June 2014 Critical Care Case of the Month: Acute Exacerbation in Cystic Fibrosis

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History of Present Illness

A 28 year-old woman with a history of cystic fibrosis, presented with worsening shortness of breath and cough associated with productive secretions. She was diagnosed with cystic fibrosis when she was 14 months old, and has a history of multiple inpatient admissions for acute pulmonary exacerbation of cystic fibrosis. Her most recent hospitalization was a month prior to this admission, and sputum culture demonstrated methicillin-resistant *Staphylococcus aureus*, multidrug-resistant *Pseudomonas aeruginosa*, and *Achromobacter xylosoxidans*. She was treated with linezolide, meropenum, colistin, and azithromycin with significant symptom improvement, then, discharged home with ciprofloxacin, linezolide and zosyn. However, she developed worsening respiratory distress again and came back to hospital. In the emergency department she required 10 L/min of oxygen to maintain an SpO_2 above 90 %.

PMH

- Cystic fibrosis
- Seizure
- Kidney stone
- Portacath placement
- Gastrostomy tube placement

Medications

- Azithromycin 500 mg 3 times a day
- Dornase alpha 1 mg/ml nebulizer twice a day
- Albuterol sulfate 2.5 mg/0.5 ml Nebulizer 4 times a day
- Ipratropium 0.02 % nebulizer 4 times a day
- Fluticasone-salmeterol 500-50 mcg/dose inhaler twice a day
- Lipase-protease-amylase 21,000-37,000-61,000 unit 4 caps a day
- Cholecalciferol 2,000 unit capsule daily
- Ferrous sulfate 325 mg PO twice a day

- Ascorbic acid 250 mg PO twice a day
- Oxycodone-acetaminophen 10-325 mg 4 times a day as needed

Social History

- No smoking
- No alcohol use
- No recreational drug use

Physical Examination

Vital signs: Temperature 37.3 °C, heart rate 114 beats/min, respiratory rate 20-24 breaths/min, blood pressure 99/69mmHg, SpO2 88-90 % on 10 L NC
General: Alert and oriented X 3, acutely distressed, tachypneic and dyspneic
Skin: Diaphoretic. No rash or lesions.
HEENT: Unremarkable.
Respiratory: Diffuse rales in all lung fields, no wheezing, no stridor
CVS: Tachycardic, regular rhythm, no murmur.
Abdomen: Soft, non-tender, no tenderness, no guarding, no hepato-splenomegaly, PEG tube placed
Lymphatics: No cervical or axillary lymphadenopathy
Extremities: No clubbing, no cyanosis, no peripheral edema, normal tone, normal range of movement
Neurological: Normal speech, no focal neurologic deficit, CN exam within normal range

Laboratory

CBC: WBC 11.9X 10^3 /µL, Hb 9.8 g/dL, Hct 30.7%, Platelets 356,000 /µL.
Chemistries: Na^+ 137 meq/L, K^+ 4.1 meq/L, Cl^- 107 meq/L, CO_2 22 mmol/L, blood urea nitrogen (BUN) 13 mg/dL, creatinine 0.7 mg/dL, glucose 106 mg/dL, calcium 8.0 mg/dL, albumin 2.6 g/dL, liver function tests within normal limits. Prothrombin time (PT) 14.0 sec, international normalized ratio (INR)1.1, partial thromboplastin time (PTT) 37.2sec

Pulmonary Function Test

FVC 48 % (1.95 L), FEV_1 36 % (1.25 L), FEF_{25-75} 14 % (0.55 L/sec)

Radiography

An old chest x-ray and thoracic CT scan were reviewed (Figure 1).

