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Viral Pneumonia

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Continuing Education Activity

The increasing role of viral pathogens in pneumonia and the increased recognition of bacterial and viral coinfections in patients with pneumonia necessitate a higher clinical index of suspicion and early identification of viral pulmonary pathogens. This activity describes the evaluation and management of viral pneumonia and highlights the role of the interprofessional team in improving care for affected patients.

Objectives:

- Describe the most common pathogens associated with viral pneumonia.
- Outline the typical presentation of a patient with viral pneumonia.
- Identify the type of viral pneumonia that can be prevented by vaccination.
- Outline the importance of collaboration among the interprofessional team to enhance patient care by educating patients about methods for preventing viral pneumonia.

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Introduction

Viral pneumonia is defined as a disease entity wherein there is the viral causation of oxygen and carbon dioxide gas exchange abnormalities at the level of the alveoli, secondary to viral-mediated and/or immune response-mediated inflammation. The traditional role of viral pneumonia was as a disease found predominantly in the very young, the elderly, and those exposed to influenza. In the past, the diagnosis of viral pneumonia was predicated on it being somewhat a diagnosis of exclusion. History, physical exam, chest radiography, and available lab work (until recently) lacked sensitivity and specificity. Once bacterial pneumonia has been excluded, then viral pneumonia diagnosis was entertained.[1][2][3]

Traditionally, the treatment of viral pneumonia revolved around supportive care:

- Supplemental oxygen when indicated
- Airway augmentation as appropriate
- Monitoring of and replacement of any fluid deficits
- Symptomatic control of temperature and cough
- Rest to reduce oxygen demand
- Treatment of any comorbidities and/or concomitant bacterial pneumonia

The concepts of diagnosis, prevalence, clinical role, and treatment of viral pneumonia are in flux for several reasons.

1. There is a growing population at increased risk of viral pneumonia:

- The increases in life span and early infant survivability have created an additional population at greater risk of viral pneumonia.
- The increased number of those receiving immune-impairing therapy (radiation and/or chemotherapy) for cancer.
- The increased use of disease-modifying hematological/immunological agents in chronic illness, resulting in secondary impaired immunity.
- The advent of HIV
- The increase in the number of patients with inborn immune impairment serving bacterial infection secondary to antibiotic therapy.
- The increased incidence of organ transplantation and immunosuppressive therapy.

2. The availability of sensitive, specific, real-time-result-available testing for viral entities:

- Polymerase chain reaction (PCR) technology is replacing viral cultures and serial viral antigen titers. Both viral culture results and serial antigen testing were problematic because test results were not available until weeks after the acute illness, and viral culturing for pneumonia could involve invasive sampling techniques to acquire.
- The availability of PCR testing has resulted in increased testing in general.
- The mechanism of PCR itself is more sensitive and specific because many viruses are notoriously difficult to grow in culture and are very sample dependent.

3. The positive feedback loop that results from improved viral pneumonia testing modalities:

- The test availability results in an increased number of diagnoses.
- The increased number of diagnosis raises the clinical index of suspicion for the entity.
- The increased clinical index of suspicion raises the number of tests ordered.

4. The availability of safe, tolerable, and somewhat specific antiviral therapies:

- Prior viral pneumonia treatment was essentially supportive measures only.
- Initial efforts at antiviral therapy were not well tolerated.
- The availability of some specific and effective treatments now spur earlier testing and a greater appreciation of the role of viral infection in pneumonia.
- Disease-modifying therapy for HIV is now available.

5. The increasing role of viral pathogens in pneumonia and the increased realization of the role of bacterial and viral co-infection necessitate a higher clinical index of suspicion and early identification of viral pulmonary pathogens. Counterbalance seeing this new clinical burden is the availability of the following:

- Enhanced laboratory detection via ELISA and PCR testing modalities
- Enhanced radiographic detection for a high thin section CAT scan
- An increasing number of safe and efficacious antiviral drugs
- Increased recognition of the role of prevention in viral infectious disease.

Etiology

As pneumonia can be considered somewhat a final common pathway of infection, especially for those who are immune-compromised, a great number of viruses can cause pneumonia. In general, these viruses can be divided into those containing DNA or RNA as their nucleic acid. As this is a bit of an artificial division, a more meaningful approach to etiology is to define by clinical syndromes produced and demographics affected.[4][5][6]

Etiologies of Viral Influenza

Respiratory syncytial virus (RSV)

- RNA virus
- RSV is the most common cause of viral pneumonia in small children and infants.

