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PATIENT MANAGEMENT

An HIV-Positive Patient with COPD Admitted to the ICU with Respiratory Failure

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Presentation of Case

Dr Bhavani Puskur (Infectious Diseases (ID) fellow):

A 54-year-old male active smoker with a history of chronic obstructive lung disease (COPD) on 2 L/min of home oxygen and human immunodeficiency virus-1 (HIV) on antiretroviral therapy with a recent CD4 count of 482 (26%) cells/cc and a suppressed viral load, presented to the Emergency Room (ER) of University of Louisville Hospital with a cough productive of thick, yellow phlegm, dyspnea for 4 days and chest tightness for one day. He complained of having a sore throat, rhinorrhea and nasal congestion during the previous week. He had been using his inhalers at home without significant relief. He denied fever or chills. He had been to the ER multiple times with worsening dyspnea and nonproductive cough, which improved with prednisone and bronchodilators. He declined frequent admission, but this was his third visit to the ER in the last two days; each via emergency medical services transportation.

In the ER, his temperature was 36.6°C, blood pressure was 210/141 mmHg, heart rate was 120 beats/min, and respiratory rate 16/min. His oxygen saturation was 98% while wearing a non-rebreather mask. On physical examination, there was no pharyngeal erythema or exudate and sinuses were non-tender. He had pursed lip breathing with significant inspiratory wheezing. After administration of a breathing treatment and steroids, there was improved aeration throughout all lung fields with decreased, but still diffuse, expiratory wheezing. A chest X-ray was obtained. (**Figure 1**) His electrocardiography was unchanged, and troponins were negative. He was admitted to the Intensive Care Unit (ICU) for use of non-invasive ventilation.

Diagnostic Approach

Dr. Viswanathan Nagarajan (ID fellow): The patient's symptoms were acute in onset with shortness of breath, cough and yellow sputum production, and an episode of chest tightness, with a history of COPD and active smoking. The differential diagnoses at this point are numerous including respiratory viruses (*e.g.*, influenza A and B, rhinovirus, respiratory syncytial virus (RSV)), and bacteria including *Hemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. The chest tightness which occurred suddenly with continued worsening of oxygenation could be from pneumonia, bronchitis or fatigue associated with use of accessory muscles. Although, the chest X-ray does not reveal a consolidation, I note a lack of vascular markings on the right upper part of the thorax when compared to the left side. Even though a high blood pressure and a lack of a pleural line argue against the possibility of a pneumothorax, my concern is that this patient has a pneumothorax of the right lung in view of his symptoms of acute onset of chest pressure, worsening oxygenation and tachycardia. Frequently, in small pneumothoraces, physical exam and blood pressure may be normal.

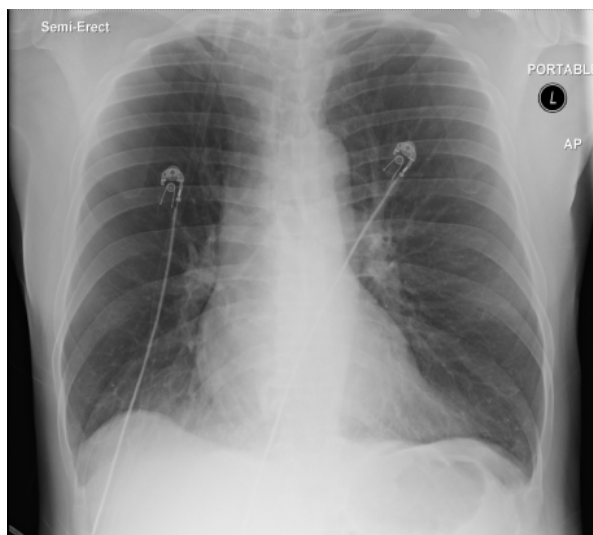


Figure 1 Portable chest X-ray taken at admission

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After reviewing the chest X-ray, my differential diagnoses take a path towards pneumonia causing pneumothorax, rupture of a bulla from COPD, any cavity producing organism like *Mycobacterium avium intracellulare* or *M. tuberculosis*.