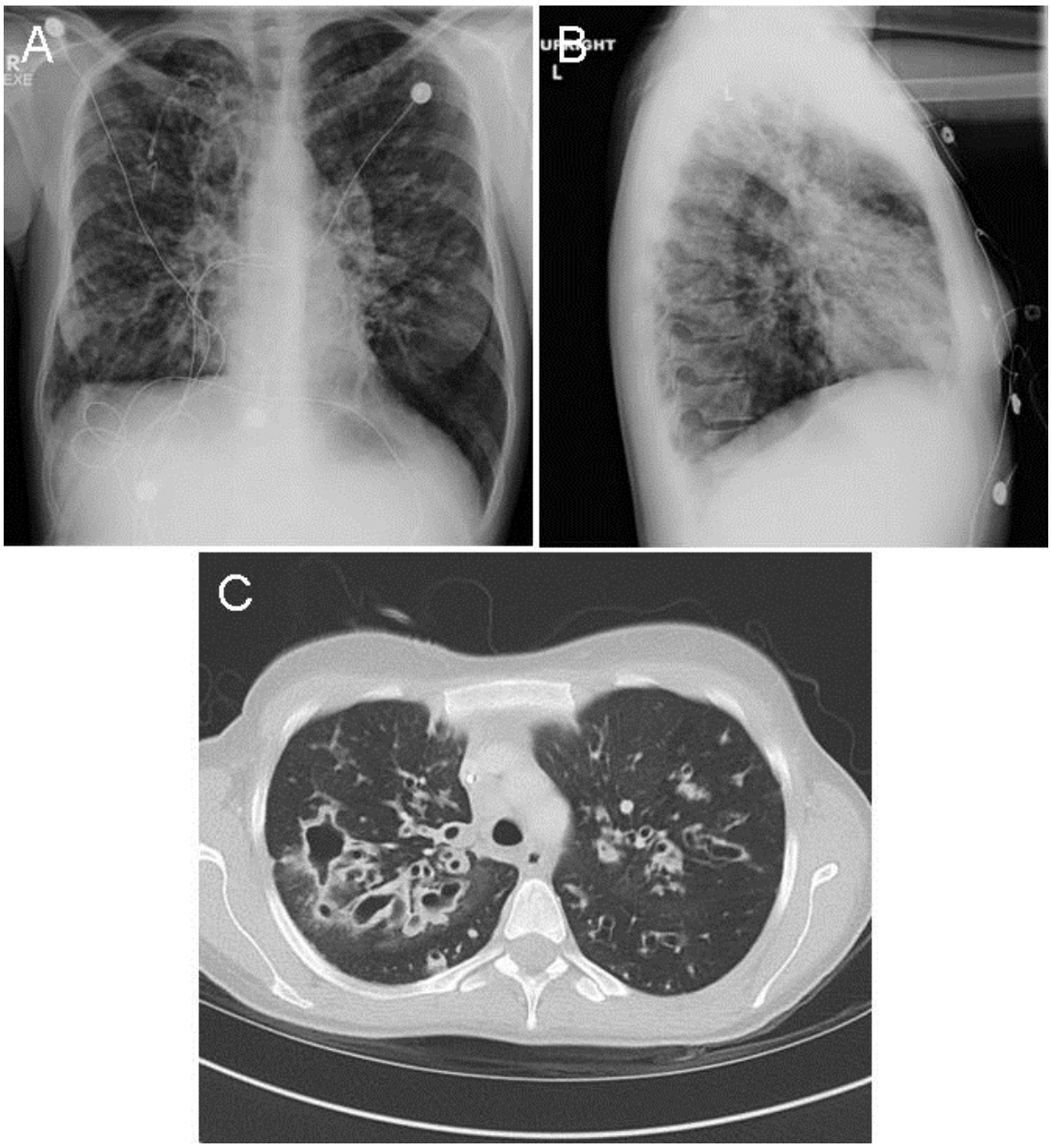

Figure 1. Previous PA (Panel A), lateral (Panel B) chest x-ray and representative image from the thoracic CT scan (Panel C).

Which of the following are ***findings of cystic fibrosis*** on chest x-ray?

1. Bronchiectasis
2. Hyperinflation
3. Lobar collapse
4. Prominent pulmonary arteries
5. All of the Above

Correct!
5. All of the Above

Bronchiectasis is a primary sign of cystic fibrosis lung disease. It typically develops in the upper lobes and presents on chest radiograph as tram-lining and cystic lesions containing air-fluid levels. On CT, bronchiectasis additionally presents as a "signet ring sign" (internal bronchial diameter exceeds that of the corresponding artery), thickening of the bronchial wall, visible bronchi within 1 cm of the costal pleura or touching the mediastinal pleura, and a lack of normal bronchial tapering (1). In addition, hyperinflation is historically recognized as one of the major causes of respiratory dysfunction in cystic fibrosis (2). Lobar collapse and atelectasis occur in 4-11% of cystic fibrosis patients and most frequently affect the upper lobes (1). Prominent pulmonary arteries are visible in cases of pulmonary hypertension, which may arise from chronic hypoxia characteristic of advanced cystic fibrosis lung disease (1).

