Bacterial Pneumonia in Patients with Cancer

Novel Risk Factors and Current Management

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KEYWORDS

• Bacterial pneumonia • Cancer • Neutropenia • Hematologic malignancy • Stem cell transplant
• Immunocompromised host pneumonia

KEY POINTS

- Bacterial pneumonias in patients with cancer cause significant morbidity and mortality, particularly among those with treatment-induced cytopenias.
- Cancer-related and cancer treatment-related derangements of lung architecture, mucositis, and impaired airway protection/swallow function all contribute to pneumonia risks.
- Neutropenia, cytotoxic chemotherapy, graft-versus host disease and other factors increase the risk of developing life-threatening bacterial pneumonia.
- Chest imaging is often nonspecific, but may aid in diagnosis. Bronchoscopy with bronchoalveolar lavage is recommended for patients with suspected bacterial pneumonia with new infiltrates on chest imaging.
- Early initiation of antibiotic therapy is recommended for those suspected of having bacterial pneumonia, ensuring coverage of pathogens commonly encountered in the health care setting.

INTRODUCTION

Bacterial pneumonias cause disproportionate morbidity and mortality in patients with cancer, despite the current aggressive use of prophylactic antibiotics and environmental hygiene measures in this population.[1–5] Pneumonias are estimated to cause or complicate nearly 10% of hospital admissions among patients with cancer, notably including patients with hematologic malignancies whose estimated risk of pneumonia during the course of treatment exceeds 30%.[3,5–8] In fact, in the transfusion era, pneumonia is the leading cause of death among patients with acute leukemias.[3,9,10] Some investigations suggest that as many as 80% hematopoietic stem cell transplant (HSCT) recipients will experience at least 1 episode of pneumonia, and pneumonia is the proximate cause of death in 20% of HSCT patients.[11–13] Patients with cancer demonstrate unique susceptibility to bacterial pneumonias owing to the complex immune dysfunction caused by the disease and its treatment, reflecting such disparate mechanisms as neutropenia, lung architectural derangements, and malnutrition.[5,14–17] Further, frequent exposure to uncommon or antibiotic-resistant organisms occurs through repeated encounters with the health care system.[15,18,19] In addition to lethality attributable to

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the infection, a diagnosis of bacterial pneumonia is associated with poorer overall outcomes in patients with cancer.[7,20,21] In some cases, worsened outcomes result from cancer progression when cytotoxic treatments are deferred in patients suspected of having pneumonia. However, independent of effects on anticancer treatment, a single episode of bacterial pneumonia is associated with an increased frequency and complexity of hospitalization.[22] This review addresses the prevention, diagnosis, and management of bacterial pneumonia in patients with cancer, with an emphasis on the host factors that contribute to susceptibility.

PATHOGENESIS OF CANCER-ASSOCIATED PNEUMONIA

In both healthy and immunocompromised patients, bacteria reach the peripheral lung via inhalation, aspiration, hematogenous spread, or locoregional progression of proximal airway infections. The overwhelming majority of inhaled or aspirated pathogens are expelled via mucociliary escalator function before reaching the alveolar level, with particulates and microbes impacted in the viscoelastic airway lining fluid by turbulent air flow.[23] Those bacteria that reach the peripheral lung must breach the barrier defenses that exclude pathogens from the lower respiratory tract.[24,25]

The barrier defenses of the lower respiratory tract are often thought of as passive barricades to pathogen translocation. However, the lungs are protected by a complex array of dynamic defenses that include both structural impediments to pathogen entry and active antimicrobial effectors. Epithelial cells express effectors such as cationic antimicrobial peptides, reactive oxygen species, and surfactant proteins into the airway lining fluid, reducing pathogen burden through direct microbiocidal effects, activation of leukocyte-mediated immunity, and enhanced pathogen opsonization.[26–28] Alveolar macrophages engulf invading pathogens and promote host response via the complement system and inflammatory mediators.[29–31] Ligation of local epithelial and macrophage pattern recognition receptors by pathogen-associated molecular patterns promotes recruitment and activation of neutrophil responses and sculpts the adaptive response in the lung.[26–28]

In the intact host, these responses are usually successful in eliminating pathogen threats. However, the immunopathology resulting from the robust expression of antimicrobial mediators may result in local tissue injury and systemic inflammation, particularly when the pathogen successfully establishes infection.[32,33] In fact, many of the classical clinical signs that characterize the syndrome of pneumonia are predominantly manifestations of these host responses. These include radiographic pulmonary infiltrates that reflect airspace filling by edema fluid, leukocytes, and debris; systemic signs such as fever and leukocytosis; and mucopurulent cough.[16,34]

Both cancer and its treatment cause derangements of innate and adaptive responses to bacteria in the lungs. As summarized in **Fig. 1**, leukocyte depletion, dysregulated inflammation, mucosal disruptions, impaired pathogen recognition, tumor-related anatomic abnormalities, and graft-versus-host responses all contribute to the tremendous susceptibility of patients with cancer to lower respiratory tract infections.[5,35] Functional and anatomic defects frequently coexist in patients with cancer. Further, recurrent health care encounters that are typical among patients with cancer promote exposure to nosocomial and drug-resistant pathogens.[15]

Thus, not only are patients with cancer uniquely susceptible to bacterial infections, but their dysfunctional immune responses make the diagnosis of bacterial pneumonia challenging. In the absence of a brisk inflammatory response, many of the cardinal features of clinical pneumonia may not be present. This diagnosis may be made even more difficult when the patient has an already abnormal chest radiograph due to the disease or its treatment, or when a patient has competing causes for fever or cough.

HOST SUSCEPTIBILITY FACTORS IN THE CANCER PATIENT

Patients with cancer encounter myriad homeostatic derangements, and susceptibility to bacterial pneumonia among patients with cancer varies according to the type of malignancy, treatment types, and timing and comorbidities.[15]

General debility, as suggested in individual patients by Eastern Cooperative Oncology Group Performance Status scores of 2 or greater, has been identified as a risk factor among patients with lung cancer for the development of bacterial pneumonia.[36] It has been suggested that this may reflect, in part, the catabolic and malnourished states that are common among patients with cancer. In particular, malignancy-related deficiencies of essential fatty acids and polyribonucleotides, have been noted to cause important (but reversible) impairments of inflammatory and cytotoxic responses that contribute to pneumonia susceptibility.[37] Preexisting lung disease, including emphysema or bronchiectasis, are also