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A 67-yo with Acute Hypoxic Respiratory Failure

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Abstract

A 67-year-old female presented to the emergency department for three days with progressive cough, shortness of breath, weakness, nausea, and vomiting. The patient was identified to have influenza-related acute hypoxic respiratory failure, and a workup was initiated in the intensive care unit with a differential diagnosis formulated. This case presentation breaks down the clinical decision-making process step by step and provides a detailed evidence-based description of the differential diagnosis. Acute Respiratory Distress Syndrome (ARDS) was identified and managed according to the current guidelines.

Conclusion: It's important to recognize and manage acute respiratory distress symptoms as a complication of influenza using evidence-based medicine early as well as consider transferring to a tertiary care facility in a timely manner.

Introduction

A 67 to 75-year-old female presented to the emergency department for three days with progressive cough, shortness of breath, weakness, nausea, and vomiting. The patient has had recent exposure to several sick contacts with influenza and verifies that she did not receive the vaccine this year. She denies fever, chills, and night sweats. Her medical history included diabetes and former cocaine use: Now on methadone maintenance. Her current medications include Lisinopril, Lantus, and Humalog. She has no significant family history of disease.

Initial Evaluation and Management

On admission, the temperature is 96.3°F (C), heart rate 109 beats per minute, blood pressure 152/80 mmHg, respiratory rate 20 breaths per minute, oxygen saturation 97% on room air, weight 68 kg, and body mass index 26.4 kg/m^2.

Physical exam

The patient is in no acute distress on examination and is alert and oriented x 2 (name and place). She has no nasal discharge, sinus tenderness, pharyngeal erythema, or exudates but noted poor dentition and dry mucosa. No lymphadenopathy or jugular vein distention is observed. There is no accessory muscle use with wheezing/coarse lung sounds, bilaterally. The cardiac exam shows tachycardia, regular rate and rhythm, and normal S1/S2 with no murmur, rubs, or gallops. The abdomen is positive for bowel sounds, soft, non-tender, and non-distended. Extremities are intact with no edema or rashes (Table 1).

Findings on imaging

Chest Radiography (CXR) shows increased interstitial markings in the right lung field. Electrocardiogram reveals sinus tachycardia with left atrial enlargement without evidence of myocardial ischemia.

Hospital course

The patient is rushed to the critical care unit for diabetic ketoacidosis treatment triggered by *Influenza A*. On critical care day two, the patient was gasping for air and slumped over: she had developed respiratory failure, despite the BiPAP therapy. Rescue intubation and mechanical ventilation are initiated immediately.

Differential Diagnosis

What is the most likely cause of this patient's illness?

- Cardiogenic pulmonary edema

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Table 1: Laboratory test results.

Test	Value	Reference range
Hemoglobin	15.5 g/dL	12.0-18.0 g/dL
White blood cells	24.4 × 10^3/uL	5.2-12.4 × 10^3/uL
Neutrophils	84.3%	40-74%
Lymphocytes	6.6%	19.0-48.0%
Monocytes	7.5%	3.0-9.0%
Eosinophils	0.0%	0-7.0%
Basophils	0.3%	0-2.0%
Platelet count	220 × 10^3/uL	130-400 × 10^3/uL
Sodium	132 mmol/L	137-145 mmol/L
Potassium	5.4 mmol/L	3.5-5.1 mmol/L
Blood urea nitrogen	22.0 mmol/dL	7.0-17.0 mmol/dL
Creatinine	0.61 mg/dL	0.52-1.04 mg/dL
Glucose	481 mg/dL	74-106 mg/dL
Calcium	9.6 mg/dL	8.4-10.2 mg/dL
Albumin	4.0 g/dL	3.5-5.0 g/dL
Alanine aminotransferase	12 U/L	4-35 U/L
Aspartate aminotransferase	32 U/L	14-36 U/L
Troponin I	0.016 ng/mL	0.00-0.034 ng/mL
Pro-Brain natriuretic peptide	216 pg/mL	0-125 pg/mL
Lactic acid	4.5 mmol/L	0.7-2.1 mmol/L
Influenza A/B antigen	Positive A	Negative
Sputum culture	No growth	No growth
Urine culture		No growth
Blood culture		No growth
Arterial blood pH	7.290	7.35-7.45
Partial pressure of carbon dioxide	34.4 mmHg	32.0-45.0 mmHg
Partial pressure of oxygen	58.8 mmHg (on room air)	83-108 mmHg
Oxygen saturation	84.6%	94.9-98.0%
Serum bicarbonate	21 mmol/L	22-30 mmol/L
Serum anion gap	23 mmol/L	8-12 mmol/L

- *Pneumocystis jirovecii* pneumonia
- ARDS/non-cardiogenic pulmonary edema
- Sarcoidosis