What is the ***underlying molecular mechanism*** of cystic fibrosis?

1. Ca ion channel mutation
2. Cl ion channel mutation
3. K ion channel mutation
4. Na ion channel mutation
5. Proton pump mutation

Correct!
2. Cl ion channel mutation

Cystic fibrosis is one of the most common genetic diseases in Caucasian population. It is caused by a single mutation in Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene which codes a protein that functions as a chloride ion channel, however, also regulates other ion channels' activity and signal transduction (3). There are six main classes of CFTR mutations. Class I stands for mutations rendering no CFTR protein production due to either stop codon or splicing mutation. Class II mutations result in a protein trafficking defect and early degradation from protein mis-folding. *Phe508del,* the most common mutation in Caucasian population, belongs to class II. Class III, IV, V and VI stand for mutations of ATP binding, channel gating, transcriptional deficiency or splicing abnormality and accelerated protein turn-over from the apical membrane, respectively (figure 2).

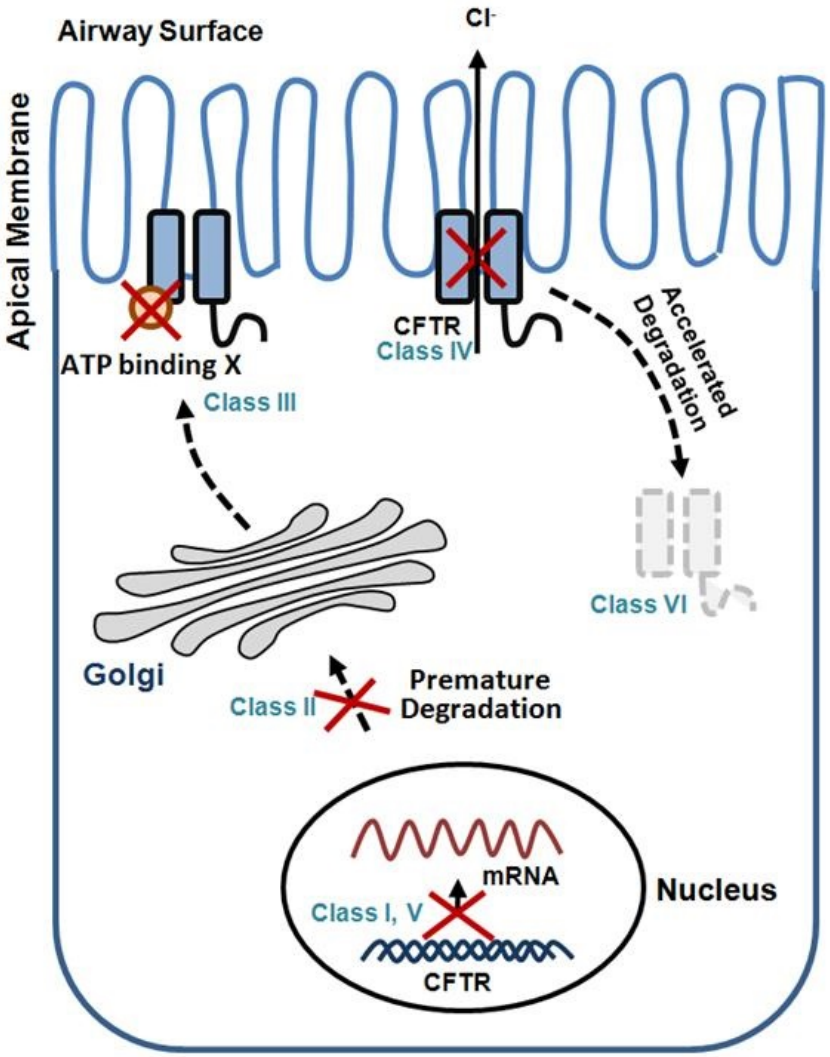

Figure 2. Classification of CFTR mutations.

The clinical manifestations of the same genotype can be very different between individuals depending on polymorphisms in other genes and environmental factors (4). The US Cystic Fibrosis Foundation suggests sweat testing as the most reliable and useful screening test for cystic fibrosis and it is recommended in all patients who have symptoms and signs of cystic fibrosis (5).

