnose sepsis in critically ill patients with systemic inflammatory response syndrome revealed an area under the receiver operating characteristic curve of 0.78 [26]. Procalcitonin is the currently favored assay for distinguishing severe infection from systemic inflammation without infection, but it has its limitations [27]. The total eosinophil count as a biomarker in the diagnosis of sepsis needs to be studied in a large, multicenter study.

Gelsolin

Gelsolin is a cytoplasmic and plasma protein that works as an actin scavenger. Actin is released during tissue injury and has been noted to be toxic [28]. Additionally, gelsolin has been shown to inhibit inflammatory mediators released during sepsis including endotoxin, lysophosphatidic acid, and platelet activating factor [29]. Plasma gelsolin deficiencies have been described in patients with a variety of severe inflammatory states [30], and animal models of sepsis reveal a survival advantage with gelsolin replacement therapy [31].

Wang and colleagues investigated the time course of plasma gelsolin concentrations in 91 critically ill surgical patients [12]. Patients with severe sepsis had significantly lower gelsolin levels (20.6 ± 11.7 mg/l) than nonseptic critically ill patients (52.3 ± 20.3 mg/l) and healthy control individuals (126.8 ± 32.2 mg/l). Plasma gelsolin levels were inversely correlated with disease severity, with the lowest levels (17.1 ± 9.1 mg/l) occurring in patients with Acute Physiology and Chronic Health Evaluation II scores >25. Baseline gelsolin levels did not distinguish between survivors and nonsurvivors from sepsis. These results are comparable with a recent study by Lee and colleagues that gelsolin deficiency is a marker of disease severity, but did not confirm its prognostic ability [32]. The optimal assay for measuring gelsolin and the cutoff value needs further evaluation.

Angiopoietin 1 and angiopoietin 2

Biomarkers of endothelial cell integrity are being studied as prognostic markers in sepsis and multiorgan failure. Inflam-

matory mediators released during the sepsis response can disrupt endothelial cell integrity and cause microcirculatory dysfunction that manifests itself as shock and acute respiratory distress syndrome. Angiopoietin 1 and angiopoietin 2 are ligands for the endothelial Tie-2 receptor that protect and disrupt the endothelial barrier, respectively [33].

Kumpers and colleagues examined angiopoietin 1 and angiopoietin 2 as predictors of mortality and for correlation with disease severity and organ injury [34]. They studied 43 medical ICU patients with septic shock, severe sepsis, or nonseptic critical illness and 29 healthy control individuals. Both angiopoietin 1 and angiopoietin 2 levels were statistically significantly higher in the critically ill population than in controls, but only angiopoietin 2 was statistically significantly higher in sepsis patients compared with the nonseptic critically ill population. Angiopoietin 2 levels strongly correlated with traditional markers of disease severity including Acute Physiology and Chronic Health Evaluation II score, Sequential Organ Failure Assessment score and lactate levels. In a multivariate analysis, angiopoietin 2 was the only independent predictor of death.

The accumulating literature on angiopoietin 2 suggests that it may not only be a marker of disease severity in acute respiratory distress syndrome but it may also be a therapeutic target. Parikh and colleagues demonstrated an inverse correlation between angiopoietin 2 levels and oxygenation. Angiopoietin 2 applied to endothelial cell monolayers increased membrane permeability [35]. A mouse model of endotoxic shock showed a survival advantage with administration of angiopoietin 1 [36]. We look forward to further investigation of the Tie-2 receptor in acute respiratory distress syndrome.

Potential new therapies

High molecular weight hyaluronan

High molecular weight hyaluronan (HMW HA) is an important component of the lung interstitium that helps to maintain the structural integrity and compliance of the lung. Low molecular weight hyaluronan (LMW HA) can be produced by degradation of HMW HA or by *de novo* synthesis. LMW HA but not HMW HA is capable of eliciting an inflammatory response. A transgenic mouse that overproduces HMW HA through the hyaluronan synthase enzyme is protective in a bleomycin model of acute lung injury [37].

The hypothesis that HMW HA could be a lung-protective molecule was tested by Liu and colleagues in a sepsis-induced lung injury model [38]. Rats were divided into four groups: nonventilated rats; ventilated rats with lipopolysaccharide challenge; ventilated rats with lipopolysaccharide challenge and pretreatment 18 hours prior to or treatment 1 hour after with HMW HA (1,600 kDa); and ventilated rats with lipopolysaccharide challenge with LMW HA (35 kDa) 18 hours before challenge. Either LMW HA or HMW HA was able to decrease neutrophil accumulation in the lung and to decrease the concentration of TNF and macrophage-inflammatory protein 2 caused by lipopolysaccharide. Only HMW HA pretreatment and post-treatment could block the monocyte accumulation and decrease lung injury. While the mechanism of protection is not clearly known, further studies are warranted to determine the dose and size of HMW HA to limit acute lung injury/acute respiratory distress syndrome.

Danaparoid

Anticoagulant molecules have recently been of great interest as potential therapies for severe sepsis and septic shock. Danaparoid is a low molecular weight heparanoid composed of 83% heparan sulfate and 12% dermatan sulfate that blocks the coagulation cascade by binding to antithrombin and inhibiting factor Xa. Inhibiting factor Xa also limits the production of proinflammatory cytokines as NF-κB is inactivated [39]. Furthermore, heparan sulfates have been shown to have numerous anti-inflammatory properties through interactions with syndecan expressed on white blood cells [40].