The cause of this patient's respiratory deterioration resulted from a complication of influenza, which progressed to Acute Respiratory Distress Syndrome (ARDS). ARDS accounts for ~10% to 15% of ICU admissions, is potentially life-threatening, occurs within seven days of a critical illness, and is characterized by bilateral pulmonary infiltrates and poor oxygenation. ARDS results from an immunologic response caused by an injured pulmonary lining, leading to increased alveolar-capillary permeability and subsequent hypoxia from the reduced gas exchange. CXR in this patient, after intubation, revealed bilateral pulmonary infiltrates not seen in the prior study. Distinguishing CXR findings for ARDS from cardiogenic pulmonary edema can pose a challenge. Still, helpful clues include pleural effusions, common in Cardiogenic Pulmonary Edema (CPE) [1,2], and Kerley-B lines more frequently associated with CPE, although rarely seen in ARDS. ARDS radiography stabilizes in 36 h, whereas CPE will see improvement/resolution with treatment [3].

CPE results from increased capillary pressure and endothelial permeability due to left or right ventricular heart failure, which can have an acute or gradual onset of respiratory distress [4]. Differentiating CPE from ARDS is very important for treatment, and it requires physical examination, laboratory data, echocardiogram and hemodynamic assessment. Physical examination often reveals inspiratory crackles/rales, neck vein distention, and peripheral edema [5], of which are not present in ARDS. Obtaining Plasma Brain-type Natriuretic (BNP) or N-Terminal BNP (NT-proBNP) greater than 100 pg/mL points to CPE but underlying medical issues such as COPD or renal dysfunction need to be considered well. Sick patients are more apt to have elevated BNP levels for reasons other than CPE [6]. One can estimate left atrial pressure with point-of-care ultrasound, subsequently obtaining an indirect pulmonary capillary wedge pressure measurement which, if elevated, is indicative of CPE [7]. Sarcoidosis is an insidious disease and commonly seen CXR findings include bilateral hilar lymphadenopathy, also called Löfgren's syndrome. Abnormal laboratory findings in Sarcoidosis include hypercalcemia, an elevated 1,25-dihydroxyvitamin D, alkaline phosphatase, serum Angiotensin-Converting Enzyme (ACE), soluble Interleukin-2 Receptor (sIL-2R), and glycoprotein KL-6 [8]. This patient's CXR was absent of lymphadenopathy and laboratory results for hypercalcemia, 1,25-dihydroxyvitamin D, alkaline phosphatase, serum Angiotensin-Converting Enzyme (ACE) are negative therefore, Sarcoidosis is less likely the diagnosis.

Pneumocystis jirovecii pneumonia is fungal pneumonia more commonly seen in immunocompromised patients, particularly those with HIV/AIDS with a CD4 count <200 cell/mm^3 [9]. Typically, patients have respiratory symptoms for a few weeks before being evaluated and usually present with pleuritic chest pain, hypoxic/hypoxemia and potentially mixed findings on lung examination, which could be normal, but if abnormal may mimic bronchial pneumonia on pulmonary exam and reveal rhonchi, crackles, or egophony [10]. CXR shows fine reticular, perihilar interstitial changes, subpleural blebs, and small pneumatocele, mimicking findings in ARDS [11]. This patient has no known underlying HIV/AIDS, autoimmune or cancer history, and HIV testing was negative.

Case Continued

The patient develops shock: IV fluid resuscitation, IV antibiotics, Tamiflu, and hemodynamic support with vasopressors are quickly started. A repeat CXR reveals new bilateral diffuse pulmonary opacities (Table 2).

ARDS Classification

We define ARDS as pre-existing respiratory illness for approximately one week with PaO_2/FiO_2 ≤ 300 mmHg in a

Table 2: Having previously diagnosed this patient with ARDS, how would you classify their condition?

Sodium	132 mmol/L	137-145 mmol/L
Arterial blood pH	7.324	7.35-7.45
Partial pressure of carbon dioxide	23.6 mmHg	32.0-45.0 mmHg
Partial pressure of oxygen	51.0 mmHg (on room air)	83-108 mmHg
FIO_2	100%	
PEEP	15	

Mild; Moderate; Severe

mechanically ventilated patient with Positive End-Expiratory Pressure (PEEP) >5 cm H_2O and CXR showing bilateral opacities not explained by cardiogenic pulmonary edema.