Mucosal obstruction and constant inflammation are the two major contributing factors for the decline of pulmonary function in cystic fibrosis, and they increase the mortality. Submucosal gland ducts in cystic fibrosis are filled with viscous mucus, and this provides a favorable environment for bacterial colonization such as *Pseudomonas aeruginosa, Staphylococcus aureus, and Burkholderia cepacia*. As the disease progresses, these pathogens eventually form a biofilm and produce capsular polysaccharide which prevent antibiotics from penetrating into the bacteria, and facilitate resistance formation. Moreover, the mucus is filled with inflammatory cells that release inflammatory cytokines such as IL-6, IL-8, TNF-α and LTB_4.These cytokines exacerbate the structural destruction of lung via constant inflammation.

Although the pathology and clinical course of cystic fibrosis are well understood, the underlying mechanisms connecting CFTR dysfunction to organ damage remain elusive. Two main hypothesis have been postulated: the “low-volume” and the “high-salt” hypotheses (Figure 3).

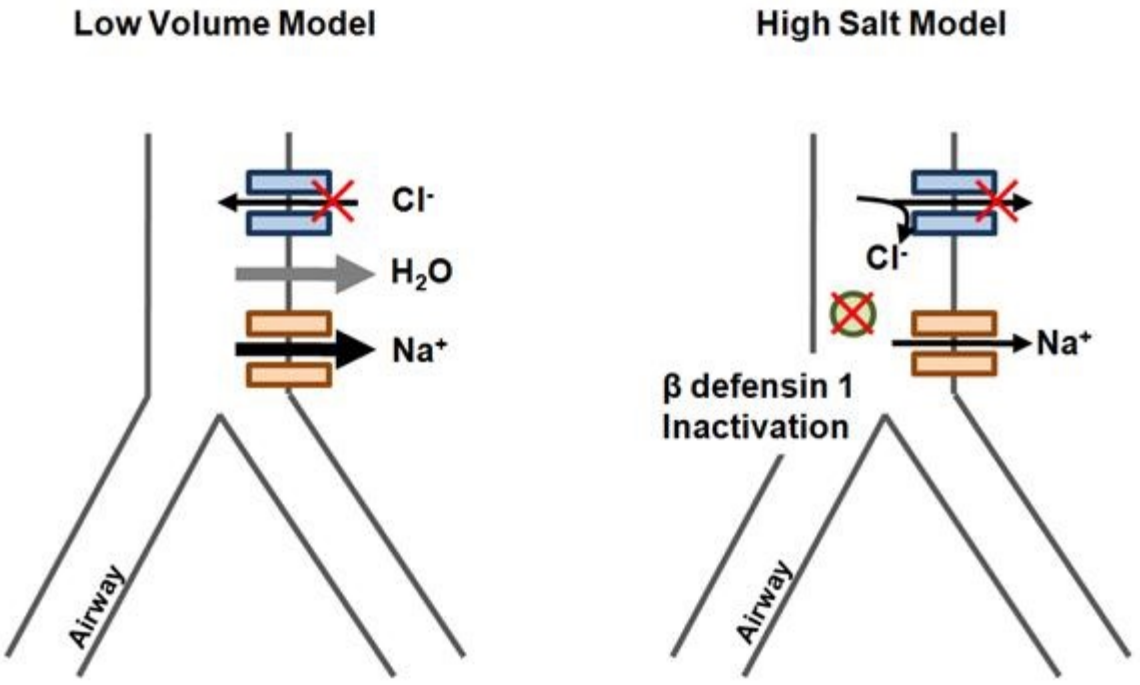

Figure 3. Models explaining viscous mucus plug formation and chronic infection in the airway of cystic fibrosis.

In the low-volume model, excess sodium and water accumulate in epithelial cells causing dehydration at the airway surface. Concurrent loss of chloride ion efflux from the epithelium to the airway surface fails to correct the water volume loss resulting in thick mucus plug formation (6). High-salt models postulate that excess sodium and chloride ions accumulate at the airway surface due to lack of CFTR function. The high concentration of these ions inhibits endogenous anti-microbial peptides such as human β-defensin 1, allowing bacterial over-growth in the viscous mucus plug (7).

