

## Diagnosis and treatment of acute pulmonary inflammation in critically ill patients: The role of inflammatory biomarkers

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### Abstract

Pneumonia and acute respiratory distress syndrome are common and important causes of respiratory failure in the intensive care unit with a significant impact on morbidity, mortality and health care utilization despite early antimicrobial therapy and lung protective mechanical ventilation. Both clinical entities are characterized by acute pulmonary inflammation in response to direct or indirect lung injury. Adjunct anti-inflammatory treatment with corticosteroids is increasingly used, although the evidence for benefit is limited. The treatment decisions are based on radiographic, clinical and physiological variables without regards to inflammatory state. Current evidence suggests a role of biomarkers for the assessment of severity, and distinguishing sub-phenotypes (hyper-inflammatory versus hypo-inflammatory) with important prognostic and therapeutic implications. Although many inflammatory biomarkers have been studied the most common and of interest are C-reactive protein, procalcitonin, and pro-inflammatory cytokines including interleukin 6. While extensively studied as prognostic tools (prognostic enrichment), limited data are available for the role of biomarkers in determining appropriate initiation, timing and dosing of adjunct anti-inflammatory treatment (predictive enrichment)

**Key words:** Acute pulmonary inflammation; Inflammatory biomarkers; Acute respiratory distress syndrome; Pneumonia; Critical illness; Diagnosis; Treatment

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**Core tip:** Community acquired pneumonia and acute respiratory distress syndrome are common and important causes of respiratory failure in the intensive care unit. Both clinical entities are characterized by acute pulmonary inflammation in response to direct or indirect lung injury and current evidence suggests a role of biomarkers for the assessment of severity, and distinguishing sub-phenotypes (hyper-inflammatory versus hypo-inflammatory) with important prognostic and therapeutic implications.

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## INTRODUCTION

Inflammation is a natural body response to infectious and non-infectious insults resulting in a complex variety of mechanisms that eventually lead to tissue repair. Inflammatory response in the lungs is most commonly due to infections, and exposure to toxins, allergens and irritants. Normal inflammation is intended to be protective but when excessive and/or prolonged can have deleterious effects associated with worse outcomes<sup>[1]</sup>. The most common acute pulmonary inflammatory conditions in the intensive care unit (ICU) are pneumonia, community or health care acquired, and acute respiratory distress syndrome (ARDS), a complication of other acute illnesses.

Community acquired pneumonia (CAP) is a leading infectious cause of hospitalizations worldwide accounting for over 1 million inpatient hospitalizations annually in the United States<sup>[2,3]</sup>. Limited data suggests about 20% of adults hospitalized for pneumonia required an ICU admission which was directly associated with a 50% increase in length of hospital stay<sup>[4]</sup>. Although less common than pneumonia, ARDS accounts for approximately 10.4% of ICU admissions worldwide with an associated 40% mortality rate depending on severity<sup>[5]</sup>. It usually occurs as a sequela of other acute illnesses including pneumonia and non-pulmonary sepsis. Other risk factors are aspiration pneumonia, trauma and transfusion of blood products.

Together, both conditions have a significant impact on morbidity and mortality in the ICU with an associated increase in overall health care utilization despite early antimicrobial therapy and lung protective mechanical ventilation<sup>[5,6]</sup>. Acute and sometimes exaggerated inflammatory response is a common and important feature in both clinical entities with important prognostic implications and reflective of an ineffective regulatory mechanism to limit inflammation-induced damage<sup>[7,8]</sup>. Adjunct anti-inflammatory treatment (*i.e.*, corticosteroids) is often used, however the treatment decisions are based on severity of illness without regards to inflammatory state.

Several inflammatory biomarkers have been identified and implicated in the pathophysiology of inflammatory response in pneumonia and ARDS. More recently, several studies have assessed the role of biomarkers as key evaluation and management tools specifically aiding diagnoses, assessing severity, prognostication and informing therapeutic strategies.