Bacterial etiologies like *Klebsiella pneumoniae*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* are capable of producing necrotizing pneumonia. Finally, fungal causes like *Aspergillus fumigatus* and other fungal lesions (e.g., *Histoplasma capsulatum*, *Blastomyces dermatitidis* and *Cryptococcus neoformans*) could also produce a cavity and cause a pneumothorax.

Since there is no cavity seen on the chest X-ray, my concern is a possibility of *Pneumocystis jirovecii* pneumonia (PCP). However, his adequate CD4 and undetectable viral load may deter one from thinking he has PCP.

Dr. Veronica Corcino (ID fellow): During the initial evaluation of a patient with the mentioned symptoms, it is of utmost importance to identify the possible causes of acute respiratory difficulty. Some elements of the history and physical exam may lead us to favor an infectious disease, a vascular problem or a malignancy. His previous empiric steroid use may have contributed to iatrogenic immunosuppression. Since he is HIV-positive, we need to broaden our diagnostic infectious considerations. The arterial blood gas results are compatible with a respiratory acidosis with some metabolic compensation. Also, the Arterial-alveolar gradient is elevated to 389 (his normal should be <18), representing a severe hypoxemic drive. The most common infectious causes of his respiratory distress are viral infections, such as parainfluenza, influenza, adenovirus, coronavirus and RSV; atypical bacteria, such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila*; mycobacterial infections and common bacteria including *S. pneumoniae* and *H. influenzae*. Also, with the decrease in vascularity on the chest X-ray, I agree we need to consider a pneumothorax, and possibly due to PCP.

To establish a definitive diagnosis, it is imperative to initially perform a chest CT scan, viral respiratory panel, atypical respiratory panel, urine Legionella and Streptococcal antigen tests, blood cultures and sputum cultures. Also, cultures from a bronchoscopic sample would be valuable.

Dr. Srikanth Ramachandrani (ID fellow): I was thinking he could possibly have a pneumatocele or pneumothorax. But if that is the case, I am not sure why ID was consulted.

Dr. Julio Ramirez (Chief of ID): We are missing some information. For this patient with a history of COPD, an older film is needed to compare if any of the abnormalities we see now are new or chronic.

Dr. Ramachandrani: Yes, that would help. It would also be good to know if he has been on multiple recent courses of prednisone. If so, he may be immunosuppressed from that perspective. If his CD4 cells were nonfunctional, although above 200 cells/ μ L, then that might expand the differential, too. Given that we know he was in the ER, was discharged and returned within a few hours, I am thinking of an acute event occurred like a pneumothorax. There are lung markings that do not extend peripherally on the right as far as they do on the left, which could be evidence of a pneumothorax. What is the most common organism that can produce a pneumothorax? PCP. And, I agree with the causes of pneumonia in a COPD patient mentioned by Drs. Viswanathan and Corcino; multiple viruses, as well as *H. influenzae*, *S. aureus*, *M. tuberculosis*, and other bacteria.

Dr. Ramirez: So, what I heard was a possible pneumothorax due to *Pneumocystis*, and I do not have a problem with that. I

have a problem with all of the organisms you all discussed that can cause pneumonia in an HIV patient when I do not see any pulmonary infiltrate here. I agree with your assessment of the lack of lung markings in the periphery on the chest X-ray. If it is not a pneumothorax then there could be bullae present because of COPD. To emphasize, the patient may have a pneumothorax and if so, it could be due to *Pneumocystis*, and *Pneumocystis* may be present without an infiltrate. If you say *S. aureus* or tuberculosis caused an abscess that eroded into the pleural space and caused a pneumothorax, then you have to have an infiltrate and there is no infiltrate. What other infectious disease might this patient have that would prompt a consult?