Collectively, CFTR dysfunction causes viscous mucus formation in the airway surface, and subsequently facilitates bacterial colonization. Neutrophils and inflammatory cytokines in this microenvironment exacerbate the destruction of the lung and consequently results in chronic bronchitis and bronchiectasis, which are seen in the imaging (Figure 1). This vicious cycle is further enhanced by the overgrowth of the bacteria causing acute exacerbations and decline of pulmonary function, which contribute to morbidity and mortality.

Which of the following is associated with ***pulmonary function improvement or prevention of acute exacerbations*** in cystic fibrosis patients?

1. Antibiotics (Azithromycin or Tobramycin)
2. DNase (Dornase alpha)
3. High dose ibuprofen
4. Inhaled hypertonic saline
5. All of the above

Correct!
5. All of the Above

The life expectancy of cystic fibrosis patients was less than 1 year when it was first described (8). However, there has been remarkable survival improvement, and patients with cystic fibrosis are now expected to live 50 years or longer (9). In many studies, maintenance of pulmonary function has been shown to be associated with survival (10), and aggressive treatment, especially during an acute exacerbation, has been associated with survival (11).

As such, several modalities have been demonstrated to improve pulmonary function or prevent its deterioration and reduce the risk of acute exacerbation. Elkins *et al.* (6) and Donaldson *et al.* (12) tested the hypothesis that hypertonic saline can hydrate airway surfaces and reduce the viscosity of mucus plugs based on the volume depletion hypothesis. In these studies, 7% of hypertonic saline compared to normal saline improved lung function (FEV1) and reduced the episode of acute exacerbations that resulted in significantly better exacerbation-free survival (13, 14). Fuchs *et al.* (15) showed that DNAse reduces the risk of exacerbations and improved pulmonary function as well as quality of life (15). As described in the previous section, constant inflammation is one of the pivotal pathophysiology causes of lung destruction in cystic fibrosis (3), and anti-inflammatory agents have been suggested to possibly preserving lung function. Saiman *et al.* (16) and Eigen *et al.* (17) demonstrated high dose ibuprofen and corticosteroids preserved pulmonary function and reduced the risk of acute exacerbation, although long term use of corticosteroids is discouraged due to its side effects. Moreover, bacterial colonization in the mucus plays an important role in disease progression, and prophylactic or maintenance antibiotic treatments with intermittent administration of inhaled tobramycin and azithromycin prevent acute exacerbations in cystic fibrosis patients chronically infected with *Pseudomonas* (18,19).

Not only pharmacological agents, but also non-pharmacological modalities including percussion and postural drainage, positive expiratory pressure devices, high frequency chest wall oscillating devices and nutrition support are essential components in the management of cystic fibrosis. Additionally, treatments of other diseases associated with cystic fibrosis such as pancreatic insufficiency, cystic fibrosis related diabetes, and osteoporosis/osteopenia are important to extend the life expectancy of cystic fibrosis as well (3).

Later, our patient developed severe hypoxemia and was put on BiPAP. However, hypoxemia was refractory requiring intubation and ICU transfer. The arterial blood gases (ABG) on BiPAP were as follows:

ABG: pH 7.15, pCO_2 67.0 mmHg, pO_2 77.0 mmHg HCO_3^- 23.3 meq/L, SaO_2 89.2 % on BiPAP (PEEP of 5 cm H_2O and pressure support 10 cm H_2O)

More than 500 ml of thick secretion was suctioned over the 24 hours after intubation. Sputum culture showed MRSA and *Pseudomonas aeruginosa*. Subsequent bronchoalveolar lavage (BAL) showed elevated total cell counts of 228 X 10^6 /ml, WBC 11.4 X 10^6 /ml, neutrophils 70 %, macrophages 30 %, lymphocytes 7 %, and eosinophils 0 %. Cultures from the BAL sample also demonstrated MRSA, multi drug resistant *Pseudomonas aeruginosa* and intracellular bacteria (Figure 4).