This review focuses on biomarkers and their potential role in the evaluation and management of acute inflammation in CAP and ARDS in critically ill patients.

## PATHOPHYSIOLOGY OF ACUTE PULMONARY INFLAMMATION

Acute pulmonary inflammation involves both the innate and adaptive immune responses. When a pathogen is encountered, the airway epithelium acts as the first line of defense mechanism. It is well equipped to release several enzymes including defensins, mucins and lysozymes along with reactive oxygen species (ROS), nitric oxide, platelet activating factor and cytokines to attract inflammatory cells. In addition, plasma cells secrete IgA which creates an overlying epithelial protective barrier preventing microbial adherence, and surfactant proteins A and D in the alveoli

sacs stick to surface bacterial molecules to facilitate opsonization<sup>[1,9]</sup>. If a pathogen is able to overcome the epithelium's defenses, it encounters a group of inflammatory cells particularly macrophages, dendritic cells and lymphocytes, residing in the airways and throughout the lung parenchyma and interstitium. Dendritic cells are antigen presenting cells which not only stimulate the naïve T cell lymphocytes but also potentiate macrophages and assist in phagocytosis. They do so with the help of toll like receptors on their surfaces also referred to as pattern-recognition receptors which identify pathogen associated molecular patterns on pathogens' surfaces<sup>[1,10]</sup>. Stimulated naïve T cells activate either a T helper 1 (Th 1) and Th2 response which results in both cell-mediated and humoral mediated immune responses against the invading organism. This culminates in further stimulation of macrophages and T lymphocytes resulting in the release of a variety of chemokines and cytokines based on the type of invading pathogen, including interferon gamma, tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1, IL-4, IL-5, IL-6, IL-8, IL-9, IL-12 and IL-13. Simultaneously, the lung insult activates the capillary endothelial cells which in addition to contributing towards chemokine release, upregulate the surface adhesion molecules facilitating the attachment and migration of inflammatory cells to the site of insult<sup>[1]</sup>. In acute inflammation, neutrophils are the primary cells to respond to the cytokine release; IL-8 being the primary neutrophil chemotactic cytokine. Neutrophils kill the phagocytosed pathogens with ROS, antimicrobial proteins and elastase. If the lung insult has been successfully controlled, a rise in anti-inflammatory cytokines particularly IL-10, TGF- $\beta$  and IL-1Ra is expected. These assist in down regulating the defense system and facilitate apoptosis of the inflammatory cells by macrophages<sup>[11]</sup>. However, in cases of overwhelming infection, the anti-inflammatory mechanisms are unable to control the underlying inflammation resulting in continuous lung injury.

In early ARDS, increased capillary permeability is the hallmark outcome of the inflammatory process resulting from direct or indirect lung injury with disruption of the capillary-alveolar interface. This leads to leakage of protein-rich fluid from the capillary into the alveoli resulting in diffuse alveolar injury triggering an overwhelming release of pro-inflammatory cytokines mainly TNF, IL-1 and IL-6 and creating an imbalance between pro-inflammatory and anti-inflammatory cytokines. This initiates the inflammation cascade and recruits' neutrophils which again play a crucial role in causing inflammation by releasing ROS and proteases. It has been noted that patients with ARDS, have transcription abnormalities involving NF-kappa B which is required for transcription of genes responsible for pro-inflammatory mediators. Other substances such as endothelin-1, angiotensin-2 and phospholipase A2 have also been found to worsen vascular permeability and underlying inflammation causing increased lung injury<sup>[12-15]</sup>. A hyper-inflammatory sub phenotype in ARDS has been recently identified and associated with worse outcomes compared to a hypo-inflammatory sub phenotype<sup>[8]</sup>.

## DIAGNOSIS, EVALUATION, AND MANAGEMENT OF CAP AND ARDS-EVIDENCE ON INFLAMMATORY BIOMARKERS

Early identification and assessment of severity are essential for institution of timely antibiotic therapy and appropriate supportive care in CAP and ARDS. As current diagnostic, evaluation, and management strategies are based on radiographic, clinical and physiological variables only, the use of biomarkers in these conditions has been proposed and extensively evaluated.