Dr. Barbara Wojda (ID faculty): ID may have been consulted because this patient has HIV.

Dr. Martin Raff (ID Faculty-Emeritus): Another thing is the isolation of *Aspergillus* from the sputum. If he is having bronchospasm that is progressively worsening, it may be a bronchopulmonary Aspergillosis. The lack of eosinophilia goes against that, but you do not necessarily have to have systemic eosinophilia to have allergic pneumoconiosis. And I do not know what his sputum showed in terms of eosinophils.

Dr. Ramirez: We have also seen patients with asthma admitted with pneumococcal bacteremia from the oropharynx, but it is more common in pediatrics.

Dr. Raff: Radiologically, there is obvious, long-term emphysema – he has widened interspaces. In patients with COPD, infiltrates might not appear as they do in a normal lung. There is something in the posterior basal segment of the right lower lobe, but it is not very impressive. I do not see a pleural line to support a pneumothorax. There is something vague, a circular density, inside the right heart border. Again, this film is difficult to interpret.

Dr. Anupama Raghuram (ID Faculty): You fellows primarily mentioned pneumocystis, but it was not as high on my differential. Having said that, we have seen patients with a suppressed HIV viral load and an increased CD4 count and percentage who had prophylactic medication for PCP that was discontinued too soon. We are supposed to wait three months before we discontinue that prophylaxis. But this patient, who I am sure has had multiple COPD exacerbations, had recurrent symptoms and rhinorrhea for a week, then got a little better over the last four days with bronchodilators. He did not really get better – because he came back in 14 hours with much worse symptoms. If I look at this presentation, he started out with something viral and then developed an infiltrate due to a superimposed bacterial infection.

Dr. Ramirez: So, if this patient has COPD and he is coughing, then what is the difference between just an exacerbation and a complicating pneumonia? The presence of a new infiltrate. So, if he has a positive polymerase chain reaction (PCR) test for Influenza, *Mycoplasma*, *Legionella* or he has a positive sputum culture for pneumococcus, *S. aureus* or other, and he does not have pneumonia, then we know his airway is colonized, and have to wonder if this caused his exacerbation or not.

Dr. Puskur: The lungs are hyperinflated. There are no focal airspace or interstitial opacities, pleural effusion or evidence for pneumothorax. The cardiomedastinal contours are within normal limits. Finally, these were redemonstrated findings of

chronic emphysema without acute cardiopulmonary process compared to a previous film. (Figure 2)



Figure 2 Portable chest X-ray taken 6 weeks prior to admission.

Dr. Ramirez: So, there were no new changes on the chest X-ray and these were all chronic changes.

Dr. Puskur: Yes. The patient was admitted to the ICU where he was placed on non-invasive ventilation, and then he was intubated and mechanically ventilated. His influenza and pneumococcal vaccines were up to date. He was started on empiric levofloxacin. A respiratory viral panel was negative except for parainfluenza-3 virus (PIV-3). (Table 1) An influenza antibody was high at 1.74 (normal ≤ 1.11).

Table 1 Results of the respiratory viral panel

Influenza A	Negative
Influenza A H1	Negative
Influenza A H3	Negative
Influenza A 2009 H1N1	Negative
Influenza B	Negative
Parainfluenza-1	Negative
Parainfluenza-2	Negative
Parainfluenza-3	Positive
Parainfluenza-4	Negative
Human Metapneumovirus	Negative
Coronavirus 229E	Negative
Coronavirus HKU1	Negative
Coronavirus NL63	Negative
Coronavirus OC43	Negative
Human Rhinovirus	Negative
Adenovirus B/E	Negative
Adenovirus C	Negative
RSV-A	Negative
RSV-B	Negative

Dr. Ramirez: Why are we ordering antibodies for influenza?! We have to discuss this with the laboratory. If you have a PCR for influenza virus, why do we want to get influenza antibodies?

