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REVIEW

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[1]. 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[2,3]. 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[4]. Although less common than pneumonia, ARDS accounts for approximately 10.4% of ICU admissions worldwide with an associated 40% mortality rate depending on severity[5]. 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[5,6]. 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[7,8]. 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 lyzozymes 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[1,9]. 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[1,10]. 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)-α, 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[1]. 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-β and IL-1Ra is expected. These assist in down regulating the defense system and facilitate apoptosis of the inflammatory cells by macrophages[11]. 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[12-15]. A hyper- inflammatory sub phenotype in ARDS has been recently identified and associated with worse outcomes compared to a hypo-inflammatory sub phenotype[8].

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"[16]. 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 programed 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[8,17]. 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[18]. 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[19]. 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[20]. 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 recentlyoccurring without active infection[21]. 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[22] (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 detec in serum within 4 h of onset of infection and peaks within 12-48 h[23-25].

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[26]. 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[22]. (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.[25,27]. 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[28].

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[29].

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[29]. 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[30]. Yet another study showed that elevated PCT was able to predict an increase in adverse events but not mortality[30,31]. 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[32-34]. A

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

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[32]. One study even demonstrated that lack of CRP decline regardless of initial value was predictive of 30-day mortality[35]. 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)[36]. 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[37].

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[17]. 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[38]. 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[39-41]. 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 protin-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[7,42,43]. This phenotype may benefit from tailored treatments such as corticosteroids[17]. 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[44] (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[45].

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[44]

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

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*[8] 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[8]. These two types persisted over time with > 94% of patients remaining within their initial phenotype by hospital day three[46]. 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)[47]. To stratify even further, inflammatory biomarkers have been shown to be elevated in mixed ICU patients but not in trauma patients[48-50]. 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, angiopoetin 1/2 and PAI-1) could be used to identify the hyper-inflammatory phenotype (AUC 0.98)[51].

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[52]. However, serial CRP levels have been shown to correlate with treatment response to corticosteroids[53]. 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[54].

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[55]. 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[56]. These result in downstream inhibition and blockade of a variety of pro-inflammatory mediators including ILs, TNF nuclear factor-kB, and suppression of inflammatory eicosanoids and cyclooxygenase 2.

Insufficient suppression of nuclear factor-kB and increased levels of pro-inflammatory cytokines are thought to be a major driver of pulmonary inflammation in ARDS[57-59] and severe CAP[60] associated with worse outcomes[61]. Therefore the use of corticosteroids to blunt these effects has been proposed[62,63]. 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[64-66]. 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[67].

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[68]. 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[69]. 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[70].

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[71]. While corticosteroids provide considerable mortality benefit in CAP from *Pneumocystis* in HIV-positive individuals[72], their benefit in other immune-suppressed hosts without HIV has not been substantiated[73]. Corticosteroid use in CAP from *Aspergillus* has shown increased mortality amongst hematopoietic cell transplant recipients[74,75], whereas solid organ transplant recipients have reduced mortality[76].

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[56], 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[77], 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[78], a subsequent individual patient data analysis and trial level meta-analysis showed prolonged corticosteroids increased both survival and ventilator-free days[79]. 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[80].

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[81]. 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[53]. 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[82].

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[67].

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[83]. 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[84], neutrophil elastase inhibitors[85], and ibuprofen[86]. 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[87].

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[88,89]. In a randomized study, early administration of aspirin to patients at risk of ARDS did not reduce the risk of ARDS[90]. 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-kB and inhibition of the nitric oxide pathway-driven inflammatory effects[91]. 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[92], 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[22], detected early[44], clearly reflect the degree of inflammation, response to treatment[25] and trajectory of illness, and identify patients at risk of worse outcomes[93]. 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.

REFERENCES

1 **Moldoveanu B**, Otmishi P, Jani P, Walker J, Sarmiento X, Guardiola J, Saad M, Yu J. Inflammatory mechanisms in the lung. *J Inflamm Res* 2009; **2**: 1-11 [PMID: 22096348 DOI: 10.2147/JIR.S4385]
2 **Ramirez JA**, Wiemken TL, Peyrani P, Arnold FW, Kelley R, Mattingly WA, Nakamatsu R, Pena S, Guinn BE, Furmanek SP, Persaud AK, Raghuram A, Fernandez F, Beavin L, Bosson R, Fernandez-Botran R, Cavallazzi R, Bordon J, Valdivieso C, Schulte J, Carrico RM; University of Louisville Pneumonia Study Group. Adults Hospitalized With Pneumonia in the United States: Incidence, Epidemiology, and Mortality. *Clin Infect Dis* 2017; **65**: 1806-1812 [PMID: 29020164 DOI: 10.1093/cid/cix647]
3 **Kochanek KD**, Murphy SL, Xu J, Tejada-Vera B. Deaths: Final Data for 2014. *Natl Vital Stat Rep* 2016; **65**: 1-122 [PMID: 27378572]
4 **Storms AD**, Chen J, Jackson LA, Nordin JD, Naleway AL, Glanz JM, Jacobsen SJ, Weintraub ES, Klein NP, Gargiullo PM, Fry AM. Rates and risk factors associated with hospitalization for pneumonia with ICU admission among adults. *BMC Pulm Med* 2017; **17**: 208 [PMID: 29246210 DOI: 10.1186/s12890-017-0552-x]
5 **Bellani G**, Laffey JG, Pham T, Fan E; LUNG SAFE Investigators and the ESICM Trials Group. The LUNG SAFE study: a presentation of the prevalence of ARDS according to the Berlin Definition! *Crit Care* 2016; **20**: 268 [PMID: 27608629 DOI: 10.1186/s13054-016-1443-x]
6 **Restrepo MI**, Mortensen EM, Velez JA, Frei C, Anzueto A. A comparative study of community-acquired pneumonia patients admitted to the ward and the ICU. *Chest* 2008; **133**: 610-617 [PMID: 17989157 DOI: 10.1378/chest.07-1456]
7 **Martínez R**, Menéndez R, Reyes S, Polverino E, Cillóniz C, Martínez A, Esquinas C, Filella X, Ramírez P, Torres A. Factors associated with inflammatory cytokine patterns in community-acquired pneumonia. *Eur Respir J* 2011; **37**: 393-399 [PMID: 20595152 DOI: 10.1183/09031936.00040710]
8 **Calfee CS**, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA; NHLBI ARDS Network. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med* 2014; **2**: 611-620 [PMID: 24853585 DOI: 10.1016/S2213-2600(14)70097-9]
9 **Adler KB**, Fischer BM, Wright DT, Cohn LA, Becker S. Interactions between respiratory epithelial cells and cytokines: relationships to lung inflammation. *Ann N Y Acad Sci* 1994; **725**: 128-145 [PMID: 8030984 DOI: 10.1111/j.1749-6632.1994.tb00275.x]
10 **Kaisho T**, Akira S. Toll-like receptor function and signaling. *J Allergy Clin Immunol* 2006; **117**: 979-87; quiz 988 [PMID: 16675322 DOI: 10.1016/j.jaci.2006.02.023]
11 **Toossi Z**, Hirsch CS, Hamilton BD, Knuth CK, Friedlander MA, Rich EA. Decreased production of TGF-beta 1 by human alveolar macrophages compared with blood monocytes. *J Immunol* 1996; **156**: 3461-3468 [PMID: 8617974]
12 **Pierrakos C**, Karanikolas M, Scolletta S, Karamouzos V, Velissaris D. Acute respiratory distress syndrome: pathophysiology and therapeutic options. *J Clin Med Res* 2012; **4**: 7-16 [PMID: 22383921 DOI: 10.4021/jocmr761w]
13 **Windsor AC**, Mullen PG, Fowler AA, Sugerman HJ. Role of the neutrophil in adult respiratory distress syndrome. *Br J Surg* 1993; **80**: 10-17 [PMID: 8428262 DOI: 10.1002/bjs.1800800106]
14 **Gadek JE**, Pacht ER. The interdependence of lung antioxidants and antiprotease defense in ARDS. *Chest* 1996; **110**: 273S-277S [PMID: 8989164 DOI: 10.1378/chest.110.6_Supplement.273S]
15 **Moine P**, McIntyre R, Schwartz MD, Kaneko D, Shenkar R, Le Tulzo Y, Moore EE, Abraham E. NF-kappaB regulatory mechanisms in alveolar macrophages from patients with acute respiratory distress syndrome. *Shock* 2000; **13**: 85-91 [PMID: 10670837 DOI: 10.1097/00024382-200013020-00001]
16 **Amur S**. Biomarker Terminology: Speaking The Same Language [Internet]. 2019. Available from: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/UCM533161.pdf
17 **Torres A**, Sibila O, Ferrer M, Polverino E, Menendez R, Mensa J, Gabarrús A, Sellarés J, Restrepo MI, Anzueto A, Niederman MS, Agustí C. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *JAMA* 2015; **313**: 677-686 [PMID: 25688779 DOI: 10.1001/jama.2015.88]
18 **Tillett WS**, Francis T. SEROLOGICAL REACTIONS IN PNEUMONIA WITH A NON-PROTEIN SOMATIC FRACTION OF PNEUMOCOCCUS. *J Exp Med* 1930; **52**: 561-571 [PMID: 19869788 DOI: 10.1084/jem.52.4.561]
19 **Male D**, Brostoff J, Roth D. Chapter 6: Mechanisms of Innate Injury. In: Immunology. 8th ed. Elsevier 2013;
20 **Chernecky CC**, Berger BJ. Laboratory Tests and Diagnostic Procedures. In: Laboratory tests and diagnostic procedures. 6th ed. St. Louis, MO: Elsevier Saunders; 2013;
21 **Ballou SP**, Kushner I. C-reactive protein and the acute phase response. *Adv Intern Med* 1992; **37**: 313-336 [PMID: 1558000]
22 **Sibila O**, Restrepo MI. Biomarkers in community-acquired pneumonia: still searching for the one. *Eur*