ARDS is further classified based on PaO_2/FiO_2 ratio and defines as:

- Mild ARDS ($200<PaO_2/FiO_2 \leq 300$ mmHg)
- Moderate ARDS ($100<PaO_2/FiO_2 \leq 200$ mmHg)
- Severe ARDS ($PaO_2/FiO_2 \leq 100$ mmHg)

This patient has severe ARDS with a PaO_2/FiO_2 ratio of 51. The current Berlin definition expands on the validity of the mild, moderate, and severe stages of ARDS by their associated increase in mortality (27%; 95% CI, 24% to 30%; 32%; 95% CI, 29% to 34%; and 45%; 95% CI, 42% to 48%, respectively; P<0.001) and increased median duration of mechanical ventilation in survivors (5 days; Interquartile [IQR], 2-11; 7 days; IQR, 4-14; and 9 days; IQR, 5-17, respectively; P<0.001) [12]. Moderate to severe ARDS calls for a combination of treatment strategies (Table 3), to reduce the associated higher risk of mortality.

Treatment Considerations for ARDS

Which of the following management options would be most appropriate for this patient?

- High Tidal Volume (TV), high Positive-End Expiratory Pressure (PEEP)
- Low tidal volume (≤ 6 ml/kg), low PEEP
- Low tidal volume, high PEEP

Tidal volume and PEEP management should be individualized to the patient after considering multiple factors–Predicted Body Weight (PBW), underlying cardiac and respiratory conditions, hemodynamic assessment, and the current illness to optimize oxygenation and minimize Ventilator-Induced Lung Injury (VILI). Ventilator management requires balancing the TV and PEEP to provide adequate oxygenation and ventilation.

Normal TV is based on PBW for height, initially set at 6 ml/kg to 8 ml/kg and adjusted as needed to ensure proper ventilation based on ABG, maintaining a plateau pressure (Pplat) ≤ 30 cmH_2O. High TV (≥10 ml/kg) is used to improve hypoxemia/oxygenation, minimize atelectasis and increase the functional residual capacity. Still, research has shown that this causes more complications with volutrauma and mimicking non-cardiogenic pulmonary edema [13,14]. Low TV (≤ 6 ml/kg) is also known as lung-protective ventilation and is the recommended/standard treatment for ARDS due to the poor lung compliance and allows for permissive hypercapnia, which has been shown to reduce mortality [15,16].

In the American Thoracic Society's (ATS) clinical practice guidelines for mechanical ventilation in adults, the use of low tidal volumes (LTVs; 4 mL/kg to 8 mL/kg PBW) was compared with traditional strategies (TVs; 10 mL/kg to 15 mL/kg PBW) in seven RCTs (1,481 patients). Although they found no significant difference in mortality rates, the largest possible effect (derived from the boundaries of the CIs) inferred a relative risk reduction in mortality of up to 30% in patients receiving LTV [17].

The former analyses did not include studies that used higher PEEPs in conjunction with LTVs. Sensitivity analyses, which included studies using LTV/higher PEEP combination strategies (a total of nine RCTs, 1,629 patients), confirmed the clinical importance of LTV, finding significantly reduced mortality (RR, 0.80; 95% CI, 0.66-0.98) compared to traditional strategies. Meta-regression analyses discovered that LTV had a dose-dependent effect on mortality in each RCT [17]. Hence, the ATS's strong recommendation is that mechanical ventilation is started at 6 mL/kg PBW, increasing to 8 mL/kg if inspiratory pressures fall below PEEP (plateau pressure <30 cmH_2O) [18].

PEEP is essential for alveolar recruitment to improve oxygenation due to poor lung compliance/stiff lungs and is adjusted in conjunction with TV to avoid lung injury. A shallow TV (<5 ml/kg PBW) would not benefit an ARDS patient as it would be close to physiologic PEEP [19]. Whereas high PEEP (>5 cmH_2O) has been associated with barotrauma from rupture of alveoli leading to pneumothorax [14], it is strongly recommended in patients with moderate to severe ARDS by the ATS [17]. This recommendation is partially based on data from an individual patient data meta-analysis of higher versus lower PEEP from three large, randomized RTCs which confirmed a significantly lower risk of mortality with high PEEP in patients with moderate-severe ARDS (adjusted RR: 0.90; 95% CI, 0.80-1.00) but found no significant effect in patients with mild ARDS [18]. However, the potential benefits must be outweighed against possible complications of reduced venous return and increased afterload, resulting in hemodynamic instability [20]. A post hoc analysis of prior randomized control trials and subsequent meta-analysis demonstrate driving pressure (DT = plateau – PEEP) is a strong predictor of outcome in ARDS than either tidal volume or plateau pressure [18]. Lastly, novel options may soon be on the horizon, such as trans-pulmonary plateau pressure-guided PEEP titration, which produced favorable results in a pilot trial and is currently being investigated in a large-scale multicenter RCT [17].

What additional treatment management would this patient benefit from?

- Supine positioning
- Elevate head-of-bed >30 degrees
- Prone positioning

Prone positioning is the best way to improve oxygenation and minimize ventilation-perfusion mismatch in moderate-to-severe ARDS patients. It facilitates the maintenance of open alveoli while preventing VILI when used in conjunction with the above strategies already discussed [21]. Although there is some debate as to the number of hours per day needed in a prone position, it is strongly recommended for a minimum of 12 consecutive hours per day, ideally 16 h, in patients with PaO_2/FIO_2 ratio <150 mmHg [15].