A biomarker is "a defined characteristic that is measureable and an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention"<sup>[16]</sup>. The quintessential biomarker that can aid early identification, prognostication, as well as guide and monitor response to treatment in critically ill patients with acute pulmonary inflammation has been long sought-after. Several other fields have successfully identified biomarkers with therapeutic implications and improvement in outcomes. The identification of the programmed cell death ligand-1 (PD-L1) and its role in several malignancies, led to the development of PD-L1 inhibitors which have revolutionized the treatment of several types of cancer. Asthma is another example of a heterogeneous disease that was revolutionized by the identification of various phenotypes and the associated biomarker(s) leading to treatments such as anti-IL-5 inhibitors. Recent evidence and ongoing efforts suggests a potential for similar success in CAP and ARDS with the recent identification of hyper-inflammatory phenotypes with important prognostic and therapeutic implications<sup>[8,17]</sup>. The biomarkers that have been most extensively studied in CAP include C-reactive protein (CRP) and procalcitonin (PCT) and in ARDS, cytokines which will henceforth be reviewed.

### CRP

CRP was first discovered in 1930. Scientists William S Tillet and Thomas Francis Jr, discovered a novel antigen on the surface of pneumococcal bacteria that was present in the initial stages of infection and resolved as the patient improved<sup>[18]</sup>. Several years later, it was discovered that this “antigen” was a protein involved in acute systemic inflammation, CRP.

CRP is an acute phase protein predominately synthesized in hepatocytes in response to IL-6. As part of the innate immune response, it binds to microorganisms and stimulates phagocytosis and activation of the classical complement pathway<sup>[19]</sup>. It is detectable in serum within 6-10 h of inflammation initiation and has a half-life of approximately 25 h accounting for its rapid disappearance as inflammation subsides<sup>[20]</sup>. It is a non-specific acute phase reactant and has been shown to be elevated in various types of inflammation including infection regardless of pathogen type, malignancy, autoimmune disorders, and systemic inflammatory response syndrome (SIRS) PCT was more recently occurring without active infection<sup>[21]</sup>. Current literature supports its use in diagnosis of pneumonia, assessment of severity of illness, prognostication, and assessment of clinical stability though the literature can be difficult to interpret due to the heterogeneous populations studied and the wide array of cut off levels suggested<sup>[22]</sup> (Table 1). Given its non-specific but direct correlation with the innate immune system, its rapid turn-around time, low cost, and wide availability, it could be used as a biomarker to help identify and guide treatment in patients with hyper-inflammatory phenotypes of CAP. Further studies are needed to help define the natural history of CRP in hyper-inflammatory CAP phenotypes.

### PCT

PCT was more recently discovered. It is a 116 amino acid peptide precursor to calcitonin and is encoded by the *CALC-1* gene. In non-infectious states, it is produced in the C cells of the thyroid gland. In the presence of infection, and in particular, systemic bacterial infection, *CALC-1* gene expression is induced in non-neuroendocrine cells throughout the body and transcription and translation of PCT occurs. In addition, release of interferon stimulated by viral infection has been shown to down-regulate the production of PCT. It is detected in serum within 4 h of onset of infection and peaks within 12-48 h<sup>[23-25]</sup>.