Respir J 2019; 53 [PMID: 30819808 DOI: 10.1183/13993003.02469-2018]
23 **Jin M**, Khan AI. Procalcitonin: Uses in the Clinical Laboratory for the Diagnosis of Sepsis. *Lab Med* 2010; **41**: 173-177 [DOI: 10.1309/LMQ2GRR4QLFKHCH9]
24 **Gilbert DN**. Use of plasma procalcitonin levels as an adjunct to clinical microbiology. *J Clin Microbiol* 2010; **48**: 2325-2329 [PMID: 20421436 DOI: 10.1128/JCM.00655-10]
25 **Shaddock EJ**. How and when to use common biomarkers in community-acquired pneumonia. *Pneumonia (Nathan)* 2016; **8**: 17 [PMID: 28702296 DOI: 10.1186/s41479-016-0017-7]
26 **Amour J**, Birenbaum A, Langeron O, Le Manach Y, Bertrand M, Coriat P, Riou B, Bernard M, Hausfater P. Influence of renal dysfunction on the accuracy of procalcitonin for the diagnosis of postoperative infection after vascular surgery. *Crit Care Med* 2008; **36**: 1147-1154 [PMID: 18379240 DOI: 10.1097/CCM.0b013e3181692966]
27 **Müller B**, Harbarth S, Stolz D, Bingisser R, Mueller C, Leuppi J, Nusbaumer C, Tamm M, Christ-Crain M. Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. *BMC Infect Dis* 2007; **7**: 10 [PMID: 17335562 DOI: 10.1186/1471-2334-7-10]
28 **Méndez R**, Menéndez R, Cillóniz C, Amara-Elori I, Amaro R, González P, Posadas T, Gimeno A, España PP, Almirall J, Torres A. Initial Inflammatory Profile in Community-acquired Pneumonia Depends on Time since Onset of Symptoms. *Am J Respir Crit Care Med* 2018; **198**: 370-378 [PMID: 29509439 DOI: 10.1164/rccm.201709-1908OC]
29 **Keramat F**, Ghasemi Basir HR, Abdoli E, Shafiei Aghdam A, Poorolajal J. Association of serum procalcitonin and C-reactive protein levels with CURB-65 criteria among patients with community-acquired pneumonia. *Int J Gen Med* 2018; **11**: 217-223 [PMID: 29942144 DOI: 10.2147/IJGM.S165190]
30 **Krüger S**, Ewig S, Marre R, Papassotiriou J, Richter K, von Baum H, Suttorp N, Welte T; CAPNETZ Study Group. Procalcitonin predicts patients at low risk of death from community-acquired pneumonia across all CRB-65 classes. *Eur Respir J* 2008; **31**: 349-355 [PMID: 17959641 DOI: 10.1183/09031936.00054507]
31 **Schuetz P**, Suter-Widmer I, Chaudri A, Christ-Crain M, Zimmerli W, Mueller B; Procalcitonin-Guided Antibiotic Therapy and Hospitalisation in Patients with Lower Respiratory Tract Infections (ProHOSP) Study Group. Prognostic value of procalcitonin in community-acquired pneumonia. *Eur Respir J* 2011; **37**: 384-392 [PMID: 20595156 DOI: 10.1183/09031936.00035610]
32 **Guo S**, Mao X, Liang M. The moderate predictive value of serial serum CRP and PCT levels for the prognosis of hospitalized community-acquired pneumonia. *Respir Res* 2018; **19**: 193 [PMID: 30285748 DOI: 10.1186/s12931-018-0877-x]
33 **Ito A**, Ishida T, Tachibana H, Ito Y, Takaiwa T. Serial procalcitonin levels for predicting prognosis in community-acquired pneumonia. *Respirology* 2016; **21**: 1459-1464 [PMID: 27398948 DOI: 10.1111/resp.12846]
34 **Farah R**, Khamisy-Farah R, Makhoul N. Consecutive Measures of CRP Correlate with Length of Hospital Stay in Patients with Community-Acquired Pneumonia. *Isr Med Assoc J* 2018; **20**: 345-348 [PMID: 29911753]
35 **Andersen SB**, Baunbæk Egelund G, Jensen AV, Petersen PT, Rohde G, Ravn P. Failure of CRP decline within three days of hospitalization is associated with poor prognosis of Community-acquired Pneumonia. *Infect Dis (Lond)* 2017; **49**: 251-260 [PMID: 27887037 DOI: 10.1080/23744235.2016.1253860]
36 **Kim MW**, Lim JY, Oh SH. Mortality prediction using serum biomarkers and various clinical risk scales in community-acquired pneumonia. *Scand J Clin Lab Invest* 2017; **77**: 486-492 [PMID: 28678546 DOI: 10.1080/00365513.2017.1344298]
37 **Wang X**, Jiao J, Wei R, Feng Y, Ma X, Li Y, Du Y. A new method to predict hospital mortality in severe community acquired pneumonia. *Eur J Intern Med* 2017; **40**: 56-63 [PMID: 28320569 DOI: 10.1016/j.ejim.2017.02.013]
38 **Fernández-Serrano S**, Dorca J, Garcia-Vidal C, Fernández-Sabé N, Carratalà J, Fernández-Agüera A, Corominas M, Padrones S, Gudiol F, Manresa F. Effect of corticosteroids on the clinical course of community-acquired pneumonia: a randomized controlled trial. *Crit Care* 2011; **15**: R96 [PMID: 21406101 DOI: 10.1186/cc10103]
39 **Christ-Crain M**, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, Müller B. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet* 2004; **363**: 600-607 [PMID: 14987884 DOI: 10.1016/S0140-6736(04)15591-8]
40 **Christ-Crain M**, Stolz D, Bingisser R, Müller C, Miedinger D, Huber PR, Zimmerli W, Harbarth S, Tamm M, Müller B. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med* 2006; **174**: 84-93 [PMID: 16603606 DOI: 10.1164/rccm.200512-1922OC]
41 **Schuetz P**, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, Neidert S, Fricker T, Blum C, Schild U, Regez K, Schoenenberger R, Henzen C, Bregenzer T, Hoess C, Krause M, Bucher HC, Zimmerli W, Mueller B; ProHOSP Study Group. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA* 2009; **302**: 1059-1066 [PMID: 19738090 DOI: 10.1001/jama.2009.1297]
42 **Fernández-Serrano S**, Dorca J, Coromines M, Carratalà J, Gudiol F, Manresa F. Molecular inflammatory responses measured in blood of patients with severe community-acquired pneumonia. *Clin Diagn Lab Immunol* 2003; **10**: 813-820 [PMID: 12965910 DOI: 10.1128/CDLI.10.5.813-820.2003]
43 **Ramírez P**, Ferrer M, Martí V, Reyes S, Martínez R, Menéndez R, Ewig S, Torres A. Inflammatory biomarkers and prediction for intensive care unit admission in severe community-acquired pneumonia. *Crit Care Med* 2011; **39**: 2211-2217 [PMID: 21705887 DOI: 10.1097/CCM.0b013e3182257445]
44 **Spadaro S**, Park M, Turrini C, Tunstall T, Thwaites R, Mauri T, Ragazzi R, Ruggeri P, Hansel TT, Caramori G, Volta CA. Biomarkers for Acute Respiratory Distress syndrome and prospects for personalised medicine. *J Inflamm (Lond)* 2019; **16**: 1 [PMID: 30675131 DOI: 10.1186/s12950-018-0202-y]
45 **Ware LB**, Koyama T, Billheimer DD, Wu W, Bernard GR, Thompson BT, Brower RG, Standiford TJ, Martin TR, Matthay MA; NHLBI ARDS Clinical Trials Network. Prognostic and pathogenetic value of combining clinical and biochemical indices in patients with acute lung injury. *Chest* 2010; **137**: 288-296 [PMID: 19858233 DOI: 10.1378/chest.09-1484]
46 **Delucchi K**, Famous KR, Ware LB, Parsons PE, Thompson BT, Calfee CS; ARDS Network. Stability of ARDS subphenotypes over time in two randomised controlled trials. *Thorax* 2018; **73**: 439-445 [PMID: 29477989 DOI: 10.1136/thoraxjnl-2017-211090]

47 **Calfee CS**, Janz DR, Bernard GR, May AK, Kangelaris KN, Matthay MA, Ware LB. Distinct molecular phenotypes of direct vs indirect ARDS in single-center and multicenter studies. *Chest* 2015; **147**: 1539-1548 [PMID: 26033126 DOI: 10.1378/chest.14-2454]

48 **Meade P**, Shoemaker WC, Donnelly TJ, Abraham E, Jagels MA, Cryer HG, Hugli TE, Bishop MH, Wo CC. Temporal patterns of hemodynamics, oxygen transport, cytokine activity, and complement activity in the development of adult respiratory distress syndrome after severe injury. *J Trauma* 1994; **36**: 651-657 [PMID: 8189465 DOI: 10.1097/00005373-199405000-00009]

49 **Cepkova M**, Brady S, Sapru A, Matthay MA, Church G. Biological markers of lung injury before and after the institution of positive pressure ventilation in patients with acute lung injury. *Crit Care* 2006; **10**: R126 [PMID: 16956410 DOI: 10.1186/cc5037]

50 **Nakamura T**, Sato E, Fujiwara N, Kawagoe Y, Maeda S, Yamagishi S. Increased levels of soluble receptor for advanced glycation end products (sRAGE) and high mobility group box 1 (HMGB1) are associated with death in patients with acute respiratory distress syndrome. *Clin Biochem* 2011; **44**: 601-604 [PMID: 21211520 DOI: 10.1016/j.clinbiochem.2010.12.014]

51 **Bos LD**, Schouten LR, van Vught LA, Wiewel MA, Ong DSY, Cremer O, Artigas A, Martin-Loeches I, Hoogendijk AJ, van der Poll T, Horn J, Juffermans N, Calfee CS, Schultz MJ; MARS consortium. Identification and validation of distinct biological phenotypes in patients with acute respiratory distress syndrome by cluster analysis. *Thorax* 2017; **72**: 876-883 [PMID: 28450529 DOI: 10.1136/thoraxjnl-2016-209719]

52 **Yu Z**, Ji M, Hu X, Yan J, Jin Z. [Value of procalcitonin on predicting the severity and prognosis in patients with early ARDS: a prospective observation study]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2017; **29**: 34-38 [PMID: 28459401 DOI: 10.3760/cma.j.issn.2095-4352.2017.01.008]

53 **Meduri GU**, Golden E, Freire AX, Taylor E, Zaman M, Carson SJ, Gibson M, Umberger R. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest* 2007; **131**: 954-963 [PMID: 17426195 DOI: 10.1378/chest.06-2100]

54 **Brunkhorst FM**, Eberhard OK, Brunkhorst R. Discrimination of infectious and noninfectious causes of early acute respiratory distress syndrome by procalcitonin. *Crit Care Med* 1999; **27**: 2172-2176 [PMID: 10548201 DOI: 10.1097/00003246-199910000-00016]

55 **Papazian L**, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Arnal JM, Perez D, Seghboyan JM, Constantin JM, Courant P, Lefrant JY, Guérin C, Prat G, Morange S, Roch A; ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; **363**: 1107-1116 [PMID: 20843245 DOI: 10.1056/NEJMoa1005372]

56 **Rhen T**, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. *N Engl J Med* 2005; **353**: 1711-1723 [PMID: 16236742 DOI: 10.1056/NEJMra050541]

57 **Franchimont D**, Kino T, Galon J, Meduri GU, Chrousos G. Glucocorticoids and inflammation revisited: the state of the art. NIH clinical staff conference. *Neuroimmunomodulation* 2002; **10**: 247-260 [PMID: 12759562 DOI: 10.1159/000069969]

58 **Meduri GU**, Annane D, Chrousos GP, Marik PE, Sinclair SE. Activation and regulation of systemic inflammation in ARDS: rationale for prolonged glucocorticoid therapy. *Chest* 2009; **136**: 1631-1643 [PMID: 19801579 DOI: 10.1378/chest.08-2408]

59 **Thompson BT**, Chambers RC, Liu KD. Acute Respiratory Distress Syndrome. *N Engl J Med* 2017; **377**: 562-572 [PMID: 28792873 DOI: 10.1056/NEJMra1608077]

60 **Puren AJ**, Feldman C, Savage N, Becker PJ, Smith C. Patterns of cytokine expression in community-acquired pneumonia. *Chest* 1995; **107**: 1342-1349 [PMID: 7750329 DOI: 10.1378/chest.107.5.1342]

