Acute Eosinophilic Pneumonia (AEP)

March 17, 2021 by Josh Farkas

Acute Eosinophilic Pneumonia (AEP) is a rare inflammatory lung disease, which can cause younger adults to develop respiratory failure requiring intubation. This is an important disorder to be aware of because, if treated aggressively with steroid, patients will rapidly recover. Although the disease is rare, it will be encountered with some regularity (e.g., one case every ~2-4 years of full-time ICU practice, depending on how frequently daptomycin is used).
symptoms

general presentation

- Acute hypoxemic respiratory failure, usually evolving within a week (but occasionally developing within a few weeks).
- This will frequently be misdiagnosed as severe pneumonia.
- AEP often precipitates the need for intubation.

findings

1. The most common symptoms are **dyspnea, cough, and fever** (each occurring in >80% of patients).(31253537)
   - The cough is usually *nonproductive*, which may be one distinguishing feature from a typical bacterial pneumonia.
2. Pleuritic chest pain is often seen.
3. Other features of systemic inflammation:
   - Myalgias in about half of patients.
   - Night sweats and chills may occur.

epidemiology

primary AEP

- Generally seen in younger adults (e.g., ~20-40 years old).
- Often triggered by inhalational exposures:
  - Most often, tobacco use (including electronic cigarettes) and marijuana. AEP is particularly related to the *initiation* of smoking, or a recent increase in tobacco exposure.
  - Inhalational substance use (e.g., cocaine, methamphetamine).
  - Other environmental stimuli (e.g., tear gas, firewood dust, indoor renovation).

secondary AEP

- Numerous medications may cause this, most notably:
  - Antibiotics, including:
    - Ceftaroline, **daptomycin**.
    - Minocycline.
    - Clarithromycin.
    - Imipenem/cilastatin, inhaled colistin.
    - Levofloxacin.
  - NSAIDs (e.g., indomethacin, mesalazine, sulfasalazine).
  - Antidepressants (e.g., sertraline, amitriptyline, duloxetine, venlafaxine).
  - Chemotherapeutics (e.g., cisplatin, fludarabine, gemcitabine).
  - Amiodarone, mexiletine.
  - Risperidone.
  - Pirfenidone.
  - Infliximab.
  - (For a complete listing of drugs implicated in AEP, see pneumotox.com(https://www.pneumotox.com/pattern/view/6/Le/acute-eosinophilic-pneumonia-aep))
- Thoracic x-ray therapy (XRT).
- HIV.
- Influenza type H1N1.

laboratory tests
Peripheral eosinophilia (defined as >500 eosinophils/mm3) is present only in about a third of patients. Thus, most patients will lack peripheral eosinophilia. 

However, the definition of eosinophilia using a cutoff of >500 eosinophils/mm3 may be suboptimal in this context. Patients admitted to the ICU due to pneumonia will usually have reduced eosinophil counts. (19519944) Therefore, the presence of eosinophil counts of ~300-500 eosinophils/mm3 may not technically constitute “eosinophilia,” but it may be abnormal within the context of a patient admitted to ICU with presumed severe pneumonia.

*Eosinophilia may emerge over time* if the patient receives no steroid therapy.

Leukocytosis with neutrophilia is often seen.

Inflammatory markers

- C-reactive protein can be markedly elevated, with values often lying in the range of ~90-200 mg/L.
- Procalcitonin can be mild-moderately elevated. (31776322)

Radiology

Features on chest X-ray and CT scan

- Three key findings are typically seen:
  - (1) Patchy, ground-glass opacities.
  - (2) Interstitial abnormalities with smooth thickening of the interlobular septa. On CT scan, this thickening can be observed directly (black arrows in figure below). On chest X-ray, interstitial abnormalities may manifest as Kerley B lines (visible in about a third of cases).
  - (3) Pleural effusions, which are often bilateral and small in size.

If the above findings are present together, they may simulate a pattern which is more commonly seen with cardiogenic pulmonary edema. Thus, if a patient with no heart disease has a CT scan suggestive of cardiogenic pulmonary edema, it might suggest the possibility of AEP (once heart failure is excluded).

In many cases, not all of these features will be present. AEP may be radiographically indistinguishable from pneumonia, or other causes of acute respiratory distress syndrome (ARDS).