While it is often used as a marker of systemic bacterial infection, it may not be elevated in isolated infections such as abscesses or empyema. Similar to CRP, it can be elevated in SIRS without infection. Accuracy in patients with renal dysfunction has been brought into questions as levels can be falsely elevated due at least in part to impaired clearance though higher cut off levels have been proposed in this population<sup>[26]</sup>. Similar to CRP, current literature supports its use in diagnosis, assessment of severity of illness, prognostication, and assessment of clinical stability in patients with CAP. In addition, it has been shown to be effective in identifying bacterial pathogens as the source of infection and in de-escalation of antibiotic therapy<sup>[27]</sup>. (Table 1)

### CRP and PCT in CAP

CRP and PCT have been shown to aid in diagnosis in CAP particularly in comparison to clinical signs and symptoms alone and in patients with co-morbid conditions that contribute to clinical ambiguity, such as chronic obstructive pulmonary disease and acute heart failure.<sup>[25,27]</sup> However, time from symptom onset to initial healthcare presentation may impact initial levels of CRP and PCT. A study looked at 541 patients who presented to the emergency department with CAP and were differentiated into early presenters (< 3 d since onset of symptoms) and late presenters (> 3 d). Results showed that CRP and PCT were lower in patients who were early presenters suggesting that time to presentation may affect the interpretation of these biomarkers<sup>[28]</sup>.

Both CRP and PCT have demonstrated moderate positive correlation with severity of disease assessed by CURB-65 with a receiver operating characteristic curves of 0.61 and 0.72 respectively<sup>[29]</sup>.

Evidence of CRP and PCT in prognostication of CAP is variable. One recent cross-sectional study of 93 hospitalized adult patients with CAP showed a statistically significant association with mortality in patients with PCT > 0.5 ng/mL<sup>[29]</sup>. Another study assessed prognostication ability of PCT alone and in conjunction with CURB-65 compared with CRP and leukocytes, and demonstrated a better prediction of mortality of PCT alone which was increased in combination with CURB-65<sup>[30]</sup>. Yet another study showed that elevated PCT was able to predict an increase in adverse events but not mortality<sup>[30,31]</sup>. The correlation of CRP with prognosis in CAP has varied with some studies demonstrating prognostic value of initial CRP while other studies demonstrate the prognostic ability of CRP trend but not initial measurement<sup>[32-34]</sup>. A



**Table 1 Summary of current evidence on biomarkers and their role in the evaluation and management of community acquired pneumonia<sup>[22]</sup>**

Role	Biomarker
Diagnosis	CRP, PCT, Ang 1, Ang 2
Severity of illness	CRP, PCT, Ang 1, Ang 2, Pro-ADM, Pro-ANP, Pro-VNP, SP-D, YKL-40, CCL 18, Endocan, NETs, FGF21,
Clinical instability	CRP, PCT, NETs, FGF21
De-escalation antibiotic	PCT
Prognostication	CRP, PCT, Ang 1, Ang 2, Pro-ADM, Pro-ANP, Pro-VNP, SP-D, YKL-40, CCL 18, NETs, FGF21

CRP: C-reactive protein; PCT: Procalcitonin; Ang 1: Barrier stabilizing angiopoietin 1; Ang 2: Barrier stabilizing angiopoietin 2; pro-ADM: Pro-adrenomedullin; pro-ANP: Pro-atrial natriuretic peptide; pro-VNP: pro-vasopressin; SP-D: Surfactant protein-D; YKL-40: Human cartilage glycoprotein YKL-40; CCL18: Chemokine ligand 18; NET: Neutrophil extracellular trap; FGF21: Fibroblast growth factor 21.

recent prospective observational study evaluated the natural history of CRP in hospitalized patients with CAP, and showed that CRP at day 3 and 5 as opposed to initial CRP measurement, predicted mortality<sup>[32]</sup>. One study even demonstrated that lack of CRP decline regardless of initial value was predictive of 30-day mortality<sup>[35]</sup>. A recent study compared independent prognostication for PCT, CRP, and three pneumonia severity scores (Pneumonia Severity Index, CURB-65, IDSA/ATS defined severe CAP) and three mortality prediction tools [Acute Physiology Chronic Health Evaluation II, Sequential Organ Failure Assessment (SOFA), and quick SOFA]. AUC for each clinical prediction tool was similar to PCT and slightly higher than CRP (AUC range of pneumonia severity scores 0.77-0.87; AUC range of mortality scores 0.81-0.85; AUC for PCT 0.83; AUC for CRP 0.77)<sup>[36]</sup>. With justification from prior studies demonstrating improved predictability with combination clinical predictor tools as well as CRP and/or PCT levels, a study proposed a new clinical decision tool for in hospital mortality in patients with severe CAP that incorporated previous prediction tool elements in conjunction with CRP<sup>[37]</sup>.