61 **Meduri GU**, Headley S, Kohler G, Stentz F, Tolley E, Umberger R, Leeper K. Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS. Plasma IL-1 beta and IL-6 levels are consistent and efficient predictors of outcome over time. *Chest* 1995; **107**: 1062-1073 [PMID: 7705118 DOI: 10.1378/chest.107.4.1062]

62 **Meduri GU**, Marik PE, Chrousos GP, Pastores SM, Arlt W, Beishuizen A, Bokhari F, Zaloga G, Annane D. Steroid treatment in ARDS: a critical appraisal of the ARDS network trial and the recent literature. *Intensive Care Med* 2008; **34**: 61-69 [PMID: 18000649 DOI: 10.1007/s00134-007-0933-3]

63 **Confalonieri M**, Urbino R, Potena A, Piattella M, Parigi P, Puccio G, Della Porta R, Giorgio C, Blasi F, Umberger R, Meduri GU. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care Med* 2005; **171**: 242-248 [PMID: 15557131 DOI: 10.1164/rccm.200406-808OC]

64 **Siemieniuk RA**, Meade MO, Alonso-Coello P, Briel M, Evaniew N, Prasad M, Alexander PE, Fei Y, Vandvik PO, Loeb M, Guyatt GH. Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia: A Systematic Review and Meta-analysis. *Ann Intern Med* 2015; **163**: 519-528 [PMID: 26258555 DOI: 10.7326/M15-0715]

65 **Horita N**, Otsuka T, Haranaga S, Namkoong H, Miki M, Miyashita N, Higa F, Takahashi H, Yoshida M, Kohno S, Kaneko T. Adjunctive Systemic Corticosteroids for Hospitalized Community-Acquired Pneumonia: Systematic Review and Meta-Analysis 2015 Update. *Sci Rep* 2015; **5**: 14061 [PMID: 26374694 DOI: 10.1038/srep14061]

66 **Marti C**, Grosgurin O, Harbarth S, Combescure C, Abbas M, Rutschmann O, Perrier A, Garin N. Adjunctive Corticotherapy for Community Acquired Pneumonia: A Systematic Review and Meta-Analysis. *PLoS One* 2015; **10**: e0144032 [PMID: 26641253 DOI: 10.1371/journal.pone.0144032]

67 **Pastores SM**, Annane D, Rochwerg B, Corticosteroid Guideline Task Force of SCCM and ESICM. Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part II): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Crit Care Med* 2018; **46**: 146-148 [PMID: 29095205 DOI: 10.1097/CCM.0000000000002840]

68 **Wan YD**, Sun TW, Liu ZQ, Zhang SG, Wang LX, Kan QC. Efficacy and Safety of Corticosteroids for Community-Acquired Pneumonia: A Systematic Review and Meta-Analysis. *Chest* 2016; **149**: 209-219 [PMID: 26501852 DOI: 10.1378/chest.15-1733]

69 **Briel M**, Spoorenberg SMC, Snijders D, Torres A, Fernandez-Serrano S, Meduri GU, Gabarrús A, Blum CA, Confalonieri M, Kasenda B, Siemieniuk RAC, Boersma W, Bos WJW, Christ-Crain M; Ovidius Study Group; Capisce Study Group; STEP Study Group. Corticosteroids in Patients Hospitalized With Community-Acquired Pneumonia: Systematic Review and Individual Patient Data Metaanalysis. *Clin Infect Dis* 2018; **66**: 346-354 [PMID: 29020323 DOI: 10.1093/cid/cix801]

70 **Wu WF**, Fang Q, He GJ. Efficacy of corticosteroid treatment for severe community-acquired pneumonia: A meta-analysis. *Am J Emerg Med* 2018; **36**: 179-184 [PMID: 28756034 DOI:

10.1016/j.ajem.2017.07.050]
71 **Wieruszewski PM**, Linn DD. Contemporary management of severe influenza disease in the intensive care unit. *J Crit Care* 2018; **48**: 48-55 [PMID: 30172033 DOI: 10.1016/j.jcrc.2018.08.015]
72 **National Institutes of Health-University of California Expert Panel for Corticosteroids as Adjunctive Therapy for Pneumocystis Pneumonia**. Consensus statement on the use of corticosteroids as adjunctive therapy for pneumocystis pneumonia in the acquired immunodeficiency syndrome. *N Engl J Med* 1990; **323**: 1500-1504 [PMID: 2136587 DOI: 10.1056/NEJM199011223232131]
73 **Wieruszewski PM**, Barreto JN, Frazee E, Daniels CE, Tosh PK, Dierkhising RA, Mara KC, Limper AH. Early Corticosteroids for Pneumocystis Pneumonia in Adults Without HIV Are Not Associated With Better Outcome. *Chest* 2018; **154**: 636-644 [PMID: 29705221 DOI: 10.1016/j.chest.2018.04.026]
74 **Nivoix Y**, Velten M, Letscher-Bru V, Moghaddam A, Natarajan-Amé S, Fohrer C, Lioure B, Bilger K, Lutun P, Marcellin L, Launoy A, Freys G, Bergerat JP, Herbrecht R. Factors associated with overall and attributable mortality in invasive aspergillosis. *Clin Infect Dis* 2008; **47**: 1176-1184 [PMID: 18808352 DOI: 10.1086/592255]
75 **Upton A**, Kirby KA, Carpenter P, Boeckh M, Marr KA. Invasive aspergillosis following hematopoietic cell transplantation: outcomes and prognostic factors associated with mortality. *Clin Infect Dis* 2007; **44**: 531-540 [PMID: 17243056 DOI: 10.1086/510592]
76 **Baddley JW**, Andes DR, Marr KA, Kontoyiannis DP, Alexander BD, Kauffman CA, Oster RA, Anaissie EJ, Walsh TJ, Schuster MG, Wingard JR, Patterson TF, Ito JI, Williams OD, Chiller T, Pappas PG. Factors associated with mortality in transplant patients with invasive aspergillosis. *Clin Infect Dis* 2010; **50**: 1559-1567 [PMID: 20450350 DOI: 10.1086/652768]
77 **Odeyemi Y**, Herasevich S, Schwegman A, Barreto E, Gajic O, Yadav H. Biomarker concordant steroid use in critically ill patients with pneumonia. *Crit Care Med* 2019; **47**: 521 [DOI: 10.1097/01.ccm.0000551834.00753.8a]
78 **Peter JV**, John P, Graham PL, Moran JL, George IA, Bersten A. Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis. *BMJ* 2008; **336**: 1006-1009 [PMID: 18434379 DOI: 10.1136/bmj.39537.939039.BE]
79 **Meduri GU**, Bridges L, Shih MC, Marik PE, Siemieniuk RAC, Kocak M. Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. *Intensive Care Med* 2016; **42**: 829-840 [PMID: 26508525 DOI: 10.1007/s00134-015-4095-4]
80 **Tongyoo S**, Permpikul C, Mongkolpun W, Vattanavanit V, Udompanturak S, Kocak M, Meduri GU. Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: results of a randomized controlled trial. *Crit Care* 2016; **20**: 329 [PMID: 27741949 DOI: 10.1186/s13054-016-1511-2]
81 **Steinberg KP**, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, Thompson BT, Ancukiewicz M; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006; **354**: 1671-1684 [PMID: 16625008 DOI: 10.1056/NEJMoa051693]
82 **Herasevich S**, Odeyemi Y, Wieruszewski P, Gajic O, Yadav H. Timeliness of corticosteroid use in ICU patients with pneumonia and ARDS. *Crit Care Med* 2019; **47**: 557 [DOI: 10.1097/01.ccm.0000551906.96335.48]
83 **Villar J**, Belda J, Añón JM, Blanco J, Pérez-Méndez L, Ferrando C, Martínez D, Soler JA, Ambrós A, Muñoz T, Rivas R, Corpas R, Díaz-Dominguez FJ, Soro M, García-Bello MA, Fernández RL, Kacmarek RM; DEXA-ARDS Network. Evaluating the efficacy of dexamethasone in the treatment of patients with persistent acute respiratory distress syndrome: study protocol for a randomized controlled trial. *Trials* 2016; **17**: 342 [PMID: 27449641 DOI: 10.1186/s13063-016-1456-4]
84 **National Heart, Lung, and Blood Institute ARDS Clinical Trials Network**. Truwit JD, Bernard GR, Steingrub J, Matthay MA, Liu KD, Albertson TE, Brower RG, Shanholtz C, Rock P, Douglas IS, deBoisblanc BP, Hough CL, Hite RD, Thompson BT. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. *N Engl J Med* 2014; **370**: 2191-2200 [PMID: 24835849 DOI: 10.1056/NEJMoa1401520]
85 **Iwata K**, Doi A, Ohji G, Oka H, Oba Y, Takimoto K, Igarashi W, Gremillion DH, Shimada T. Effect of neutrophil elastase inhibitor (sivelestat sodium) in the treatment of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS): a systematic review and meta-analysis. *Intern Med* 2010; **49**: 2423-2432 [PMID: 21088343 DOI: 10.2169/internalmedicine.49.4010]
86 **Bernard GR**, Wheeler AP, Russell JA, Schein R, Summer WR, Steinberg KP, Fulkerson WJ, Wright PE, Christman BW, Dupont WD, Higgins SB, Swindell BB. The effects of ibuprofen on the physiology and survival of patients with sepsis. The Ibuprofen in Sepsis Study Group. *N Engl J Med* 1997; **336**: 912-918 [PMID: 9070471 DOI: 10.1056/NEJM199703273361303]
87 **Jabaudon M**, Boucher P, Imhoff E, Chabanne R, Faure JS, Roszyk L, Thibault S, Blondonnet R, Clairefond G, Guérin R, Perbet S, Cayot S, Godet T, Pereira B, Sapin V, Bazin JE, Futier E, Constantin JM. Sevoflurane for Sedation in Acute Respiratory Distress Syndrome. A Randomized Controlled Pilot Study. *Am J Respir Crit Care Med* 2017; **195**: 792-800 [PMID: 27611637 DOI: 10.1164/rccm.201604-0686OC]
88 **Chen W**, Janz DR, Bastarache JA, May AK, O'Neal HR, Bernard GR, Ware LB. Prehospital aspirin use is associated with reduced risk of acute respiratory distress syndrome in critically ill patients: a propensity-adjusted analysis. *Crit Care Med* 2015; **43**: 801-807 [PMID: 25559436 DOI: 10.1097/CCM.0000000000000789]
89 **Erlich JM**, Talmor DS, Cartin-Ceba R, Gajic O, Kor DJ. Prehospitalization antiplatelet therapy is associated with a reduced incidence of acute lung injury: a population-based cohort study. *Chest* 2011; **139**: 289-295 [PMID: 20688925 DOI: 10.1378/chest.10-0891]
90 **Kor DJ**, Carter RE, Park PK, Festic E, Banner-Goodspeed VM, Hinds R, Talmor D, Gajic O, Ware LB, Gong MN; US Critical Illness and Injury Trials Group: Lung Injury Prevention with Aspirin Study Group (USCIITG: LIPS-A). Effect of Aspirin on Development of ARDS in At-Risk Patients Presenting to the Emergency Department: The LIPS-A Randomized Clinical Trial. *JAMA* 2016; **315**: 2406-2414 [PMID: 27179988 DOI: 10.1001/jama.2016.6330]
91 **Emmet O'Brien M**, Restrepo MI, Martin-Loeches I. Update on the combination effect of macrolide antibiotics in community-acquired pneumonia. *Respir Investig* 2015; **53**: 201-209 [PMID: 26344609 DOI: 10.1016/j.resinv.2015.05.003]
92 **Walkey AJ**, Wiener RS. Macrolide antibiotics and survival in patients with acute lung injury. *Chest* 2012;

141: 1153-1159 [PMID: 22116799 DOI: 10.1378/chest.11-1908]
93 **Krüger S**, Welte T. Biomarkers in community-acquired pneumonia. *Expert Rev Respir Med* 2012; **6**: 203-214 [PMID: 22455492 DOI: 10.1586/ers.12.6]

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CASE REPORT

Tuberculosis septic shock, an elusive pathophysiology and hurdles in management: A case report and review of literature

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Abstract

BACKGROUND

Tuberculosis (TB) is a rare etiology of the septic shock. Timely administration of the anti-microbial agents has shown mortality benefit. Prompt diagnosis and a high index of suspicion are crucial to the management. We present three cases of TBSS with poor outcome in the majority despite timely and susceptible antibiotic administration.

