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Bacterial pneumonia in cancer patients: novel risk factors and current management

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Synopsis

Bacterial pneumonias exact unacceptable morbidity upon patients with cancer. While the risk is often most pronounced amongst patients with treatment-induced cytopenias, the numerous contributors to life-threatening pneumonias in cancer populations range from derangements of lung architecture and swallow function to complex immune defects associated with cytotoxic therapies and graft-vs.-host disease. These structural and immunologic abnormalities often make the diagnosis of pneumonia challenging in cancer patients and impact the composition and duration of therapy. This manuscript addresses the host factors that contribute to pneumonia susceptibility, summarizes diagnostic recommendations, and reviews current guidelines for management of bacterial pneumonia in cancer patients.

Keywords

bacterial pneumonia; cancer; neutropenia; hematologic malignancy; stem cell transplant; immunocompromised host pneumonia

Introduction

Bacterial pneumonias cause disproportionate morbidity and mortality in cancer patients, 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

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10% of hospital admissions among cancer patients, 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 one episode of pneumonia, and pneumonia is the proximate cause of death in 20% of HSCT patients [11-13]. Cancer patients demonstrate unique susceptibility to bacterial pneumonias due to 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 healthcare system [15, 18, 19]. In addition to lethality attributable to the infection, a diagnosis of bacterial pneumonia is associated with poorer overall outcomes in cancer patients [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 anti-cancer treatment, a single episode of bacterial pneumonia is associated with increased frequency and complexity of hospitalization [22]. This review addresses the prevention, diagnosis and management of bacterial pneumonia in cancer patients, with 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 will be expelled via mucociliary escalator function prior to 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 both 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 Figure 1, leukocyte depletion, dysregulated inflammation, mucosal disruptions, impaired pathogen recognition, tumor-related anatomic abnormalities and graft-versus host responses all contribute to cancer patients' tremendous susceptibility to lower respiratory tract infections [5, 35]. Functional and anatomical defects frequently coexist in cancer patients. Further, recurrent healthcare encounters that are typical among cancer patients promote exposure to nosocomial and drug-resistant pathogens [15].

Thus, not only are cancer patients 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 x-ray 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

Cancer patients encounter myriad homeostatic derangement, and susceptibility to bacterial pneumonia among cancer patients 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 (ECOG) Performance Status scores of 2, has been identified as a risk factor among lung cancer patients for development of bacterial pneumonia [36]. It has been suggested that this may reflect, in part, the catabolic and malnourished states that are common among cancer patients. 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]. Pre-existing lung disease, including emphysema or bronchiectasis, are also associated with increased risk of cancer-related bacterial pneumonia and mortality [38, 39].

Aspiration Events—Poorly coordinated swallow function and impairments of airway protection are frequently observed among cancer patients. Structural lesions associated with head and neck cancer (HNC) and neurological defects associated with central nervous system lesions are well recognized causes of aspiration of orogastric contents, placing patients at increased pneumonia risk [40, 41]. Similarly, pneumonia risks are elevated among patients with esophageal cancers, due to excessive gastric reflux and to tracheoesophageal fistulae [42, 43]. Unfortunately, these risks may persist after completion of cancer treatment in each of these conditions, due to persistent neuropraxias or permanent anatomic derangements caused by radiation fibrosis, laryngectomy or esophagectomy [44-46].

Mass lesions are not the only causes of aspiration-related lower respiratory tract infections in cancer patients. Oral mucositis and esophagitis commonly affect patients with hematologic malignancies or those receiving stem cell transplantation, also causing impairments of swallow function that result in bacterial pneumonias. Interestingly, while the oral microbial diversity of cancer patients does not much differ from the general population, the incidence of periodontal disease is significantly greater in those undergoing cancer chemotherapy [47-49]. It has been subsequently suggested that optimized dental care in patients receiving chemotherapy may reduce the incidence of aspiration events and reduce the frequency of fever, productive cough and positive blood cultures [50]. Relatedly, whereas gut dysbiosis has been associated with such HSCT complications as bloodstream infections and graft-vs.-host disease (GVHD), it has recently been reported that altered gut microbiota may also be predictive of pulmonary complications of HSCT, including bacterial pneumonias [51].