Dr. Puskur: This was before ID consultation. Additionally, blood cultures were negative. The Legionella and Streptococcal urine antigens were negative. The sputum culture grew *H. influenzae* β -lactamase negative, and *S. pneumoniae*, which was sensitive to ceftriaxone and was intermediately resistant to

penicillin with a minimal inhibitory concentration of 4 dilutions.

Dr. Ramirez: An MIC of 4 – we have not seen this. Regardless, this is a COPD exacerbation and now that we do PCRs, I go back to the idea that we are getting a PCR for everything now. The question is, and we are learning, “What is the microbiome of the respiratory tract?” I used to teach with Dr. Raff years ago that below the glottis the airway was sterile in a normal person. Now we know that below the glottis in a normal person there are millions of bacteria and viruses. All of the lung is filled with bacteria and viruses that we previously were not able to detect with culture and we were not aware of. The microbiome of the respiratory tract - the bacteriome of the lung, the virome of the lung - comprises bacteria and viruses that we normally have in the lung. We are learning that our entire airway is full of bacteria that we did not previously recognize were there. We already knew this of the gastrointestinal tract. My point is that now that we have started doing PCRs from the respiratory tract, we are finding, for example, parainfluenza. Is parainfluenza part of the normal flora of the respiratory tract in a normal person? I do not know. Is parainfluenza part of the normal flora in someone with COPD? I do not know, but chances are, the answer is, “Yes.”

We have started doing all these PCRs in all these patients and we are finding everything in every patient. I am exaggerating, but the problem is that we are going to start finding, for example, parainfluenza, *H. influenzae* and pneumococcus. Are we going to treat every time we find a positive PCR from the respiratory tract? This is going to be the new ID frontier. This is the new antimicrobial stewardship management because the FDA is ready to approve more tests. We already have the viral panel with 15 PCRs. A patient has whatever virus is in the airway. This patient has COPD. Are the organisms detected his normal flora? Or is the acute exacerbation due to one of the organisms? How are you going to know? At least until now, we had a culture that requires 10^3 or 10^4 organisms to be significant, so having a negative culture meant that there were not enough organisms to cause disease. But now with the PCR, everybody is going to be positive.

When we say that 20-30% of the population has pneumococcus colonized in the oropharynx, it is because you can culture 20-30%. We looked at patients in our database with community-acquired pneumonia with negative cultures, and our colleagues in the Clinical Translational & Research Building figured out the microbiome. They found *Streptococcal pneumoniae* in 9 out of 10 cultures. So, if you do a PCR from a bronchoscopy sample, you find the pneumococcus in nearly everybody. Does this mean that they have pneumococcal pneumonia or does this mean that the pneumococcus is part of their normal flora?

In this patient with a COPD exacerbation, I imagine someone gave him oxygen, which led to CO_2 retention leading to hypoventilatory respiratory failure and metabolic acidosis necessitating intubation and mechanical ventilation. An endotracheal aspirate was performed and the results were *H. influenzae*, pneumococcus resistant to penicillin and parainfluenza. And what did we do? The patient was probably placed on ceftriaxone. It is good that we did not find *Pseudomonas*, but only because a PCR for that was not ordered. I'm sure, as a COPD patient, he carries *Pseudomonas* in his airway. If we had a positive PCR for *Pseudomonas*, what would you do? Put him on meropenem for 10 days for a COPD exacerbation? In the past, we would not have known what everyone was colonized with, and so we would treat empirically with penicillin or tetracycline. But soon, we will walk around the hospital and everybody will be on a carbapenem – because

everybody will have an extended-spectrum β -lactamase infection in some place. This is what is coming for us.

We are always going to get something from PCR tests for bacteria and viruses in patients without a pulmonary infiltrate. To me, this is a critical issue. There is not a pulmonary infiltrate in this patient. What do we do? My suggestion would be until we know any better, I would not treat. Now, do we need to treat COPD exacerbations? That is a different question.