Rhinovirus

- RNA
- Rhinovirus is the most common cause of upper respiratory tract infection across all age groups, although it is not as commonly represented as a cause of viral pneumonia.

Influenza A, B and C viruses

- RNA
- Influenza A is the greatest cause of mortality and morbidity among the viral types of pneumonia.
- There are multiple subtypes of Influenza A. Two particularly concerning subtypes to be aware of are the avian flu (H5N1)and swine flu (H1N1).

Human metapneumovirus

- RNA
- Human Metapneumovirus is a novel viral pathogen that is increasingly recognized as a cause of viral pneumonia and is implicated as the cause of the SARS outbreak.

Parainfluenza viruses type 1, 2, 3, and 4

- RNA
- Parainfluenza virus has multiple serotypes and is most commonly associated with pneumonia-like illness in young children seasonally. Spring and fall predominate.

Human bocavirus Coronavirus

- RNA
- Coronal viruses are already viruses that cause pneumonia, typically in immune incompetent people.
- However, one subtype of coronavirus is the virus causing Middle Eastern respiratory syndrome, and another has been implicated in severe acute respiratory syndrome.

Adenovirus

- DNA

- Adenovirus most commonly causes pneumonia in people with solid organ transplantation or hematological transplantation

Enteroviruses

- RNA
- Enteroviruses, although common causes of polio, gastrointestinal, and upper respiratory tract syndromes, are less common causes of viral pneumonia.

Varicella-zoster virus

- DNA
- Varicella-zoster virus is associated with both chickenpox and shingles and may cause severe types of pneumonia, particularly in non-immune pregnant women, non-gravid-adults with chickenpox. It is a fairly common cause of pneumonia in people with HIV post-shingles outbreak

Hantavirus

- RNA
- Hantavirus is a zoonotic viral pathogen that emerged in the American Southwest and is associated with rodent feces exposure.
- Hantavirus pneumonia is associated with frequent rapid respiratory failure and cardiovascular collapse.

Parechoviruses Epstein-Barr virus (EBV)

- DNA
- Epstein-Barr virus, although commonly implicated in mono-like syndromes, can be rarely associated with viral pneumonia. The majority of which occur in people with hematological dyscrasias.

Human herpesvirus 6 and 7

- DNA

Herpes simplex virus

- DNA
- HSV I and II are both associated with viral pneumonia in immune-compromised patients, including those with HIV, solid organ transplantation, and hematopoietic transplantation.

Minimi virus Cytomegalovirus (CMV)

- DNA
- CMV is a significant cause of pneumonia in HIV-infected patients with a CD4 count less than 100 cells per millimeter squared.
- CMV is also frequently implicated in pneumonia in recipients of solid organ transplant and hematopoietic transplant.

Measles

- RNA
- A childhood exanthemata's illness that, although less common in the industrialized world secondary to vaccination, remains a major contributor to worldwide childhood mortality secondary to viral pneumonia as a sequela.

Middle East Respiratory Syndrome (Coronavirus)

- RNA
- A subset of the coronavirus associated with severe pneumonia. This was first observed in the Middle East and had an initial mortality rate of 30%.

Severe Acute Respiratory Syndrome (Metapneumovirus)

- RNA
- A subset of Coronavirus causing life-threatening pneumonia

Epidemiology

A number of epidemiological cues can aid in the diagnosis of viral pneumonia, including the following:

Age - Viral pneumonia is most common in the very young and in the elderly. There is a steep decline in the incidence of viral pneumonia from adolescence through the fifth or sixth decade of life. Then an upsurge as age-related immunosuppression and age-related pathologies result in immunosuppression increase.[7][8][9]

Pregnancy - Viral pneumonia continues to be quite concerning in pregnancy. Of particular concern is influenza-related pneumonia secondary to the ubiquitous nature of influenza from late fall to late spring; the last two major flu epidemics, 1918 and 1957, produced respective mortality rates of 50% and 10%. This increased mortality is a major factor in the CDC recommendation that all otherwise healthy women receive an inactivated influenza virus vaccine during the second and third trimesters of pregnancy. An additional, though less common, cause of viral pneumonia in pregnant women is varicella. Limited data reflects a very substantial mortality rate, and current recommendations are for treatment with varicella-zoster immune globulin within 96 hours of exposure to varicella in a non-immune gravid female.