CASE SUMMARY

Sixty-seven-year-old woman with latent TB presented with fever, cough, and shortness of breath. She was promptly diagnosed with active TB and started on the appropriate anti-microbial regimen; she had a worsening clinical course with septic shock and multi-organ failure after initiation of antibiotics. Thirty-three-year-old man immunocompromised with acquired immune deficiency syndrome presented with fever, anorexia and weight loss. He had no respiratory symptoms, and first chest X-ray was normal. He had enlarged liver, spleen and lymph nodes suspicious for lymphoma. Despite broad-spectrum antibiotics, he succumbed to refractory septic shock and multi-organ failure. It was shortly before his death that anti-TB antimicrobials were initiated based on pathology reports of bone marrow and lymph node biopsies. Forty-nine-year-old woman with asthma and latent TB admitted with cough and shortness of breath. Although Initial sputum analysis was negative, a subsequent broncho-alveolar lavage turned out to be

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positive for acid fast bacilli followed by initiation of susceptible ant-TB regimen. She had a downward spiral clinical course with shock, multi-organ failure and finally death.

CONCLUSION
Worse outcome despite timely initiation of appropriate antibiotics raises suspicion of TB immune reconstitution as a possible pathogenesis for TB septic shock.

Key words: Tuberculosis septic shock; Tuberculosis and immune reconstitution; Tuberculosis in intensive care unit; Case fatality for tuberculosis septic shock; Case report

Core tip: Tuberculosis septic shock is a rare entity. We present three cases of tuberculosis septic shock with varied clinical manifestations. Mycobacterium tuberculosis culture or nucleic acid amplification testing confirmed diagnosis of tuberculosis. All of our presented cases had poor outcome despite timely administration of appropriate anti-tuberculosis regimen. There was clinical and radiological deterioration after administration of anti-microbial agents. This deteriorating clinical course raises a concern for immune reconstitution as possible pathogenesis for tuberculosis septic shock.

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INTRODUCTION

Sepsis is a significant burden on healthcare across the globe[1]. In United States, there are 970000 cases of sepsis annually[2]. In United States overall sepsis, related mortality is 12.5%. The severity of sepsis affects outcomes, with 35% mortality in septic shock[2]. Prompt diagnosis and early treatment is key to management. Any delay in antibiotics administration is associated with the worsening of sepsis severity[3].

Martin *et al*[4] analyzed 2.6 million sepsis cases from the premier database in United States, for six years. Fifteen percent of patients did not manifest sepsis at the time of hospitalization. The mortality outcomes were worst in this group of patients. The group of patients with sepsis at presentation have lower mortality. This improved outcome may be attributed to the timely diagnosis and prompt antibiotics administration.

Empiric antibiotic administration within one hour of presentation has been proven to lower sepsis-related mortality[5]. Broad spectrum anti-microbial agents are selected based on the most common gram positive and gram negative bacterial infection[6]. Respiratory tract infection is the most common etiology for sepsis and septic shock[7]. Tuberculosis (TB) is an uncommon but well-recognized etiology of sepsis and is seldom discussed in the western population.

Mycobacterium tuberculosis is an acid-fast bacteria with a predominant pulmonary presentation[8], though not a frequent cause of pneumonia in the western population. Only twenty percent of the cases have a sole extra-pulmonary manifestation[8]. The incidence of TB septic shock (TBSS) though not reported, is sporadic. The Center for Disease Control and Prevention have reported a declining incidence in the diagnosis of TB[9]. The rarity of TBSS makes this case series novel. We describe three cases of TBSS that presented in our institution. Despite the diagnosis of sepsis at presentation, case fatality rate is very high, as opposed to the general expectation in sepsis epidemiology[2]. Each case is unique with its presentation, and this case series provides an excellent opportunity to analyze the demographic features, clinical characteristics, radiologic and laboratory findings as well as the pitfalls in the management of patients with TBSS.

CASE PRESENTATION

Case 1

Chief complaint: A 67-year-old female presented to the emergency department with progressively worsening shortness of breath and fever.

History of present illness: The patient complained of twenty pounds' weight loss over three months. She had shortness of breath, fever and productive cough for a duration of four weeks.

History of past illness: She had medical conditions of hypertension, chronic obstructive pulmonary disease, gastroesophageal reflux disease, gout and a 40-pack year history of smoking. She lived at home and had a history of exposure to TB when she was 9 years old as well as a known positive tuberculin skin test. She had never traveled outside the country.

Physical examination: Her vital signs were significant for low-grade fever of 37.9 °C, heart rate of 110 beats per minute, blood pressure of 165/100 mm of Hg and oxygen saturation of 96% on room air. She had bilateral rales on lung auscultation and rest of the physical exam was unremarkable

Laboratory examinations: Blood analysis was significant for hyponatremia (sodium 118 mEq/L) and anemia (Hemoglobin 7.3g/dL).

Imaging examinations: Chest X-ray and computed tomography (CT) scan on admission showed bilateral patchy infiltrates predominantly in the upper lobes (Figure 1A and B).

Treatment: Ceftriaxone and azithromycin were initiated for community-acquired pneumonia (CAP), and she was admitted to intensive care unit (ICU) for sepsis and hyponatremia. She was also placed in respiratory isolation due to high suspicion for TB. On day 2 of admission, sputum acid fast bacilli (AFB) stain was reported positive, and the patient was started on isoniazid, rifampin, ethambutol, and pyrazinamide (RIPE) for *Mycobacterium tuberculosis*. Human immunodeficiency virus (HIV) test was negative. *Mycobacterium tuberculosis* was confirmed by polymerase chain reaction (PCR) before the final culture report. Subsequently, she became progressively more hypoxic and hypotensive requiring mechanical ventilation and vasopressor support. Chest X-ray after intubation showed worsening of bilateral lung infiltrates (Figure 1C). She developed multi-organ failure secondary to shock including hepatic and renal dysfunction requiring hemodialysis. Patient was also initiated on high dose steroids, and antibiotic coverage was broadened with no significant improvement in hemodynamic status.

Final diagnosis: Septic shock due to *Mycobacterium tuberculosis*.

Outcome and follow up: Due to poor prognosis and no improvement in the patient's condition, the family wished for transfer to hospice care and patient died on day 22 of hospitalization. Final culture and susceptibility reports confirmed sensitivity to RIPE.

Case 2

Chief complaints: A 33-year-old man was called to come to the emergency department for abnormal laboratory results.

History of present illness: In the emergency department he reported subjective fever, poor appetite and weight loss for one month. He also reported diarrhea for past few days but no abdominal pain, nausea, vomiting, cough or shortness of breath.

History of past illness: Patient had known history of HIV/acquired immune deficiency syndrome (AIDS) not adherent to antiretroviral medications with very high viral load and CD4 count of less than 20, past intravenous drug use and active tobacco dependence. He had history of anemia and deep vein thrombosis and was living in a nursing home for few months prior to presentation. He was born in Puerto Rico and came to the Unites States a year ago.

Physical examination upon admission: His vital signs were significant for hypotension with blood pressure of 91/60 mmHg, tachycardia with heart rate of 130 beats per minute and fever with temperature of 39.4 °C. On physical examination he was lethargic and confused. Hypotension initially improved with intravenous fluids

Laboratory examinations: Initial laboratory data was significant for leukocytosis of 31151/μL and hyponatremia (sodium 121 mEq/L).

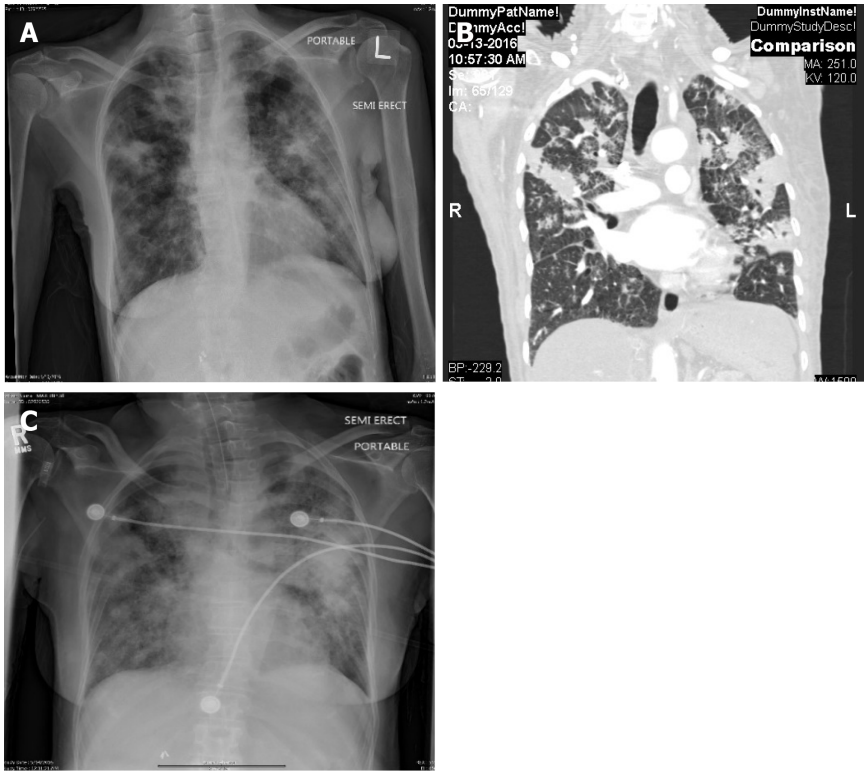

Figure 1 Chest X-ray and computed tomography (case 1). A: Chest X-ray demonstrating the bilateral patchy infiltrates at the time of admission; B: Computed tomography scans of chest with coronal section demonstrating bilateral patchy infiltrates at the time of admission; C: X-ray chest demonstrating worsening of the bilateral infiltrates after intubation and initiation of anti tuberculosis medications.