PSEUDOMONAS AERUGINOSA, MUCOID

Antibiotic	Sensitivity	Microscan
Amikacin	Resistant	>32
Aztreonam	Resistant	>16
Cefepime	Resistant	>16
Chloramphenicol	No Interp	>16
Ciprofloxacin	Resistant	>2
Gentamicin	Resistant	>8
Meropenem	Resistant	>8
Piperacillin + Tazobactam	Resistant	>64
Tobramycin	Resistant	>8
Colistin	Susceptible	0.50
Doripenem	Resistant	>32

STAPHYLOCOCCUS AUREUS COAGULASE POSITIVE

Antibiotic	Sensitivity	Microscan
Clindamycin	Resistant	4
Erythromycin	Resistant	>=8
Gentamicin	Susceptible	<=0.5
Linezolid	Susceptible	2
Oxacillin	Resistant	>=4
Rifaximin	Susceptible	<=0.5
Tetracycline	Resistant	>=16
Trimethoprim + Sulfamethoxazole	Susceptible	<=.5/9.5
Vancomycin	Susceptible	1

Figure 4. Culture and sensitivities from the BAL.

What is the ***best antibiotic treatment*** in this patient? [(S)=Susceptible, (R)=Resistant]

1. Colistin (S)
2. Colistin (S) + Vancomycin (S)
3. Colistin (S) + Meropenum (R)
4. Colistin (S) + Meropenum (R) + Vancomycin (S)
5. Colistin (S) + Meropenum (R) + Vancomycin (S) + Inhaled Colistin (S)

Correct!
5. Colistin + Meropenum + Vancomycin + Inhaled Colistin

Chronic bacterial infection in the viscous airway plugs is one of the major driving factors for the vicious cycle in cystic fibrosis. The most common pathogens include *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, and *Burkholderia cepacia* complex, which are associated with a worse prognosis and higher mortality. Other pathogens frequently identified include *Haemophilus influenza, Stenotrophomonas maltophilia, Achromobacter xylosoxidans, Mycobacterium avium* complex and *Aspergillus* species. The initial bacterial infection can be cured by intravenous antibiotic treatment, however as the disease progresses, chronic infection develops from biofilm formation causing poor antibiotic penetration and acquired or native resistance. Therefore, current guideline recommends periodic cultures to guide antibiotic treatment when the patient experiences an acute pulmonary exacerbation (20).

For pseudomonal infection, combination treatment of tobramycin with other anti-pseudomonal agents including a third generation cephalosporin, carbapenem or aztreoman is the most commonly used regimen, and the benefit of using two different classes of anti-pseudomonal antibiotics rather than single regimen has been shown (21). However, in cases with multi-drug resistant pseudomonal infection as in our case, IV colistin in combination with other anti-pseudomonal agents (except an aminoglycoside due to renal toxicity) is recommended since the goal of antibiotic treatment in this setting is reducing the bacterial burden rather than eradication. Moreover, by using concomitant inhaled colistin, the systemic toxicity from intravenous colistin can be reduced. For MRSA, vancomycin or linezolide are recommended antibiotics.

The optimal duration of antibiotic treatment in pulmonary exacerbation remains unknown. Current guideline recommends IV antibiotic treatment until symptoms and signs of pulmonary exacerbation resolve with a minimum of 10 days treatment.

Our patient was initially put on mechanical ventilation with settings of volume control, TV 400 ml, FiO_2 100 %, RR 36, PEEP 10 cm H_2O. However, hypoxemia and hypercapnia were refractory even with multiple trials of ventilator adjustment. Moreover, patient developed hypotension with BP of 60/30 mmHg and acute kidney injury with her creatinine rising to 2.4 mg/dL (baseline 0.8), requiring levophed, vasopressin, epinephrine, steroids and continuous renal replacement therapy. ABG on above ventilator setting were as follows: pH 7.06, pCO_2 78.1mmHg, pO_2 126 mmHg, HCO_3^- 22.1meq/L and SaO_2 91.8%.

Chest x-ray and chest CT are shown in Figure 5.