Immune competence - Decreased immune competence can be a result of the following:

- Chemotherapy (and/or) radiation therapy for neoplasm
- Treatment of chronic inflammatory illness with immunosuppressive therapy
- Organ transplantation requiring immunosuppressive medications
- Acquired immune incompetence secondary to HIV
- Inherited diseases of diminished immune competency

The aforementioned may result in increased susceptibility to viral pneumonia.

Comorbid circumstances - A number of comorbid circumstances can predispose patients to viral pneumonia including:

- Trauma
- Severe burns

- Uncontrolled diabetes
- Malnutrition
- Poverty
- Environmental exposure
- Group living

Pathophysiology

On a macroscopic level, viral pneumonia can occur through one of three mechanisms:

1. Direct inoculation of viral particle into the lung (e.g., RSV or influenza)
2. Spread in a contiguous fashion from viral infections near the upper respiratory tract (e.g., measles)
3. Hematogenous spread from a distant viral infection (e.g., CMV)

On a microscopic level, the general pattern of viral pneumonia pathogenesis is as follows. Note that individual viral species causing pneumonia will have some variation from this scheme.

- The target cell is the pneumocyte with resultant alveolar damage.
- The submucosa of the alveoli is targeted, causing inflammation and secondary edema, microhemorrhage, and cellular immune reaction.
- The cellular reaction consists of mononuclear lymphocytes and progresses to PMNs recruitment.
- Fibrin is released.
- Both CD4 and CD8 cells are involved, beginning a cascade of immune product secretion that can end in increased vascular permeability and resultant edema.
- This process may lead to intra-alveolar organization and an obliterans clinical picture.
- The far end of the spectrum of the process includes interstitial pneumonia, pulmonary edema, and cardiogenic shock.

History and Physical

There are no pathognomonic history cues for the diagnosis of viral pneumonia as opposed to bacterial pneumonia. However, cues are suggestive in the differential diagnosis of viral pneumonia:

- Gradual onset as opposed to the sudden onset of symptoms.
- Lower temperature
- Lack of purulent sputum
- History of immunosuppression
- Prodromal viral upper respiratory tract illness
- History of HIV
- History of solid organ transplantation or hematopoietic transplantation
- History of neoplasm

- Concomitant flu symptoms
- Concomitant gastrointestinal symptoms

There are no pathognomonic physical examination findings for the diagnosis of viral pneumonia as opposed to bacterial pneumonia. However, physical findings are suggestive in the differential diagnosis of viral pneumonia:

- Tachycardia or tachypnea out of proportion to the temperature
- Temperature elevation disproportionately low to the level of debility
- Concomitant upper respiratory tract infection
- Rash
- The paucity of physical findings on pulmonary exam disproportionate to the level of debility
- Bilateral positive lung findings

Evaluation

As noted above, both history and physical examination may provide few diagnostic cues as to the etiology of pneumonia (bacterial versus virus). With the existence of specific effective treatment modalities, diagnoses of and identification of viruses causing pneumonia is of increased importance. Fortunately, the diagnostic acuity of laboratory examination in combination with radiography and history and physical examination has progressed.[10][11][12] **Laboratory Examination** ***CBC with differential*** - There are no absolute diagnostic findings as viral pneumonia may result in elevated, normal, or decreased WBC counts. However, viral etiology is less commonly associated with elevated WBC and "left shifts" of the differential than bacterial types of pneumonia. ***Chemistry panel*** - Useful for gauging the degree of dehydration, relative renal dysfunction, and dosing of renal excreted medications ***C-reactive protein*** - As a reactive phase reactant, the CRP level may be elevated with viral pneumonia, although this is not a specific or sensitive finding. ***ELISA - rapid antigen tests*** - ELISA tests allow real-time data for a number of viral pneumonia pathogens. Commonly available ELISA tests include the following:

- Herpes simplex virus (HSV)
- Respiratory syncytial virus (RSV)
- Influenza A and B
- Cytomegalovirus (CMV)