Imaging examinations: Chest X-ray on admission showed no infiltrates (Figure 2A). Ultrasound of abdomen was significant for hepatosplenomegaly, ascites and enlarged peri-pancreatic lymph nodes

Treatment: Patient was admitted to the critical care unit with a presumptive diagnosis of sepsis and initiated on the broad spectrum antibiotics (vancomycin and piperacillin-tazobactam). He was started on metronidazole for suspected *Clostridium difficile* colitis. Subsequently he developed acute hypoxic respiratory failure and septic shock requiring intubation and vasopressor support. Chest X-ray after intubation showed new bilateral infiltrates (Figure 2B). Blood cultures were negative. He underwent lumbar puncture which showed an opening pressure of 35 cm of H_2O, red blood cell (RBC) of 1825 cells/dL, white blood cell count of 1 cell/dL, glucose of 65 mg/dL and protein 36 mg/dL. In view of significant RBC count in cerebrospinal fluid (CSF) and high opening pressure, he was also initiated on acyclovir as empiric treatment for herpes simplex encephalitis. Broncho alveolar lavage (BAL) was negative for bacterial, viral, fungal and *Pneumocystis jirovecii* cultures. Initial smears for AFB were negative. The CSF bacterial cultures and herpes simplex virus PCR were negative. He was initiated on antiretroviral therapy on day 8 of hospitalization after preliminary cultures were negative. In view of persistent fever spikes and lymphadenopathy, hematology consultation was obtained and patient underwent bone marrow biopsy, and right axillary lymph node biopsy. Caspofungin was added to his antibiotic regimen for refractory septic shock and persistent fever. Bone marrow biopsy was positive for acid fast organisms. Pathology of right axillary lymph node biopsy reported as necrotizing granulomas with mycobacteria. An empiric treatment for *Mycobacterium tuberculosis* and mycobacterium avium complex with Isoniazide, Ethambutol, Rifabutin, pyrazinamide and clarithromycin was initiated awaiting final confirmation

Final diagnosis: Septic shock due to *Mycobacterium tuberculosis*.

Outcome and follow up: Patient died secondary to worsening shock and multi organ failure after 22 d of admission. Sputum, BAL and peritoneal fluid cultures were reported positive for *Mycobacterium tuberculosis* complex post mortem and susceptibility reports confirmed no resistance.

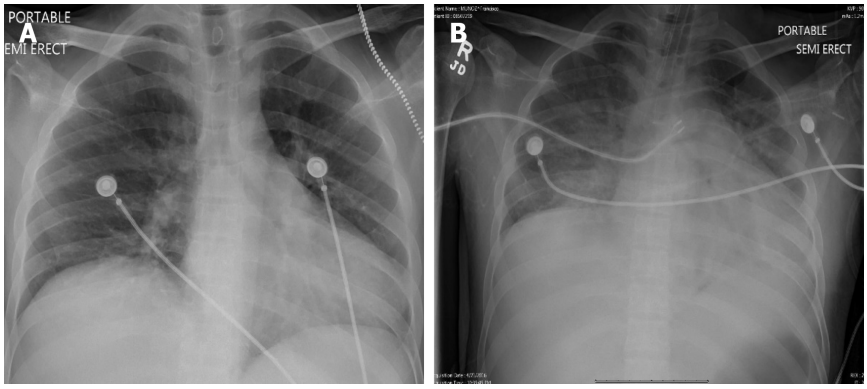

Figure 2 X-ray chest (case 2). A: X-ray chest with no infiltrates at the time of admission; B: X-ray chest with new infiltrates and hypoxia requiring intubation and mechanical ventilation.

Case 3

Chief complaints: A 49-year-old woman presented to the hospital with productive cough for three to four weeks.

History of present illness: Patient presented with worsening cough, shortness of breath and wheezing. She denied fever, chills, weight loss, recent travel or sick contacts.

History of past illness: Her medical conditions included hypertension, latent TB (treated for 6 mo in 2007 as per patient), Asthma and smoking.

Physical examination upon admission: Vital signs were significant for mild tachycardia with heart rate of 114 beats per minute. She was afebrile with normal blood pressure and oxygen saturation of 98% on room air. There was bilateral wheezing on auscultation and rest of the examination was unremarkable.

Laboratory examinations: Initial blood analysis revealed leukocytosis with white blood cell count of 11300 cells/μL. Her electrolytes and liver function tests were normal except a high alkaline phosphatase level of 111 unit/dL.

Imaging examinations: Chest X-ray on admission showed a stable left upper lobe thick walled cavity and new left lower lobe infiltrates in comparison to the chest X-ray done few weeks ago (Figure 3A). CT of the chest was done which revealed additional left lung thick walled cavities and multiple nodules on both sides (Figure 3B).

Treatment: Given the high suspicion for TB she was placed on respiratory isolation, and started on broad spectrum antibiotics with intravenous piperacillin-tazobactam and vancomycin. Three sputum samples were initially negative for AFB. Differential diagnoses included pulmonary TB, atypical mycobacteria and fungal infections. She underwent bronchoscopy, BAL and trans bronchial biopsy. The BAL stains were positive for AFB and mycobacterium TB was identified with DNA probe and subsequent cultures. Cultures from BAL also grew pseudomonas aeruginosa in low colony counts of 1000-9000 CFU/mL. Pseudomonas was pan sensitive. Antibiotics were titrated, with initiation of RIPE and discontinuation of vancomycin.

Final diagnosis: Septic shock due to *Mycobacterium tuberculosis*.

Outcome and follow up: On day 6 of admission, her respiratory status declined to require intubation for hypoxic respiratory failure and transfer to ICU. She developed worsening bilateral infiltrates (Figure 3C), hyponatremia (sodium 125 mEq/L) and septic shock. She remained in shock and died on day 12 of hospitalization.

DISCUSSION

There is ample literature to support the case fatality of TBSS[10]. It is evident that prompt identification and early antibiotic administration improves mortality. The mortality risk factors of TB patient who are critically ill have been identified[11]. However, given the scantiness of TBSS, no standard protocol is constructed to improve the outcomes of this rare entity. We reviewed our cases and analyzed them to determine the hurdles in the management of TBSS. To better understand the

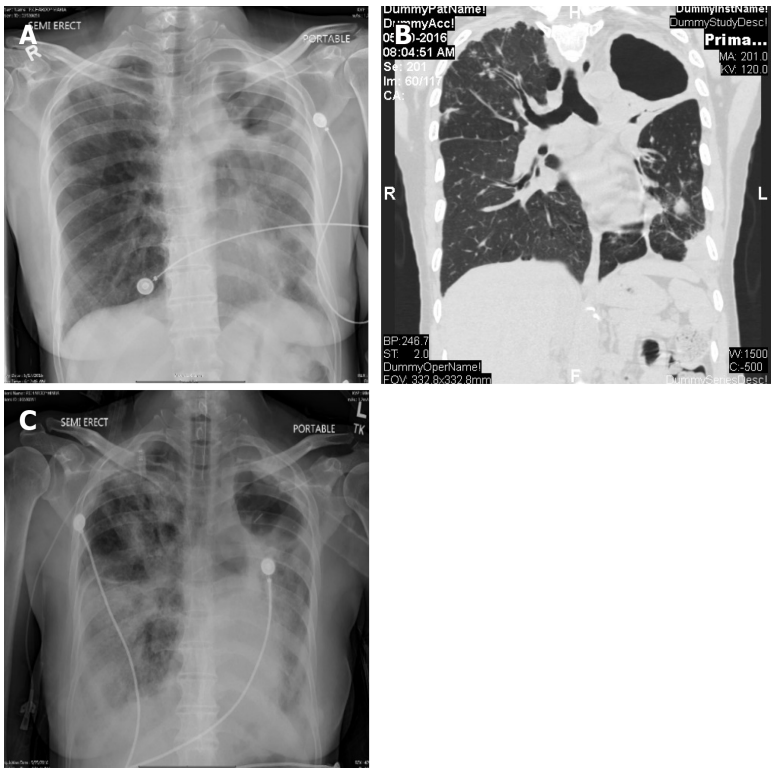

Figure 3 X-ray chest and computerized axial tomography (case 3). A: X-ray chest revealing the left upper lobe cavity and left lower lobe infiltrates at time of admission; B: Computerized axial tomography scan of the chest at time of admission revealing left lung thick walled cavities and multiple nodules on both side; C: X-ray chest revealing worsening of the bilateral infiltrate after intubation and of the anti-tuberculosis medications.

management of TBSS we divided it into several categories. This includes understanding pathophysiology of TBSS, high risk clinical features, modalities for prompt diagnosis and utility of empiric TB treatment based on clinical suspicion.

TBSS is extremely rare. Kethireddy *et al*[10], in a limited institutional review across the globe, could identify TBSS as etiology of septic shock in 1% of the cases in a pool of 5419 patients. A Majority of them were identified outside the United States. The incidence in United States was almost undetectable. Given the clinical rarity of TB in a low prevalence area[10] the suspicion for diagnosis is low. Hence areas of high prevalence of TB should be identified. California leads the TB incidence rate in United States, followed by Texas, New York, and Florida[12]. Over a one-year duration in New York, there was a 10% increase in the number of TB cases from 2016 to 2017[13]. Each institution should identify their level of risk for TB based on the geography and the time trends in the incidence of TB.

Clinical features such as fever of prolonged duration, typical chest radiograph findings, latent TB as diagnosed by a positive skin tuberculin test[14] are highly suspicious for active TB infection. Akin to these clinical parameters a predictive model has been proposed for the diagnosis of TB in hospitalized patients[15]. Hence, the amalgam of high geographic prevalence along with time trends and symptomatic suspicion for active TB should be used towards the clinical acumen for early identification of high-risk cases.

An efficient testing protocol should be promptly paired with high clinical suspicion for TB to arrive at a definitive diagnosis. Pulmonary manifestations are the most common presentations. Typical chest radiologic findings have a major role in high clinical suspicion. However, it lacks specificity[16]. Chest X-ray and clinical features can be miss-interpreted as CAP[17]. Patients are frequently managed with the CAP targeted anti-microbial agents prior to diagnosis of TB[18]. Sputum microscopy with acid-fast staining, the initial step in diagnosis, is prompt and simple though at the expense of reliability due to low sensitivity[19]. The determination of pulmonary TB, as per WHO recommendation, requires demonstration of bacteria in the sputum[20]. A sputum culture is reliable, preferred and gold standard for diagnosis of pulmonary TB. However, cultures come with the expense of time and take two to six weeks for them to be reported[19]. The nucleic acid amplification testing (NAAT) in sputum is a perfect blend of swiftness and reliability[21] to derive a microbiological conclusion and to initiate the TB anti-microbial agents. The sensitivities differ in the sputum positive

and negative TB patient[21]. There is an increase in the utilization of the NAAT over time[22]. There is no consensus on performing NAA for all hospitalized patients with suspected active TB. Centers for Disease Control recommends sputum NAAT on at least one sputum specimen in a patient with clinical signs suggestive of TB if the intended test changes the management by establishing the diagnosis[23,24].

The clinical manifestations of TB for patients with HIV induced immunosuppression are unalike to immunocompetent host. HIV infected individuals are more likely to have extra-pulmonary TB as compared to HIV negative individuals[25]. Those with lower CD4 count are more likely to have extra-pulmonary TB[26]. A wide array of the differentials for the systemic illness in patients with advanced AIDS, as in our scenario, makes the diagnosis of the disseminated TB challenging. HIV infected individuals with TB can have atypical chest radiological findings[27], with a small proportion of them with normal chest radiographs[24]. These adversities of atypical manifestations in conjunction with uncharacteristic radiological findings in patients with HIV hinders the early administration of anti-TB medication and hence can have worse outcomes in TBSS.