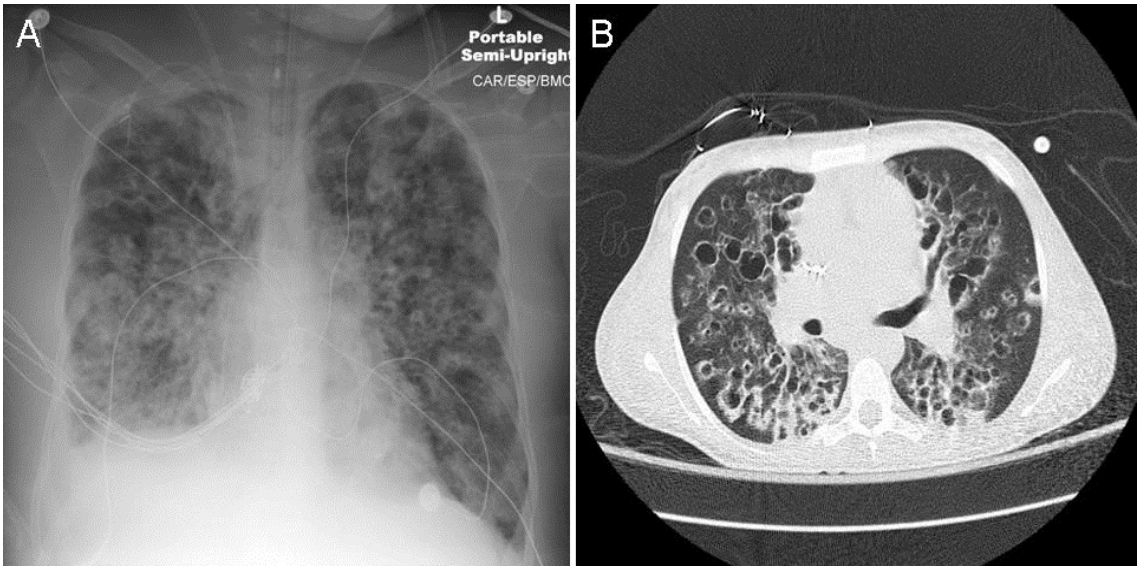

Figure 5. Chest x-ray AP (Panel A) and representative image from chest CT scan (Panel B).

What are possible ***alternative treatment(s)*** for this patient?

1. ECMO (Extracorporeal Membranous Oxygenation)
2. HFOV (High Frequency Oscillatory Ventilation)
3. INO (Inhaled Nitric Oxide)
4. Prone positioning
5. All of the above

Correct!
5. All of the above

Refractory hypoxemia occurs in patients who are on ventilator support, and alternative therapies can be tried when there is no clinical improvement with standard care (22).

One of the most popular modalities is extracorporeal membrane oxygenation (ECMO), which is commonly used in patients with severe hypoxemia with maximum mechanical ventilation. Oxygenation and carbon dioxide exchange occur in the extracorporeal circuit in ECMO and damaged lung can be protected with low tidal volumes and lower positive pressure minimizing atelectrauma and volutrauma (23). Two recent studies, one retrospective and the other a prospective randomized trial, demonstrated significant survival benefit in ECMO patients (24,25). Although these studies are limited by their incapability to differentiate the effect of ECMO from the one from higher level of care at tertiary centers, ECMO is a reasonable option in patients with refractory hypoxemia who do not respond to standard ventilator care.

Inhaled nitric oxide (INO) is known as a selective pulmonary vasodilator and shown to be effective in improving gas exchange. However, the PaO_2 improvement is transient and the positive effect mostly disappears in 48~72 hours. Moreover, the benefit in oxygenation with INO failed to translate into benefit of survival in many trials (26,27). Currently, routine use of INO is not recommended, however short term improvement in oxygenation can be expected in patients with refractory hypoxemia.

Supine position increases the risk of atelectasis in dependent lung regions and it exacerbates intrapulmonary shunting. Prone positioning can obviate the effect of gravity minimizing compression of lung with other organs and preventing atelectasis. Many studies demonstrate the benefit of prone position in oxygenation (28, 29), and a recent meta-analysis showed a significant survival benefit in selected patients with severe hypoxemia (30).

High flow oscillatory ventilation (HFOV) is an alternative mode of mechanical ventilation. It delivers 300-900 breaths/min to maximize lung protection and alveolar recruitment with relatively less tidal volume compared to conventional ventilator (31). Previous studies have shown oxygenation improvement with HFOV (32), and a recent meta-analysis demonstrate a significant survival benefit in patients with refractory hypoxemia receiving HFOV (33).

Our patient's family declined the use of ECMO, but INO and prone positioning were tried with PaO_2 improvement. However, the patient developed multiple tension pneumothoraces and chest tubes were placed with no clinical improvement. Sadly, the family decided on comfort care and patient passed away the same day.

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