In a large multi-center randomized control trial, evaluating steroid treatment in hospitalized patients with severe community-acquired pneumonia (CAP), an inclusion criterion of CRP > 150 mg/L on admission was utilized. The results of this study demonstrate a reduction in treatment failure in the steroid group compared with placebo and indicates that, CRP may be a useful tool to help identify the population that may benefit from adjunctive corticosteroid therapy<sup>[17]</sup>. In addition, CRP may have the potential to help guide duration of treatment as steroid therapy has been shown to decrease the level of CRP<sup>[38]</sup>. PCT has been used to guide initiation and duration of antibiotic therapy without worse outcomes but has not been used to guide treatment with corticosteroids or other anti-inflammatory specific treatments<sup>[39-41]</sup>. Other less studied biomarkers are listed in [Table 1](#).

### **Cytokines in pneumonia**

Elevated pro-inflammatory cytokine (include IL-1, 6, and 8; TNF-alpha; and macrophage inflammatory protein-1beta) levels in CAP are indicative of a hyper-inflammatory phenotype and are associated with increased disease severity, length of ICU and hospital stay, ventilator days, and mortality<sup>[7,42,43]</sup>. This phenotype may benefit from tailored treatments such as corticosteroids<sup>[17]</sup>. While cytokine panels may accurately identify the hyper-inflammatory phenotype, these panels are expensive, not universally available, and have a slow turn-around time that limits their ability to help guide potential treatments. Correlation of the natural history of CRP in relation to these cytokine patterns may allow for CRP to be a surrogate of these more expensive and cumbersome diagnostic panels.

### **Biomarkers in ARDS**

Similar to CAP, biomarkers have the potential to aid in diagnosis, risk stratification, prognostication, and treatment response in ARDS. A wide variety of biomarkers have been studied in the ARDS population and many have been found to correlate with worse outcomes<sup>[44]</sup> ([Table 2](#)). A combination of biomarkers that pull from multiple areas described in conjunction with clinical predictors was found to be superior to any single component at mortality prediction<sup>[45]</sup>.

### **Cytokines in ARDS**

Inflammatory cytokines have been extensively studied in ARDS and have proven useful at identifying hyper-inflammatory phenotypes. Utilizing latent class analysis and cytokine panels consisting of protein C, plasminogen activator inhibitor-1 (PAI-1),

**Table 2 Biomarkers in acute respiratory distress syndrome<sup>[14]</sup>**

Pathways	Biomarkers	
Epithelial	RAGE	
	SP-D	
	KL-6	
	CC16	
	KGF	
Endothelial	Ang-1/2	
	vWF	
	VEGF	
Inflammatory	Pro-inflammatory	IL-1 $\beta$
		IL-6
		TNF $\alpha$
		IL-8
		IL-18
	Anti-Inflammatory	ILRA
		sTNF-RI/II
Coagulation and Fibrinolysis	PAI-1	IL-10

RAGE: Receptor for advanced glycation end-product; SP-D: Serum surfactant protein D; KL-6: Kreb von den Lungen-6; CC16: Clara cell secretory protein; KGF: Keratinocyte growth factor; Ang 1/2: Barrier stabilizing angiopoietin 1/2; vWF: Von willebrand factor; VEGF: Vascular endothelial growth factor; IL: Interleukin; sTNF-RI/II: Soluble tissue necrosis factor receptor I/II; PAI-1: Plasminogen activator inhibitor-a.