The culture of empiric treatment of TB differs across the globe. We assume that the incidence and prevalence of the disease guides the trend. The term "empiric" depicts two fundamental concepts. First is the presumptive treatment for a suspicious disease while awaiting the diagnosis. Second is the presumptive regimen while expecting the culture and sensitivity. Both parameters will affect the outcomes in sepsis. Molecular drug-resistance tests is prompt in detecting the drug resistance to isoniazid and rifampicin[28] and can be used to titrate the anti-TB medication. However, given our limited experience and the rare entity of TBSS, it is difficult to opine on routine use of molecular drug-resistance tests for the management of TBSS. We performed a standard drug susceptibility testing in the management of our patients, and no drug resistance was identified.

Time is of the essence in the management of sepsis. The timing of the antibiotics is categorized as: (1) The timing from emergency room triage; and (2) Timing from the onset of sepsis or septic shock[29]. We carefully dissected Kethireddy *et al*[10]'s findings to review the "timing" of antibiotics administration and outcome of TBSS. The administration of the anti-tuberculous medications within 24 h of septic shock had improved mortality outcomes. In our cases, we used our clinical acumen to arrive at a prompt diagnosis of TB with appropriate susceptibility testing and timely administration of anti-TB medications. Despite optimal management, the outcomes were worst. These paradoxical findings ignited our curiosity to dig deeper into the pathogenesis of TBSS.

The systemic inflammatory response syndrome (SIRS) is defined by the host immune response in the form of four variables: Heart rate, respiratory rate, temperature and leukocytosis[30]. Given the variable immune response, there were some shortcomings to this definition of sepsis[31]. The inflammatory response can be severe enough to cause the circulatory and metabolic abnormality identified as a septic shock[32]. A prompt antibiotic administration targeting the inciting etiology of SIRS should lead to the prevention of septic shock. However, in our cases, we observed a paradoxical clinical worsening after administration of TB anti-microbial agents which may be explained by post-antibiotic immune reconstitution inflammatory syndrome (IRIS).

In our immunocompetent patients, the clinical course worsened after the initiation of anti-TB medications. In Kethireddy *et al*[10]'s cases and other series[33] of critically ill TB patients, we were unable to retrieve any similar observations of exacerbation of TB induced sepsis after antibiotics administration. In HIV coinfection the entity of IRIS is well recognized[34]. However, a paradoxical worsening during the anti-TB therapy may be linked to TB IRIS in the HIV negative population[35]. In HIV uninfected TB IRIS has an extra-pulmonary presentation and a chronic course[36]. The pathogenesis of TB IRIS in the non-HIV has been proposed[37] but is not widely implemented in clinical practice. TB bacillary load has been identified as one of the risk factors for TB IRIS[38]. Prednisone has been utilized for the prevention of IRIS[39]. However, there is no clear consensus on steroid use in HIV negative patients, but can be considered[37]. A careful review of the clinical course in a few case reports and series depicts a similar clinical course[40-42]. Hence, one should evaluate the possibility of IRIS in clinical scenarios of TBSS after TB antimicrobial administration.

Hyponatremia is another striking feature in our patients. Hyponatremia is prevalent in patients with pulmonary TB and severity correlates with extensive pulmonary parenchymal involvement and sputum positivity[43]. This correlation depicts the possibility of a high TB bacterial load in patients with hyponatremia. The pathogenies of hyponatremia, though poorly understood, has been linked to inappropriate secretion of the antidiuretic hormone[44]. Hyponatremia, though not statistically significant, has been related to high mortality rates in a patient with

pulmonary TB[45]. But the rapid demise of the immunocompetent patients after TB antimicrobial administration begs to ask the question if there is any correlation of hyponatremia to high TB bacterial load and IRIS. To our knowledge, there is no study protocol exploring this specific rationale. Given the scarcity of data, we do want to conclude on this fact of hyponatremia and TB IRIS as an "observation" rather than "strong association".

The pathogenesis and clinical course of TB differ in immunocompromised patients with frequent atypical presentation and extrapulmonary dissemination[46]. TB may lead to worsening of HIV viremia and acceleration of immunosuppression[47], hence increasing HIV related mortality[48]. In our patient with HIV co-infection, the onset of the septic shock was before the TB diagnosis and medication administration. Clinical findings were suggestive of the disseminated TB. The patient was on intravenous steroids prior to the anti-TB microbial administration. This reveals different pathophysiology then our immunocompetent hosts. The immune dysregulation is more likely from the bacterial infection rather than immune-reconstruction. However, advanced HIV could have contributed to the mortality despite anti-TB microbial administration.

CONCLUSION

TBSS is well recognized and widely reported though at risk of delayed diagnosis because of rare incidence in the United States. Antibiotics administration within 24 hours of the septic shock has been shown to improve mortality outcome in TBSS. High degree of suspicion and sputum NAA can be utilized towards rapid diagnosis and prompt administration of susceptible antibiotics. The pathogenesis of TBSS does differ in immunocompromised patients as opposed to immunocompetent. The paradoxical clinical worsening of patients with TB after susceptible antibiotics administration leading to TBSS does arise the possibility of TB IRIS. Our series though limited to 'observational remark' for TB IRIS as pathogenesis in an immunocompetent host does appeal a need for the future registry to evaluate this phenomenon.

REFERENCES

1 **Rudd KE**, Kissoon N, Limmathurotsakul D, Bory S, Mutahunga B, Seymour CW, Angus DC, West TE. The global burden of sepsis: Barriers and potential solutions. *Crit Care* 2018; **22**: 232 [PMID: 30243300 DOI: 10.1186/s13054-018-2157-z]

2 **Paoli CJ**, Reynolds MA, Sinha M, Gitlin M, Crouser E. Epidemiology and Costs of Sepsis in the United States-An Analysis Based on Timing of Diagnosis and Severity Level. *Crit Care Med* 2018; **46**: 1889-1897 [PMID: 30048332 DOI: 10.1097/CCM.0000000000003342]

3 **Whiles BB**, Deis AS, Simpson SQ. Increased Time to Initial Antimicrobial Administration Is Associated With Progression to Septic Shock in Severe Sepsis Patients. *Crit Care Med* 2017; **45**: 623-629 [PMID: 28169944 DOI: 10.1097/CCM.0000000000002262]

4 **Martin GS**, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; **348**: 1546-1554 [PMID: 12700374 DOI: 10.1056/NEJMoa022139]

5 **Ferrer R**, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, Artigas A, Schorr C, Levy MM. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: Results from a guideline-based performance improvement program. *Crit Care Med* 2014; **42**: 1749-1755 [PMID: 24717459 DOI: 10.1097/CCM.0000000000000330]

6 **Buckman SA**, Turnbull IR, Mazuski JE. Empiric Antibiotics for Sepsis. *Surg Infect (Larchmt)* 2018; **19**: 147-154 [PMID: 29341844 DOI: 10.1089/sur.2017.282]

7 **Mayr FB**, Yende S, Angus DC. Epidemiology of severe sepsis. *Virulence* 2014; **5**: 4-11 [PMID: 24335434 DOI: 10.4161/viru.27372]

8 **Heemskerk D**, Caws M, Marais B, Farrar J. Tuberculosis in Adults and Children 2015 [PMID: 26937536 DOI: 10.1007/978-3-319-19132-4]

9 **Sosa LE**, Njie GJ, Lobato MN, Morris SB, Buchta W, Casey ML, Goswami ND, Gruden M, Hurst BJ, Khan AR, Kuhar DT, Lewinsohn DM, Mathew TA, Mazurek GH, Reves R, Paulos L, Thanassi W, Will L, Belknap R. Tuberculosis Screening, Testing, and Treatment of U.S. Health Care Personnel: Recommendations from the National Tuberculosis Controllers Association and CDC, 2019. *MMWR Morb Mortal Wkly Rep* 2019; **68**: 439-443 [DOI: 10.1111/ajt.15512]

10 **Kethireddy S**, Light RB, Mirzanejad Y, Maki D, Arabi Y, Lapinsky S, Simon D, Kumar A, Parrillo JE, Kumar A; Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Group. Mycobacterium tuberculosis septic shock. *Chest* 2013; **144**: 474-482 [PMID: 23429859 DOI: 10.1378/chest.12-1286]

11 **Silva DR**, Menegotto DM, Schulz LF, Gazzana MB, Dalcin PT. Mortality among patients with tuberculosis requiring intensive care: A retrospective cohort study. *BMC Infect Dis* 2010; **10**: 54 [PMID: 20205952 DOI: 10.1186/1471-2334-10-54]

12 **Talwar A**, Tsang CA, Price SF, Pratt RH, Walker WL, Schmit KM, Langer AJ. Tuberculosis—United States, 2018. *MMWR Morb Mortal Wkly Rep* 2019; **68**: 257-262 [DOI: 10.15585/mmwr.mm6811a2]

13 **New York city bureau of tuberculosis control**. Available from: https://www1.nyc.gov/assets/doh/downloads/pdf/tb/tb2017.pdf

14 **Frigati L**, Maskew M, Workman L, Munro J, Andronikou S, Nicol MP, Zar HJ. Clinical Predictors of Culture-confirmed Pulmonary Tuberculosis in Children in a High Tuberculosis and HIV Prevalence Area.