To summarize, consider the patients we enroll for pneumonia. Some fulfill the criteria for pneumonia and are treated as such, but eventually it is clear that they just have COPD. Initially, we start ceftriaxone and azithromycin. In two days the patient looks and feels better and the sputum culture grows multidrug-resistant *Pseudomonas*. By that time, we know the *Pseudomonas* is colonization because they got better without antibiotic coverage for it. This is colonization, and we just continue with the cephalosporin and macrolide. We always look at the patient first. Now, with these new tests, the patient is going to arrive to the hospital. You are going to know in three hours that you have a multidrug-resistant *Pseudomonas* or *Klebsiella* with a carbapenemase because of a PCR for Gram negatives and a PCR for resistance genes. Are you going to continue with the ceftriaxone and azithromycin, or are you going to give meropenem or colistin? This is going to be the issue that we are going to face.

We have three organisms and a COPD exacerbation - what do you think is the cause of the COPD exacerbation?

Dr. Puskur: It could be PIV-3 and the copathogens – *H. influenzae* and *S. pneumoniae*. PIV-3 is the most prevalent serotype in both children and adults and is associated with pneumonia and bronchiolitis; bronchiolitis is typically only seen in children. Number 3 is the least predictable PIV and is endemic, but outbreaks do occur in the spring [1,2]. In the United States, PIV-1 usually causes outbreaks biennially during the fall of odd-numbered years [1]. PIV-2 occurs in annual epidemics in the fall [1]. PIV-1 and -2 are detected less frequently in adults and are usually associated with upper respiratory tract infection, although lower tract disease has been described [4]. PIV-4 usually causes mild upper respiratory tract infection in both adults and children. Seasonal patterns of PIV-4 infections have not been established since the disease is usually mild and the virus is difficult to detect. So I was thinking this is parainfluenza virus causing an exacerbation with superimposed *H. influenzae* or pneumococcus.

Dr. Ramirez: Again, I cannot disagree or agree, but I can tell you it could be PIV-1, -2, all of the above or none of the above. The way that you state this, the patient will need antibiotic therapy. The point I am trying to make is that this patient is colonized with all these pathogens.

Dr Raff: Were there any white cells in the sputum smear?

Dr Ramirez: When we look at the literature on COPD exacerbation, people are still using the Anthonisen criteria for antibiotic therapy [4,5]. And we go back to the idea to which Dr Raff eluded. Are there white blood cells? What is the quality of the sputum? Has the sputum increased? Has the sputum changed from yellow to green? You say, “This is pre-history,” but these are the elements we use to see if we have an active

infection. If not, a person does not need antibiotics.

Dr Puskur: He had thick sputum when he came in.

Dr Ramirez: To evaluate the cause of the thick sputum, we do a Gram stain to evaluate if the bacteria and viruses that are always going to be living in the airways of patients – always living in us – are causing disease.

Dr. Raff: And the thing about it is, you can never be certain of anything, the overwhelming odds here are that this gentleman does not have infection that needs treatment. Is that 100%? Of course not. But, we make clinical decisions all the time.

Dr. Ramirez: Then you evaluate the risks versus the benefits. The possibility of infection is low. If I treat this patient’s penicillin-intermediate *S. pneumoniae*, I will have to use high-dose ceftriaxone. The patient is in the unit on a ventilator. Do I treat? Well, I probably wait and see. The advantage of having the patient in the hospital is being able to check him every day. This is going to be the balance. I can tell you with all this new technology there is going to be so much overuse of antibiotics. The antimicrobial stewardship team will be very busy, and we will all be very busy. We need to define when we are going to stop antibiotics, and when it will be appropriate to wait and re-evaluate.

Dr. Puskur: The patient was treated empirically with levofloxacin, which was continued for one week.

Anatomical Diagnosis

COPD exacerbation with colonization due to parainfluenza-3, *Streptococcus pneumoniae* and *Hemophilus influenzae*.

This case was presented at the University of Louisville Division of Infectious Diseases Patient Management Conference.

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