IL-6 and 8, TNF receptor-I, intercellular adhesion molecule-1 (ICAM-1), surfactant protein D, and von Willebrand factor antigen, Calfee *et al*<sup>[8]</sup> identified two ARDS phenotypes, a hyper and hypo-inflammatory type. The hyper-inflammatory phenotype was associated with increased inflammatory biomarker levels (IL-6 and 8, TNFr1, PAI-1, and ICAM-1) vasopressor use, prevalence of sepsis, acidosis, and 90-d mortality, and decreased ventilator and organ failure free days. Furthermore, a high PEEP strategy was associated with a significant decrease in mortality in the hyper-inflammatory group suggesting a possible therapeutic implication of distinguishing phenotypes<sup>[8]</sup>. These two types persisted over time with > 94% of patients remaining within their initial phenotype by hospital day three<sup>[46]</sup>. A follow up study with 2 distinct cohorts demonstrated increased levels of markers of epithelial cell injury with decreased levels of markers of endothelial injury in direct ARDS (defined as those with pulmonary cause such as pneumonia) compared with indirect ARDS (caused by non-pulmonary etiologies such as sepsis)<sup>[47]</sup>. To stratify even further, inflammatory biomarkers have been shown to be elevated in mixed ICU patients but not in trauma patients<sup>[48-50]</sup>. More recently, a study utilizing logistic regression, evaluated 20 biomarkers including those in the inflammatory, coagulation, and endothelial activation categories and again identified a hyper and hypo-inflammatory phenotype with the hyper-inflammatory phenotype demonstrating higher ICU mortality. Furthermore, it was discovered that a mere 4 biomarkers (IL-6, interferon gamma, angiopoietin 1/2 and PAI-1) could be used to identify the hyper-inflammatory phenotype (AUC 0.98)<sup>[51]</sup>.

### CRP and PCT in ARDS

The combination of PCT and CRP have been shown to correlate with severity of disease in patients with ARDS however, this is not true for either biomarker independently, and even less so for CRP<sup>[52]</sup>. However, serial CRP levels have been shown to correlate with treatment response to corticosteroids<sup>[53]</sup>. In addition, and in agreement with previous studies that found higher levels of inflammatory biomarkers in indirect ARDS, PCT levels are significantly higher in ARDS patients with sepsis making it a useful tool in identification of this population<sup>[54]</sup>.

## CURRENT EVIDENCE ON ADJUNCT ANTI-INFLAMMATORY THERAPIES

Early antimicrobial therapy and lung protective ventilation are essential management strategies in pneumonia and ARDS. In addition early neuromuscular blockade has been associated with improved survival and decreased ventilator days in severe ARDS<sup>[55]</sup>. As antimicrobial therapy alone is insufficient to curb an exaggerated inflammatory response, several studies have evaluated the use of anti-inflammatory agents including corticosteroids in these conditions.

### Corticosteroids

Corticosteroids have wide-ranging therapeutic application in the critically ill, particularly as anti-inflammatory agents for a variety of acute illnesses. Corticosteroids bind to glucocorticoid receptors intracellularly prompting genomic signaling with subsequent effects on gene transcription and post-translation<sup>[56]</sup>. These result in downstream inhibition and blockade of a variety of pro-inflammatory mediators including ILs, TNF nuclear factor- $\kappa$ B, and suppression of inflammatory eicosanoids and cyclooxygenase 2.

Insufficient suppression of nuclear factor- $\kappa$ B and increased levels of pro-inflammatory cytokines are thought to be a major driver of pulmonary inflammation in ARDS<sup>[57-59]</sup> and severe CAP<sup>[60]</sup> associated with worse outcomes<sup>[61]</sup>. Therefore the use of corticosteroids to blunt these effects has been proposed<sup>[62,63]</sup>. Translational efforts of these hypotheses however have been inconsistent in demonstrating clinical benefit.