Iba and Miyasho investigated the effect of danaparoid in an intravenous lipopolysaccharide challenge model in rats [41]. The rats were divided into two groups and received either danaparoid 400 U/kg or saline immediately after an intravenous lipopolysaccharide challenge. Blood samples were taken at different time points for makers of organ injury, coagulation markers and cytokines. Compared with saline-treated rats, the rats receiving danaparoid presented less evidence of organ injury, marginally better maintenance of antithrombin and platelet levels, and significant suppression of proinflammatory cytokine production [41]. The results of this study were in keeping with those published by Hagiwara and colleagues, where danaparoid improved survival in an endotoxin-induced lung injury model and was associated with decreased production of high mobility group box 1 (HMGB-1) and proinflammatory cytokines [42]. It remains to be seen whether danaparoid will be taken forward in clinical trials of sepsis given the recent negative results of heparin in a severe sepsis trial [43].

Immunoparalysis

While a majority of papers in the sepsis literature focus on an exuberant proinflammatory and procoagulant response to critical illness, it is clear that a state of immune suppression or immunoparalysis also occurs in this setting. Lymphocyte death by programmed cell death or apoptosis occurs in critical illness patients via two pathways. The extrinsic pathway is triggered by TNFα and Fas ligand – which bind to death domains and ultimately activate caspase 8 and caspase 3, leading to DNA fragmentation and cell death. The intrinsic mitochondrial pathway is triggered by loss of growth factors IL-2, IL-4 or granulocyte–macrophage colony-simulating factor or by the addition of IL-6, IL-1, reactive oxygen intermediates or nitric oxide. These signals can either activate the proapoptotic BCL-2 family members Bax and t-Bid or the anti-apoptotic BCL-2 and MCI-1 proteins [44].

Hostmann and colleagues performed an in-depth assessment of the apoptotic kinetics in an animal model of hemorrhagic shock. Mice who underwent bleeding to a mean arterial pressure of 35 mmHg for 1 hour from the femoral artery followed by fluid resuscitation were compared with sham operated mice and control mice at 0 hours, 24 hours and 72 hours for lymphocyte counts, splenic lymphocyte apoptosis, caspase activity, and proapoptotic and antiapoptotic protein levels. The authors found that lymphopenia occurs very early in the mice undergoing hemorrhagic shock and that it persists throughout the 72-hour observation period. Furthermore, splenic apoptosis in hemorrhagic shock occurs at 0 hours and 72 hours, and is associated with increased activity of caspase 3/7, caspase 8 and caspase 9, and with increased mitochondrial proapoptotic BAX levels and low antiapoptotic Bcl-2 proteins. Interestingly, the antiapoptotic protein MCl-1 is elevated at the 24 hours time point. These data suggest a biphasic response to traumatic hemorrhage where there is an attempt to counter-regulate proapoptotic forces by antiapoptotic proteins that ultimately fails [45]. These findings support the notion that attempts to intervene in trauma and sepsis by regulating the proapoptotic/antiapoptotic balance might be a useful therapeutic strategy.

High mobility group box-1 polymorphisms and sepsis

HMGB-1 is a fascinating and markedly complex nuclear and cytoplasmic protein that is readily measurable in the systemic circulation in response to severe injury. The protein has the propensity to bind to a variety of inflammatory mediators such as lipopolysaccharide and proinflammatory cytokines, including IL-1 [46]. HMGB-1 functions as an alarmin or damage-associated molecular pattern molecule, and acts as an endogenous ligand for pattern recognition receptors of the innate immune system.

In an important study on the outcome effects of polymorphisms of the *HMGB-1* gene locus on human chromosome 13, Kornblit and colleagues reported the first evidence of the *HMGB-1* genotype's impact on the risk of systemic inflammatory response and sepsis [47]. These investigators performed a long-term, 4-year study comparing *HMGB-1* sequencing data in 239 ICU patients with HMGB-1 blood levels and clinical outcomes. The authors report significant disease associations with two of the eight major polymorphisms they discovered in the *HMGB-1* gene complex. A promoter variant (–1377delA) was associated with a markedly reduced long-term survival rate after ICU admission in systemic inflammatory response syndrome patients (15% vs. 44% without this promoter variant; $P<0.01$). Kornblit and colleagues also observed a significant interaction with a polymorphism within the coding region of the *HMGB-1* gene at position 982 (C>T) in exon 4. Carriers of the polymorphism had an increased frequency of early death from infection along with higher Simplified Acute Physiology Score II compared with wild-type genotypes. Interestingly, this 982C>T variant was accompanied by significantly lower HMGB-1 blood levels ($P<0.01$).

Gene association studies need to be interpreted with caution, and causality will remain elusive until larger datasets are available in diverse patient populations of differing genetic backgrounds. Linkage disequilibrium with other relevant gene loci and attention to the Hardy–Weinberg equilibrium needs to be carefully considered in small gene association studies. Gene association reports in the ICU literature are improving with respect to statistical methods and analytic detail but have further room for improvement [48].

Conclusions

The pace of discovery in critical care research and allied fields of inflammation research and infectious disease is truly remarkable. *Critical Care* is helping the clinical investigator, basic scientist, and clinician alike by reporting an array of scientific papers in sepsis research. This trend is continuing in 2009 and we are confident that exciting discoveries will continue in this fast-paced area of critical care research.

Competing interests

The authors declare that they have no competing interests.

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