Pediatr Infect Dis J 2015; **34**: e206-e210 [PMID: 26376315 DOI: 10.1097/INF.0000000000000792]
15 **Wisnivesky JP**, Kaplan J, Henschke C, McGinn TG, Crystal RG. Evaluation of clinical parameters to predict Mycobacterium tuberculosis in inpatients. *Arch Intern Med* 2000; **160**: 2471-2476 [PMID: 10979058 DOI: 10.1001/archinte.160.16.2471]
16 **Kumar N**, Bhargava SK, Agrawal CS, George K, Karki P, Baral D. Chest radiographs and their reliability in the diagnosis of tuberculosis. *JNMA J Nepal Med Assoc* 2005; **44**: 138-142 [PMID: 16751817]
17 **Woodring JH**, Vandiviere HM, Fried AM, Dillon ML, Williams TD, Melvin IG. Update: The radiographic features of pulmonary tuberculosis. *AJR Am J Roentgenol* 1986; **146**: 497-506 [PMID: 3484866 DOI: 10.2214/ajr.146.3.497]
18 **Wang M**, Fitzgerald JM, Richardson K, Marra CA, Cook VJ, Hajek J, Elwood RK, Bowie WR, Marra F. Is the delay in diagnosis of pulmonary tuberculosis related to exposure to fluoroquinolones or any antibiotic? *Int J Tuberc Lung Dis* 2011; **15**: 1062-1068 [PMID: 21740669 DOI: 10.5588/ijtld.10.0734]
19 **WHO**. World Health Organization. Early detection of tuberculosis: An overview of approaches, guidelines and tools. Geneva: World Health Organization 2011;
20 **WHO**. World Health Organization. Definitions and reporting framework for tuberculosis: 2013 revision (updated December 2014). Geneva: World Health Organization, 2013.
21 **Greco S**, Girardi E, Navarra A, Saltini C. Current evidence on diagnostic accuracy of commercially based nucleic acid amplification tests for the diagnosis of pulmonary tuberculosis. *Thorax* 2006; **61**: 783-790 [PMID: 16738037 DOI: 10.1136/thx.2005.054908]
22 **Tyrrell F**, Stafford C, Yakrus M, Youngblood M, Hill A, Johnston S. Trends in Testing for Mycobacterium tuberculosis Complex From US Public Health Laboratories, 2009-2013. *Public Health Rep* 2017; **132**: 56-64 [PMID: 28005481 DOI: 10.1177/0033354916679989]
23 **Centers for Disease Control and Prevention**. Available from: https://www.cdc.gov/tb/publications/guidelines/amplification_tests/reccomendations.htm
24 **Ryu YJ**. Diagnosis of pulmonary tuberculosis: Recent advances and diagnostic algorithms. *Tuberc Respir Dis (Seoul)* 2015; **78**: 64-71 [PMID: 25861338 DOI: 10.4046/trd.2015.78.2.64]
25 **Chaisson RE**, Schecter GF, Theuer CP, Rutherford GW, Echenberg DF, Hopewell PC. Tuberculosis in patients with the acquired immunodeficiency syndrome. Clinical features, response to therapy, and survival. *Am Rev Respir Dis* 1987; **136**: 570-574 [PMID: 3631730 DOI: 10.1164/ajrccm/136.3.570]
26 **Jones BE**, Young SM, Antoniskis D, Davidson PT, Kramer F, Barnes PF. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. *Am Rev Respir Dis* 1993; **148**: 1292-1297 [PMID: 7902049 DOI: 10.1164/ajrccm/148.5.1292]
27 **Geng E**, Kreiswirth B, Burzynski J, Schluger NW. Clinical and radiographic correlates of primary and reactivation tuberculosis: A molecular epidemiology study. *JAMA* 2005; **293**: 2740-2745 [PMID: 15941803 DOI: 10.1001/jama.293.22.2740]
28 **Chavalertsakul K**, Boonsarngsuk V, Saengsri S, Santanirand P. TB-PCR and drug resistance pattern in BALF in smear-negative active pulmonary TB. *Int J Tuberc Lung Dis* 2017; **21**: 1294-1299 [PMID: 28992819 DOI: 10.5588/ijtld.17.0326]
29 **Sterling SA**, Miller WR, Pryor J, Puskarich MA, Jones AE. The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis. *Crit Care Med* 2015; **43**: 1907-1915 [PMID: 26121073 DOI: 10.1097/CCM.0000000000001142]
30 **Marik PE**, Taeb AM. SIRS, qSOFA and new sepsis definition. *J Thorac Dis* 2017; **9**: 943-945 [PMID: 28523143 DOI: 10.21037/jtd.2017.03.125]
31 **Vincent JL**, Opal SM, Marshall JC, Tracey KJ. Sepsis definitions: Time for change. *Lancet* 2013; **381**: 774-775 [PMID: 23472921 DOI: 10.1016/S0140-6736(12)61815-7]
32 **Singer M**, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315**: 801-810 [PMID: 26903338 DOI: 10.1001/jama.2016.0287]
33 **Duro RP**, Figueiredo Dias P, Ferreira AA, Xerinda SM, Lima Alves C, Sarmento AC, Dos Santos LC. Severe Tuberculosis Requiring Intensive Care: A Descriptive Analysis. *Crit Care Res Pract* 2017; **2017**: 9535463 [PMID: 28250986 DOI: 10.1155/2017/9535463]
34 **Meintjes G**, Lawn SD, Scano F, Maartens G, French MA, Worodria W, Elliott JH, Murdoch D, Wilkinson RJ, Seyler C, John L, van der Loeff MS, Reiss P, Lynen L, Janoff EN, Gilks C, Colebunders R, International Network for the Study of HIV-associated IRIS. Tuberculosis-associated immune reconstitution inflammatory syndrome: Case definitions for use in resource-limited settings. *Lancet Infect Dis* 2008; **8**: 516-523 [PMID: 18652998 DOI: 10.1016/S1473-3099(08)70184-1]
35 **Cheng VC**, Ho PL, Lee RA, Chan KS, Chan KK, Woo PC, Lau SK, Yuen KY. Clinical spectrum of paradoxical deterioration during antituberculosis therapy in non-HIV-infected patients. *Eur J Clin Microbiol Infect Dis* 2002; **21**: 803-809 [PMID: 12461590 DOI: 10.1007/s10096-002-0821-2]
36 **Lanzafame M**, Vento S. Tuberculosis-immune reconstitution inflammatory syndrome. *J Clin Tuberc Other Mycobact Dis* 2016; **3**: 6-9 [DOI: 10.1016/j.jctube.2016.03.002]
37 **Sun HY**, Singh N. Immune reconstitution inflammatory syndrome in non-HIV immunocompromised patients. *Curr Opin Infect Dis* 2009; **22**: 394-402 [PMID: 19483618 DOI: 10.1097/QCO.0b013e32832d7aff]
38 **Cheng SL**, Wang HC, Yang PC. Paradoxical response during anti-tuberculosis treatment in HIV-negative patients with pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2007; **11**: 1290-1295 [PMID: 18034948 DOI: 10.1080/01902140701756778]
39 **Meintjes G**, Stek C, Blumenthal L, Thienemann F, Schutz C, Buyze J, Ravinetto R, van Loen H, Nair A, Jackson A, Colebunders R, Maartens G, Wilkinson RJ, Lynen L; PredART Trial Team. Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS. *N Engl J Med* 2018; **379**: 1915-1925 [PMID: 30428290 DOI: 10.1056/NEJMoa1800762]
40 **Bridges DA**, Bedimo RG. Severe tuberculosis sepsis in an immunocompetent patient. *Am J Med* 2006; **119**: e11-e14 [PMID: 16490454 DOI: 10.1016/j.amjmed.2005.08.033]
41 **Nidadavolu VG**, Shah M, Kuriti M. Tuberculosis Presenting As "SEPSIS"! -An Interesting Presentation Of Miliary Tuberculosis. *ATS J* 2013; A3213-A3213
42 **Michel P**, Barbier C, Loubière Y, Hayon JH, Ricôme JL. Three cases of septic shock due to tuberculosis without HIV pathology. *Intensive Care Med* 2002; **28**: 1827-1828 [PMID: 12447531 DOI: 10.1007/s00134-002-1526-9]
43 **Bokam BR**, Badikillaya VU. Prevalence of hyponatremia in pulmonary tuberculosis–A pilot study from a

tertiary care center in south India. *Int J Med Sci Public Health* 2017; **6**: 75-79 [DOI: 10.5455/ijmsph.2017.20062016560]

44 **Lee P**, Ho KK. Hyponatremia in pulmonary TB: Evidence of ectopic antidiuretic hormone production. *Chest* 2010; **137**: 207-208 [PMID: 20051406 DOI: 10.1378/chest.09-0405]

45 **Vargasa T**, Morales-Garza LA, Maya R, Llamas-Lopez A. Available from: https://idsa.confex.com/idsa/2018/webprogram/Paper72122.html

46 **Aaron L**, Saadoun D, Calatroni I, Launay O, Mémain N, Vincent V, Marchal G, Dupont B, Bouchaud O, Valeyre D, Lortholary O. Tuberculosis in HIV-infected patients: A comprehensive review. *Clin Microbiol Infect* 2004; **10**: 388-398 [PMID: 15113314 DOI: 10.1111/j.1469-0691.2004.00758.x]

47 **Garrait V**, Cadranel J, Esvant H, Herry I, Morinet P, Mayaud C, Israël-Biet D. Tuberculosis generates a microenvironment enhancing the productive infection of local lymphocytes by HIV. *J Immunol* 1997; **159**: 2824-2830 [PMID: 9300705]

48 **Whalen C**, Horsburgh CR, Hom D, Lahart C, Simberkoff M, Ellner J. Accelerated course of human immunodeficiency virus infection after tuberculosis. *Am J Respir Crit Care Med* 1995; **151**: 129-135 [PMID: 7812542 DOI: 10.1164/ajrccm.151.1.7812542]

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CASE REPORT

Successfully non-surgical management of flail chest as first manifestation of multiple myeloma: A case report

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Abstract

BACKGROUND

Multiple myeloma is a malignant neoplasm of the bone marrow characterized by neoplastic proliferation of monoclonal plasma cells with a high relationship with destructive bone disease. We present a case of a patient diagnosed with multiple myeloma and sternal fracture in association with multiple bilateral rib fractures and thoracic kyphosis, who developed a severe acute respiratory failure, thus complicating the initial presentation of multiple myeloma. We discuss the therapeutic implications of this uncommon presentation.

CASE SUMMARY

A 56-year-old man presented to Hematological Department after he had been experiencing worsening back pain over the last five months, with easy fatigability and progressive weight loss. He had no history of previous trauma. The chemical blood tests were compatible with a diagnosis of multiple myeloma. A radiographic bone survey of all major bones revealed, in addition to multiple bilateral rib fractures, a sternal fracture and compression fracture at T9, T10, T11 and L1 vertebrae. Subcutaneous fat biopsy was positive for amyloid. We started treatment with bortezomib and dexamethasone. After 24 h of treatment, he presented dyspnea secondary to flail chest. He required urgent intubation and ventilatory support being transferred to intensive care unit for further management. The patient remained connected to mechanical ventilation (positive pressure) as treatment which stabilized the thorax. A second cycle of bortezomib plus dexamethasone was started and analgesia was optimized. The condition of the patient improved, as evidenced by callus formation on successive computed tomography scans. The patient was taken off the ventilator one month later, and he was extubated successfully, being able to breathe unaided without paradoxical

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motion.

CONCLUSION
This case highlights the importance of combination between bortezomib and dexamethasone to induce remission of multiple myeloma and the initiation of positive airway pressure with mechanical ventilation to stabilize chest wall to solve the respiratory failure. This combined approach allowed to obtain a quick and complete resolution of the clinical situation.

Key words: Multiple myeloma; Flail chest; Bortezomib; Mechanical ventilation; Case report

Core tip: This case report describes an adult patient with acute respiratory failure, secondary to flail chest because of a multiple myeloma. It shows how positive pressure in airway, in conjunction with an early treatment with bortezomib and dexamethasone, may lead to a successful outcome for such patients with an otherwise poor prognosis.

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INTRODUCTION

Multiple myeloma is a malignant neoplasm of the bone marrow characterized by neoplastic proliferation of monoclonal plasma cells[1]. Approximately 70%-80% of patients with multiple myeloma eventually develop destructive bone disease[2]. Most of the lesions are localized in the spine, pelvis or proximal extremities, according to the regions of hematological active bone marrow[1,3].

CASE PRESENTATION

Chief complaints

We present a case of multiple bilateral rib fractures in association with sternal fracture and thoracic kyphosis who developed a severe acute respiratory insufficiency complicating the initial presentation of multiple myeloma.

History of present illness

A 56-year-old man presented to Hematological Department after he had been experiencing worsening back pain over the last five months, with easy fatigability, and progressive weight loss. He had no history of previous trauma.

History of past illness

Hypertension and mellitus diabetes, both under pharmacological treatment.

Physical examination

At intake, his blood pressure was 130/70 mmHg; pulse rate 70 beats/min; respiratory rate 14/min and body temperature 35.7 °C.