### CAP

Early studies and subsequent meta-analyses found improvements in mortality, ventilator-free days, time to clinical stabilization, and reduced lengths of stays<sup>[64-66]</sup>. The recent society of critical care medicine (SCCM)/ European society of intensive care medicine (ESICM) guidelines thus suggest the use of adjunctive corticosteroids in hospitalized patients with CAP<sup>[67]</sup>.

Unfortunately, these studies included heterogeneous populations and more importantly patients with CAP of wide-ranging severities. Nonetheless, there appeared to be early signal that patients with severe CAP may be those who benefit greatest from corticosteroids. A more contemporary meta-analysis of nine randomized controlled trials and six observational studies found no difference in survival, even in patients with severe CAP<sup>[68]</sup>. Interestingly, progression to ARDS was reduced in corticosteroid recipients. Furthermore, an individual patient data meta-analysis of six studies found corticosteroids reduced time to clinical stabilization and time in the hospital, but had no effects on survival, regardless of severity of the disease<sup>[69]</sup>. More recently, a meta-analysis of ten studies of severe CAP found corticosteroids were associated with improved in-hospital survival, but no clinical effect or differences in ventilator duration<sup>[70]</sup>.

The ESCAPE trial a multicenter, randomized controlled study in patients with severe CAP requiring ICU admission who met IDSA/ATS guideline criteria (NCT01283009) was recently concluded and results due to be published. Patients were randomized to methylprednisolone 40 mg per day for 7 d followed by 20 mg per d for 7 d followed by 12 mg per day for 6 d followed by 4 mg per day for 6 d or placebo with a primary outcome of 60-d all-cause mortality.

Corticosteroid use in pathogen-specific CAPs has had somewhat more consistent findings. Studies of corticosteroids for CAP from influenza have rather consistently shown delayed viral clearance and increased mortality<sup>[71]</sup>. While corticosteroids provide considerable mortality benefit in CAP from *Pneumocystis* in HIV-positive individuals<sup>[72]</sup>, their benefit in other immune-suppressed hosts without HIV has not been substantiated<sup>[73]</sup>. Corticosteroid use in CAP from *Aspergillus* has shown increased mortality amongst hematopoietic cell transplant recipients<sup>[74,75]</sup>, whereas solid organ transplant recipients have reduced mortality<sup>[76]</sup>.

Because of their propensity to induce hyperglycemia, neuropsychiatric effects, immune-suppression and thereby potentially increased infection, suppressed wound healing, sodium retention, among other adverse effects<sup>[56]</sup>, judicious use of corticosteroids in the critically ill - a population already at high risk of poor outcome - is becoming increasingly more important. Use of biomarkers may therefore inform steroid use, dosing and duration in patients with severe CAP and may potentially provide individualized selection of patients most likely to benefit. However, evaluation of contemporary clinical practice reveals corticosteroid use in CAP is not consistent with CRP and PCT concentrations<sup>[77]</sup>, and requires further investigation.

### ARDS

A major contributor to the controversy of using corticosteroids for treatment of ARDS is the heterogeneity of studies published, wherein different dosing strategies are used, timing of initiation of steroids varies, outcomes studied are different, and the evolution of identifying and classifying the syndrome overtime. While a meta-

analysis of nine studies found increase ventilator-free days but did not demonstrate survival benefit<sup>[78]</sup>, a subsequent individual patient data analysis and trial level meta-analysis showed prolonged corticosteroids increased both survival and ventilator-free days<sup>[79]</sup>. More recently, a study of hydrocortisone initiated within 12 hours of severe sepsis-associated ARDS found improved oxygenation but not time to liberation of the ventilator or survival<sup>[80]</sup>.

Timing of corticosteroid initiation may be an important consideration in ARDS. The ARDSNet trial randomized patients with ARDS that was persistent beyond 7 d and found improved oxygenation and ventilator compliance resulting in increased ventilator-free days, but again, no survival benefit<sup>[81]</sup>. More importantly, when corticosteroids were initiated late after ARDS onset (defined by 14 d), they were associated with increased mortality. Other studies have had similar findings where greater survival and ventilator-free days were observed if corticosteroids were initiated within 72 h<sup>[53]</sup>. When concomitant pneumonia is present, initiation of corticosteroids within 12 h may result in more beneficial outcomes including reduced need for and duration on the ventilator and reduced hospital mortality<sup>[82]</sup>.