A caveat is that many viruses may be detected via ELISA in the presence of other known bacterial pathogens, and in some cases, the detection of a viral pathogen does not always indicate active disease. ***Gene amplification*** - First and second-generation PCR testing exists and may allow viral pneumonia etiology diagnosis within clinically relevant timing. Clinically available tests using PCR methodology include the following:

- CMV
- RSV
- HPV
- Coronal viruses

Cytological evaluation - No single cytological evaluation of patient tissue cells is entirely diagnostic for viral pneumonia. However, the generalization can be made that DNA viruses typically produce intra-nuclear inclusions, and RNA viruses typically produce cytoplasmic inclusions. ***Viral culture*** - Although viral cultures are the gold standard for the final diagnosis of viral pneumonia, there are limitations such as the following:

1. Viral cultures are routinely not available for 10 to 15 days, which limits them for acute clinical care decisions.
2. The cultures are very dependent on obtaining a valid specimen.
3. The success of delivering a viable specimen to the lab varies as many of the viruses have very specific transport requirements.
4. The fastidious nature of some viral pathogens limits the validity of a negative culture result.

Viral antigens serology - The great majority of the viral entities involved in viral pneumonia have serological markers that can be obtained in the tract. Diagnostic problems include positive serology obtained for people with chronic viral infections that are not a factor in the presence of pneumonia and the limited use in acute treatment and decision making of viral pneumonia. ***Chest x-ray*** - As there is a tremendous overlap in findings on chest x-ray with both bacterial pneumonia and viral pneumonia, no one finding or set of findings is pathognomonic.

Features that are suggestive of bacterial pneumonia include the following:

- Alveolar infiltrates
- Lobar consolidation
- Nodular densities
- Pleural effusion

Features that are more suggestive of viral pneumonia include the following:

- Interstitial infiltrates
- Patchy distribution of interstitial infiltrates
- Bilateral infiltrates
- Pneumonia-like syndrome with an unremarkable chest x-ray

Chest CT scan - The advent of thin-section CT scan has revolutionized the radiographic diagnosis of viral pneumonia. It has been observed, particularly in cases of viral pneumonia-like clinical presentation and normal chest radiography, thin-section CT scan will be positive for parenchymal defects and aid in diagnosis.

Treatment / Management

The cornerstone of treatment of viral pneumonia consists of the following: **Supportive Care**

- The first priority of supportive care is to maintain oxygenation as needed. This may entail nasal cannula, noninvasive airway, or mechanical ventilation.
- The second priority of supportive care is to maintain hydration either via supervised oral intake or intravenous fluids.

- The third priority of supportive care is to maintain rest and decrease oxygen demand.
- A final priority of supportive care is to meet the increased calorie needs of the patient, secondary to the increased respiratory effort.

Management of Comorbid Illnesses Appropriate treatment of Coexisting Bacterial Types of Pneumonia

Most current evidence indicates the frequent existence of concomitant bacterial types of pneumonia. The prototypical example is the observation that the majority of mortality during the 1917-1918 influenza pandemic was secondary to bacterial pneumonia, superimposed on the initial influenza pneumonia.[13][14][15]

Specific antiviral therapy for a number of viral pneumonia exists as does preventative or prophylactic therapies for those at high risk would have been exposed:

Influenza virus

- Treatment: Oseltamivir or peramivir or zanamivir
- Prophylaxis: Influenza vaccine and/or chemoprophylaxis with zanamivir or oseltamivir

Respiratory syncytial virus (RSV)

- Treatment: Ribavirin
- Prophylaxis: RSV immunoglobulin and/or palivizumab

Parainfluenza virus

- Treatment: Ribavirin
- Prophylaxis: Not available

Herpes simplex virus (HSV)

- Treatment: Acyclovir
- Prophylaxis: Not available

Adenovirus

- Treatment: Ribavirin
- Prophylaxis: Not available

Measles virus

- Treatment: Ribavirin
- Prophylaxis: intravenous immunoglobulin

Cytomegalovirus (CMV)

- Treatment: Ganciclovir or foscarnet
- Prophylaxis: intravenous immunoglobulin

Varicella-zoster virus (VZ)

- Treatment: Acyclovir

- Prophylaxis: Varicella-zoster immunoglobulin (VZIG)

Differential Diagnosis

The differential diagnosis for viral pneumonia is broad and includes the following:

- Bacterial pneumonia
- Bacterial or viral bronchitis
- Fungal pneumonia
- Lipoid pneumonia
- Sarcoidosis
- Amyloidosis
- Pulmonary edema
- Congestive heart failure
- Pulmonary embolism
- Pulmonary hypertension
- Pulmonary fibrosis
- Hyperreactive airway disease

Prognosis

Multiple variables determine the prognosis of each case of viral pneumonia, such as the following:

- The relative for virulence of the species of infecting virus-for example, hantavirus, SARS, or MERS carries a much worse prognosis than RSV or influenza virus.
- The immune competence of the patient such that immune impaired patients with HIV carry a much worse prognosis than a gravid female or a previously well, immuno-competent baby.
- The underlying pathologies of the patient, such as the presence of COPD, congestive heart failure, diabetes, cancer, and/or hematological dyscrasias, greatly increases the anticipated morbidity and mortality.
- The presence or absence of concomitant bacterial infection
- The relative point during the infective process at which diagnosis was made and definitive treatment started (if available).

Complications

Complications of viral pneumonia include the following:

- Concomitant bacterial infection, resulting in an abscess, empyema, and or pleural effusion
- Sepsis with secondary multiple organ failure
- Acute respiratory failure
- Cardiovascular collapse

- Acute respiratory distress syndrome

Consultations

1. Consultation with infectious disease specialists can be useful in both ascertaining the etiology of viral pneumonia and its relative clinical role if bacterial co-infection is suspected.
2. Consultation with a pulmonary/critical care physician is advisable if the patient is hypoxic or requires advanced airway or placement in a critical care setting.

Deterrence and Patient Education

Patient education and preventative medicine play a key role in the clinical management of viral pneumonia:

- Education to promote universal vaccination against measles and varicella
- Education to promote appropriate influenza vaccination and post-exposure prophylaxis
- Education of prenatal patient's about influenza and varicella immunity
- HIV prevention and CD4 count surveillance with appropriate prophylaxis
- Education and surveillance of the chronically immunosuppressed, including those receiving chemotherapy, radiation therapy, immunosuppressive drugs

Pearls and Other Issues

1. The role of viruses in primary pneumonia is increasing, and viral respiratory pathogens are increasingly recognized as a cofactor in bacterial pneumonia secondary to the increasing prevalence of immunosuppression-cancer treatment, organ transplant, and HIV.
2. Prevention, especially in the form of immunization against influenza and measles, can significantly decrease the incidence of viral pneumonia.
3. Increasingly, specific and sensitive real-time diagnostic laboratory tools are available in the form of ELISA and PCR modalities for the specific diagnosis of viral pneumonia and assignment of specific treatment when existent.
4. Although there are no pathognomonic history or physical findings for viral pneumonia as opposed to bacterial pneumonia, there are a number of clinical cues that are quite suggestive.
5. Although specific antiviral agents do exist, the cornerstone of treatment for viral pneumonia remains supportive care.

Enhancing Healthcare Team Outcomes

An interprofessional team of healthcare workers manages viral pneumonia. While physicians may treat the infection, the role of the nurse and pharmacist are vital for prevention. The patient should be urged to get the annual influenza vaccine, as this can lower the morbidity and mortality. Pharmacists review prescriptions for dose and interactions and educate patients about side effects and the importance of compliance. All patients should be urged to quit smoking and abstain from alcohol. Further, patients should be educated about hand and personal hygiene to prevent transmission of the virus to others. Patients who are immunocompromised should be educated about the symptoms of pneumonia and when to seek medical care. Finally, patients should be urged to lead a healthy lifestyle, eat healthily, and exercise regularly. Close

communication between the interprofessional team is essential if one wants to improve outcomes. [16][9] (Level 5)

Outcomes

The outcomes in most healthy people with viral pneumonia are excellent. However, in individuals who are immunocompromised or at extremes of age, the prognosis is guarded. Several adenovirus serotypes are known to cause severe pneumonia leading to bronchiectasis and irreversible atelectasis. It is estimated that anywhere from 10%-40% of children may suffer some irreversible lung damage after adenovirus pneumonia. Viral pneumonia in a patient with an underlying disease can add morbidity and lead to marked hypoxia. Overall, most patients recover with supportive measures and have no residual sequelae. [17][18](Level 5)

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