Laboratory examinations

Blood chemical test results were as follows: creatinine 4.22 mg/dL; glomerular filtration rate 15 mL/min; calcium 15.9 mg/dL and hemoglobin 6.7 g/dL. Serum β2-microglulin level was elevated at 9.42 mg/L and serum albumin level was 2.7 g/dL. The diagnosis of Kappa -light chain Bence-Jones multiple myeloma was established on the basis of a bone marrow infiltration by 66% atypical plasmatic cells and a monoclonal component kappa in serum (86 mg/dL) and in urine with a proteinuria of 2.9 g/24 h. Urine was positive for Bence-Jones proteins

Imaging examinations

A radiographic bone survey of all major bones revealed, in addition to multiple bilateral rib fractures (4th to 11th), the presence of a sternal fracture and compression fracture at T9, T10, T11 and L1 vertebrae. The thoracic computed tomography (CT) scan confirmed a depressed pathological fracture of the sternum (Figure 1A).

Further diagnostic work-up

With the results of the different tests, the patient was diagnosed with multiple myeloma. It was staged as Durie-Salmon stage IIIB and International Staging System IIIB. Subcutaneous fat biopsy was positive for amyloid.

FINAL DIAGNOSIS

The final diagnosis of the presented case was spontaneous sternal fracture secondary to multiple myeloma, with flail chest and acute respiratory failure as the main consequence.

TREATMENT

On the third day bortezomib was initiated at dose of 1.3 mg/m^2 and dexamethasone at dose of 40 mg/24 h by intravenous route as remission induction. After 24 h of treatment, the patient suddenly presented dyspnea secondary to flail chest resulting from multiple bilateral rib and sternum fractures (Figure 1B). Oxygen saturation by pulse oximetry was 86% (FiO_2 0.21). He required urgent intubation and ventilatory support being transferred to intensive care unit (ICU) for further management. At the ICU, paradoxical inward movements of the rib cage were evident bilaterally on inspiration. The patient remained connected to mechanical ventilation as treatment which stabilized the thorax on pressure control ventilation of 15 cm H_2O and positive end expiratory pressure of 7 cm H_2O. The arterial pH was 7.4, PaO_2 80 mmHg and $PaCO_2$ 43 mmHg, breathing 28% oxygen. The patient, at ICU admission, was febrile (axillary temperature, 38 °C), with white blood cells, 19000/μL. Chest radiography revealed an infiltrate in the right lower lung. Methicillin-sensitive *Staphylococcus aureus* was identified from tracheobronchial aspirates and the patient was treated with cloxacillin at dose of 2 g/6 h by i.v. route, resulting in the eradication of the infection after 14 d of treatment. The patient received selective digestive decontamination during ICU-stay. Attempts to wean the patient caused the return of paradoxical movements and respiratory failure. A second cycle of bortezomib plus dexamethasone was started and analgesia was optimized. Surgical stabilization with an external fixator was considered by Thoracic Surgery team but the idea was finally dropped.

OUTCOME AND FOLLOW-UP

The condition of the patient improved, as evidenced by callus formation on successive CT scans (Figure 1C and D), improvement in his respiratory status and a marked decrease in urine kappa light chain levels to less than half the original value (0.55 g/24 h). The patient was taken off the ventilator one month later, and was extubated successfully, being able to breathe unaided without paradoxical motion. On breathing room air, arterial blood gas analysis revealed: pH, 7.49, PaO_2, 70 mmHg and $PaCO_2$, 40 mmHg. He was discharged from ICU and from the hospital 5 and 9 wk after his hospitalization, respectively. The patient received further treatment with 4 cycles of bortezomib with a good response. An allogenic transplantation was planned five months after, but patient refused the therapy and subsequently was re-treated with 2 cycles of bortezomib at low doses. One year after his hospital admission the patient is being followed up at the Department of Hemato-Oncology without further dyspnea.

DISCUSSION

Spontaneous flail chest is rare in multiple myeloma[4-7]. The main interest of this case resides in restoring chest stabilization with the use of continuous positive pressure ventilation during a short period of time, without need to perform surgery and tracheostomy, while providing definitive chemotherapy. This objective was achieved

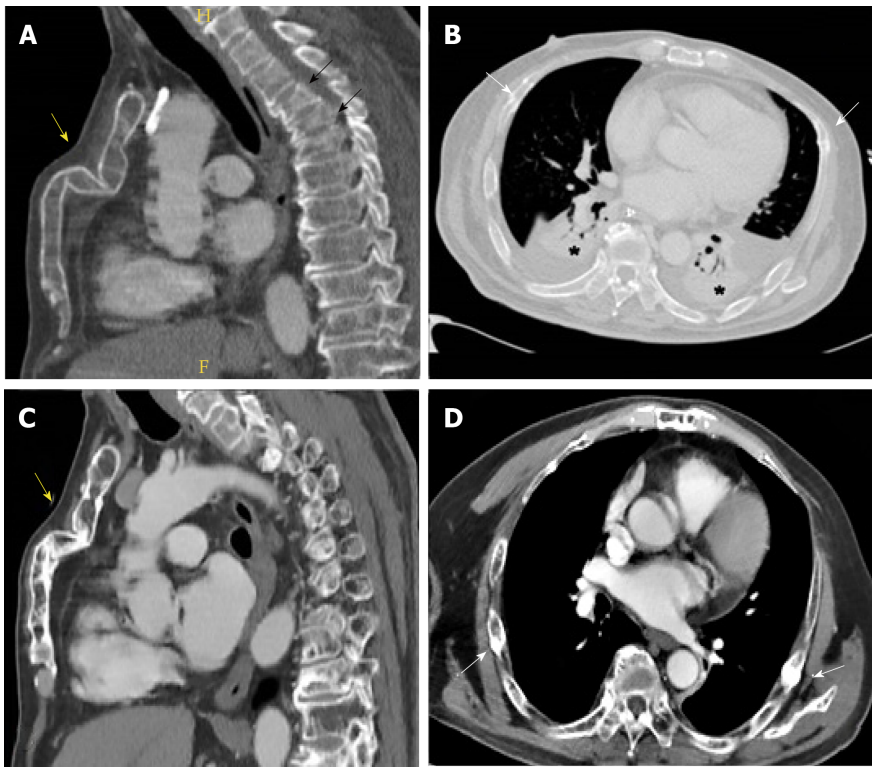

Figure 1 Sagittal computed tomography image. A: A depressed pathological fracture of the sternum (yellow arrow) resulting in an evident deformity of the anterior chest wall. Multiple spontaneous compression fractures of the thoracic spine can also be observed (black arrows); B: Axial computed tomography (CT) image demonstrates multiple rib fractures (white arrows) associated to bilateral lung consolidations (asterisks) and pleural effusion; C and D: Control CT scan, realized months later, shows important improvement of both sternal (C, yellow arrow) and rib fractures (D, white arrows), with the appearance of fracture calluses. Complete resolution of lung consolidations and pleural effusion (D).

as determinated by the relationship between the substantially decreased urine kappa light chain level, the tolerance to the weaning of the ventilator and the signs of partial bone healing in the control by CT. It is well known that bortezomib has significant activity in patients with relapsed/refractory multiple myeloma and its efficacy and safety in renal failure has been observed in phase II studies[8] and more recently the Phase III HOVON-65/GMMG-HD4 trial[9] describes the potential benefit of bortezomib in patients with organ failure. The role of surgery for pathological sternal fractures is not well defined and to date there is no standard treatment method for his clinical condition[10]. Recently, Lee *et al*[6] described a case of multiple myeloma, who presented flail chest and severe respiratory failure following blunt trauma successfully treated by the Nuss operation. On the other hand, Abisheganaden *et al*[4] described the use of continuous positive airway pressure ventilation through a tracheostomy for pathological flail chest in multiple myeloma but after a long period of ICU stay (> 3 mo). Surgery was not required in this case.

CONCLUSION

Despite its alarming presentation, the association of multiple myeloma and flail chest does not necessarily predict a poor prognosis. Starting positive airway pressure to stabilize the chest wall, as well as the association of bortezomib and dexamethasone to induce a remission, may solve the respiratory insufficiency, in a short period of time, without requiring surgical fixation.

REFERENCES

1 **Angtuaco EJ**, Fassas AB, Walker R, Sethi R, Barlogie B. Multiple myeloma: Clinical review and diagnostic imaging. *Radiology* 2004; **231**: 11-23 [PMID: 14990813 DOI: 10.1148/radiol.2311020452]
2 **Terpos E**, Dimopoulos MA. Myeloma bone disease: Pathophysiology and management. *Ann Oncol* 2005; **16**: 1223-1231 [PMID: 15928069 DOI: 10.1093/annonc/mdi235]

3 **Kyle RA**, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, Fonseca R, Rajkumar SV, Offord JR, Larson DR, Plevak ME, Therneau TM, Greipp PR. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc* 2003; **78**: 21-33 [PMID: 12528874 DOI: 10.4065/78.1.21]

4 **Abisheganaden J**, Chee CB, Wang YT. Use of bilevel positive airway pressure ventilatory support for pathological flail chest complicating multiple myeloma. *Eur Respir J* 1998; **12**: 238-239 [PMID: 9701444 DOI: 10.1183/09031936.98.12010238]

5 **Muldoon K**, Chu P, Pathria M, Resnick D. Association of posterior rib fractures with exaggerated kyphosis and sternal collapse. *Clin Imaging* 1999; **23**: 311-313 [PMID: 10665349 DOI: 10.1016/S0899-7071(99)00153-9]

6 **Lee SA**, Hwang JJ, Chee HK, Kim YH, Lee WS. Flail chest stabilization with Nuss operation in presence of multiple myeloma. *J Thorac Dis* 2014; **6**: E43-E47 [PMID: 24822124 DOI: 10.3978/j.issn.2072-1439.2014.02.10]

7 **Pickard L**, Whittaker C, Jayakar V. Spontaneous sternal collapse in multiple myeloma. *Br J Haematol* 2015; **168**: 316 [PMID: 25377148 DOI: 10.1111/bjh.13204]

8 **Chanan-Khan AA**, Kaufman JL, Mehta J, Richardson PG, Miller KC, Lonial S, Munshi NC, Schlossman R, Tariman J, Singhal S. Activity and safety of bortezomib in multiple myeloma patients with advanced renal failure: A multicenter retrospective study. *Blood* 2007; **109**: 2604-2606 [PMID: 17138816 DOI: 10.1182/blood-2006-09-046409]

9 **Sonneveld P**, Schmidt-Wolf IG, van der Holt B, El Jarari L, Bertsch U, Salwender H, Zweegman S, Vellenga E, Broyl A, Blau IW, Weisel KC, Wittebol S, Bos GM, Stevens-Kroef M, Scheid C, Pfreundschuh M, Hose D, Jauch A, van der Velde H, Raymakers R, Schaafsma MR, Kersten MJ, van Marwijk-Kooy M, Duehrsen U, Lindemann W, Wijermans PW, Lokhorst HM, Goldschmidt HM. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: Results of the randomized phase III HOVON-65/ GMMG-HD4 trial. *J Clin Oncol* 2012; **30**: 2946-2955 [PMID: 22802322 DOI: 10.1200/JCO.2011.39.6820]

10 **Slobogean GP**, MacPherson CA, Sun T, Pelletier ME, Hameed SM. Surgical fixation vs nonoperative management of flail chest: A meta-analysis. *J Am Coll Surg* 2013; **216**: 302-311.e1 [PMID: 23219148 DOI: 10.1016/j.jamcollsurg.2012.10.010]

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