Based on this cumulative evidence, the recent SCCM/ESICM guidelines suggests the use of corticosteroid in patients with early moderate to severe ARDS within 14 d of onset<sup>[67]</sup>.

The DEXA-ARDS trial a multicenter, randomized controlled study in patients with moderate to severe ARDS persistent beyond 24 h was recently concluded and results due to be published<sup>[83]</sup>. Patients were randomized to dexamethasone 20 mg per day for 5 d followed by 10 mg per day for 5 d or placebo with ventilator-free days as primary outcome.

## OTHER ANTI-INFLAMMATORY THERAPIES

Many different pharmacotherapies exerting anti-inflammatory actions have been mechanistically believed to provide benefits for pulmonary inflammation in ARDS and CAP. The majority of these therapies have failed to show clinical benefit, including statins<sup>[84]</sup>, neutrophil elastase inhibitors<sup>[85]</sup>, and ibuprofen<sup>[86]</sup>. An open-label study of moderate to severe ARDS found improved oxygenation at 48 h and reductions in inflammatory markers with use of inhaled sevoflurane<sup>[87]</sup>.

Anti-platelet agents have been proposed to suppress neutrophil-recruitment induced by platelet activation. Early observational studies found a signal of aspirin use prior to admission to the hospital reduced progression to ARDS<sup>[88,89]</sup>. In a randomized study, early administration of aspirin to patients at risk of ARDS did not reduce the risk of ARDS<sup>[90]</sup>. There have been no investigations of aspirin for the treatment of those who have already developed ARDS.

Macrolide antimicrobials have been shown to suppress proinflammatory actions of nuclear factor- $\kappa$ B and inhibition of the nitric oxide pathway-driven inflammatory effects<sup>[91]</sup>. In an observational ARDS study, LARMA, a subset of patients who received macrolide antimicrobials as part of their clinical management had a signal towards improved long-term mortality<sup>[92]</sup>, though these benefits have not been substantiated in larger, controlled studies.

The PETAL network recently completed a study evaluating the effect of early vitamin D3 administration in patients at high risk of ARDS and is awaiting release of results (NCT03096314). A study evaluating the efficacy, safety, and effects on inflammatory biomarkers of inhaled carbon monoxide in ARDS will be recruiting soon (NCT03799874).

## FUTURE DIRECTIONS

In the era of precision medicine, biomarkers have the potential to guide disease specific evaluation and management strategies in critically ill patients with CAP and ARDS with the goal of improvement in outcomes of both conditions and early ARDS prevention. The ideal biomarker should be accurate, reproducible<sup>[22]</sup>, detected early<sup>[44]</sup>, clearly reflect the degree of inflammation, response to treatment<sup>[25]</sup> and trajectory of illness, and identify patients at risk of worse outcomes<sup>[93]</sup>. Furthermore, an ideal biomarker in pneumonia and ARDS should be inexpensive, easily available, rapidly analyzable and consistent across all groups of patients for generalizability to be useful in clinical practice.

Pragmatic clinical trials with an adaptive design are needed to further define the roles of inflammatory biomarkers (individually or as a panel) as predictive and/or prognostic enrichment tools as well as therapeutic guides in acute pulmonary



inflammation in critically ill patients.

## CONCLUSION

In addition to early antibiotics, safe lung ventilation strategies and neuromuscular blockade, corticosteroids are the only anti-inflammatory medications with potential benefits in these conditions. Inflammatory biomarkers have been used for early diagnosis, assessment of severity, and prognostication in CAP and ARDS. The use of biomarkers for patient selection and for guiding adjunct anti-inflammatory treatment is appealing however, further studies are needed to define their role in clinical practice.

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