Lymph node enlargement may be seen on CT scan. (29206477)
### thoracic ultrasonography

- (1) **B-lines** are seen on the anterior lung field in a pattern consistent with noncardiogenic pulmonary edema:
  - B-lines are widely distributed across the lung fields.
  - Areas with B-lines may be interspersed with areas of normal lung (with an A-line pattern). This *patchy* distribution argues against cardiogenic pulmonary edema.
- (2) Effusions are often seen (15/22 patients in one series had at least one effusion). ([25894572](https://pubmed.ncbi.nlm.nih.gov/25894572/))
- (3) Dense *consolidation* is usually absent. ([25894572](https://pubmed.ncbi.nlm.nih.gov/25894572/))

### invasive testing

**Thoracentesis**

- Effusions are exudative.
- Typically they will reveal *eosinophilia*, with 10-50% eosinophils.
- The differential diagnosis of a pleural effusion with >10% eosinophils includes the following:
  - Blood or air in the pleural space (including serosanguinous effusions due to pulmonary embolism, or post-CABG effusions).
  - Parasitic infections, psittacosis, and some fungal infections (histoplasmosis, coccidioidomycosis).
  - Medication-induced pleural effusion.
  - Churg-Strauss Syndrome.
  - Malignancy (lymphoma, carcinoma).
  - Tuberculosis.
  - Benign asbestos pleural effusion.

**Bronchoscopy with bronchoalveolar lavage (BAL)**

- Findings on bronchoalveolar lavage:
  - Eosinophilia will be seen (>25%), unless steroid has already been administered.
Lymphocytosis and neutrophilia may also occur.\(^\text{(29206477)}\)

The differential diagnosis of pneumonia with >25% eosinophils on bronchoalveolar lavage:

- Acute eosinophilic pneumonia.
- Chronic eosinophilic pneumonia.
- Churg-Strauss syndrome (suggested by a history of asthma, peripheral eosinophilia).
- Hypereosinophilic syndrome (suggested by marked peripheral eosinophilia).
- Paraneoplastic eosinophilia (e.g., due to Hodgkin's disease or lung cancer).
- Parasitic infection (e.g., Ascaris, Strongyloides, Toxocara, or Paragonimus).
- Coccidioidomycosis may rarely cause eosinophilic pneumonia.\(^\text{(29206477)}\)

**overall approach to the diagnosis**

**differential diagnosis & index of suspicion**

- AEP is rare and often not suspected initially. However, some clues may be helpful:
  - Acute illness following initiation of smoking, vaping, or other overt inhalational injury.
  - Respiratory failure following initiation of high-risk medications (especially *daptomycin*).
  - Severe "pneumonia" in a young and generally healthy person, who wouldn't be expected to develop severe pneumonia.
  - Peripheral eosinophilia can be a useful clue (although this is usually absent).
- The differential diagnosis will depend on the clinical context. For example:
  - In a young and immunocompetent patient, the differential may be relatively narrow (e.g., AEP versus bacterial pneumonia).
  - In an immunosuppressed patient, or a patient with significant infectious exposures, the differential diagnosis will be broader.

**bronchoscopy versus empiric therapy**

- Empiric therapy with steroid (and sometimes also antibiotics) may be considered in some situations, especially if:
  - Clinical context is highly suggestive of AEP (e.g., respiratory failure following smoking initiation).
  - The differential diagnosis is narrow enough to empirically treat all likely etiologies with a reasonably narrow treatment regimen (e.g., corticosteroid plus azithromycin and ceftriaxone).
  - The patient is too unstable for bronchoscopy, or at significant risk from bronchoscopy (e.g., bronchoscopy would probably precipitate or require intubation).
- Bronchoscopy will often be required. Reasons to perform bronchoscopy may include the following:
  - Bronchoscopy is required for a definitive diagnosis of AEP.
  - A broad differential diagnosis exists, which cannot be treated empirically without a ridiculously broad array of antibiotics (e.g., the differential diagnosis includes Pneumocystis pneumonia, bacterial pneumonia, AEP, and fungal pneumonia).
  - If the patient has already been intubated, then bronchoscopy may be performed with minimal additional risk to the patient.
  - Thoracentesis revealing eosinophilia might abrogate the need for bronchoscopy in some situations.

**treatment**

**steroid**

- The initial regimen for a critically ill patient might be ~60-125 mg methylprednisolone IV q6hr, until substantial improvement is seen (usually ~1-3 days). Less ill patients may be started on lower doses of steroid (e.g., 40-60 mg prednisone daily). Steroid may be tapered off within about two weeks (a recent series found equivalent efficacy between a 2-week and a 4-week steroid course).\(^\text{(29206477)}\)
- Patients should respond rapidly to steroid, usually within 1-2 days. Failure to respond to steroid suggests an alternative diagnosis.
- *AEP generally doesn't relapse*, although multiple episodes are possible if patients are re-exposed to triggering antigens (especially smoking).

This is unlike many other interstitial lung diseases, which may flare as steroid is being tapered.

**empiric antibiotics**
Patients will often receive empiric antibiotics initially, before the diagnosis of AEP has been secured. Once a diagnosis of AEP has been reached, antibiotics should be discontinued.

- Failure to consider AEP as a cause of respiratory failure.
- Incorrect belief that a lack of peripheral eosinophilia excludes AEP.
- Inadequate search for drugs causing AEP, eventually leading the patient to be re-exposed to a causative drug.

**references**