Supine positioning has the effect of gravity producing an increased weight on the lungs and heart, especially in obese patients, increasing pleural pressure and decreasing lung ventilation [22]. Elevate Head-of-Bed (HOB) also causes lung impairment with reduced compliance and poor gas exchange, as previously discussed. Both HOB elevated and supine positioning have been associated with an increase in lower lobes atelectasis in patients with ARDS and are therefore not beneficial in conjunction with ventilation [23].

In addition to the treatment strategies discussed above (LTV, High PEEP, prone positioning), a couple of commonly employed important management options must be addressed: Neuromuscular

Table 3: Key points in the diagnosis and management of ARDS.

Diagnosis
➢ $PaO_2/FiO_2 \leq 300$
➢ PEEP ≥ 5 cmH_20
➢ Non-cardiogenic pulmonary edema:
• Bilateral lung opacities
• Pulmonary wedge pressure ≤ 18 mmHg.
➢ One week of a known clinical insult
➢ Fever, Cough, and chest pain **if** ARDS is caused by pneumonia.
➢ Infection (white blood cell count >12,000 per mm^3); pulse >90 beats/min; temperature >100.9°F (38.3°C) or <96.8°F (36°C) and altered mental state **if** ARDS is due to sepsis [24].
Management
➢ Mechanical ventilation using Lower Tidal Volumes (LTD) starting at 6 mL/kg PBD and lower inspiratory pressures (plateau pressure <30 cmH_2O).
➢ Higher PEEP in patients with moderate-severe ARDS (>12 cmH_2O), **NOT** in mild ARDS, which benefits from keeping PEEP ~ 6 cmH_2O.
➢ Prone position, during ventilation, for 12-16 hours per day.
➢ Recruitment Maneuvers (RMs) in patients with moderate-severe ARDS.*
➢ Stress ulcer prophylaxis and Nutritional support
➢ Paralytics and other pharmacological agents: their use was not addressed in the current ATS guidelines due to resource constraints but will be addressed in future guidelines.

* Use caution about using RMs in patients exhibiting pre-existing hypovolemia or shock

ATS guidelines **do not support the routine use** of the following:

➢ Extracorporeal Membrane Oxygenation (ECMO): Should be used with caution in severe ARDS (currently, there is not enough evidence for ATS to make a definitive recommendation **for** or **against** ECMO)

ATS guidelines strongly recommend **against** the following**:**

➢ High-Frequency Oscillatory Ventilation (HFOV) in moderate-severe ARDS.

blocking agents and ECMO.

Neuromuscular blockade is used in patients undergoing mechanical ventilation to improve oxygenation and decrease ventilator-induced lung injury but it may also cause muscle weakness [25]. There is a strong expert recommendation for their use in ARDS patients with a PaO_2/FiO_2 ratio <150 mmHg to reduce mortality [18]. A multicenter, double-blind trial of 339 patients receiving either the neuromuscular blocking agent Cisatracurium besylate or placebo, found that the hazard ratio for 90-day mortality in the cisatracurium group was 0.68 (95% CI 0.48–0.98; p=0.04), with improved survival in patients with PaO_2/FiO_2 ratio <120 mmHg, more days alive and free of mechanical ventilation [25]. Importantly, in this trial, tidal volume was maintained between 6 mL/kg to 8 mL/kg PBW, and the neuromuscular blocking agent was administered early (within 48 h from the start of ARDS) and for no longer than 48 h. Patients receiving neuromuscular agents in conjunction with mechanical ventilation must be evaluated daily [18].

Venovenous Extracorporeal Membrane Oxygenation (VV ECMO) employs a gaseous-exchange device that oxygenates and removes carbon dioxide in blood drained from a central vein before being reinfused back into the patient. Although its use has increased due to advanced state-of-the-art extracorporeal support techniques, there is limited evidence to support its benefit. RTCs have shown no significant difference in mortality between patients who underwent ECMO and those who did not. Thus, ATS guidelines state that further research is needed and caution against using ECMO in patients with severe ARDS [17]. The evidence-based management strategies recommended and discussed previously in this article (Table 3 for a summary) should be employed before considering ECMO.

Take-home points

- Be cognizant of complications of influenza.
- ARDS requires prompt recognition and intervention with management strategies (see Table 3: Key Points in the Diagnosis and Management of ARDS).
- ARDS management: Optimizing ventilator settings (low tidal volume, high PEEP), prone position ~16 hours per day, recruitment maneuvers, and neuromuscular blockades
- Consider early transfer to tertiary centers for necessary resources.

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