Mucositis and Bacterial Translocation—In addition to the aspiration risk, cancer-related mucositis also facilitates pneumonia caused by hematogenous spread of pathogens that translocate from the upper and lower gastrointestinal tract.

Due to the profound effects on rapidly replicating gastrointestinal epithelial cells, chemotherapy-related mucositis represents a serious threat to mucosal integrity. This has been long observed with the use of drugs that alter DNA synthesis, and has been classically described with such agents as methotrexate, 5-fluoruracil and cytosine arabinoside. However, the chemotherapeutic agents known to cause mucositis are many and varied in mechanism of action, including melphalan-based regimens [52-55], cyclophosphamide [52], docetaxel and vinorelbine to note a few [56, 57]. Repetitive treatment cycles are associated with an increasing risk and severity of mucositis [58]. Even when clinical mucositis scores are low, even the modest degrees of mucositis still represent potentially important breakdowns in the host innate defense barriers [59].

Unfortunately, while targeted therapies generally have fewer off-target effects than do conventional cytotoxic therapies, mucositis is still widely reported with many tyrosine kinase, mammalian target of rapamycin (mTOR), epidermal growth factor receptor (EGFR), and vascular endothelial growth factor receptor (VEGFR) inhibitors [60, 61].

Pneumonia-relevant mucositis is also extremely common among patients receiving radiation therapy to the head and neck, mediastinum, esophagus, and to a lesser extent among any patient receiving thoracoabdominal radiation [62-64].

Anatomic Derangements—As in non-cancer patients, distorted lung anatomy due to pre-existing lung disease or prior infections predisposes to colonization and infection with bacterial pathogens [65-67]. Further, architectural changes specific to cancer and its treatment also place patients at increased risk for bacterial pneumonia. Airway obstruction caused by endoluminal disease or extrinsic compression may impede normal mucociliary clearance and promote postobstructive pneumonias [68-70]. Lymphangitic disease may obstruct airways and may impair leukocyte responses to infected lung segments. Similarly, airway distortion caused by prior radiotherapy or surgical intervention may lead to increased bacterial infections.

Neutropenia—In 1977, Bodey and colleagues described the inverse association of absolute neutrophil count and risk of infection [71]. Since then, chemotherapy-induced neutropenia has become the most widely recognized risk factor for cancer-associated bacterial pneumonias. Neutrophils are particularly sensitive to nucleoside analogues and alkylating agents, both causing dose-dependent reductions in circulating neutrophil levels. Severe neutropenia (<500 cells/ μ l) is especially associated with serious lung infections and poor outcomes. Underscoring the relevance of this risk factor, Vento, et al., estimate that nearly 60% of cancer patients experiencing chemotherapy-induced neutropenia will develop pulmonary infiltrates on radiographic examination [72]. The rapidity of onset, duration, severity and underlying physiologic process all further impact susceptibility to neutropenic pneumonia [18, 30, 35-39, 73]. Moreover, impairments of neutrophil phagocytosis and chemotaxis follow common cancer-related insults such as radiation, corticosteroids, hypovolemia, acidosis and hyperglycemia [5, 40]. Thus, functional neutropenia can also contribute to cancer-related pneumonia risk [3].

Although chemotherapy-induced neutropenia is most commonly associated with treatment of hematologic malignancies and conditioning regimens for HSCT, a number of regimens to treat solid tumors also cause neutropenia [74-77].

Non-neutropenic defects—Chemotherapy regimens also cause a wide array of non-neutropenic leukocyte defects that predispose patients to bacterial pneumonias. For example, alkylating agents also cause immune dysfunction through disproportionate depletion of $CD4^+$ T cells, relative to $CD8^+$ T cells [78-80]. Tyrosine kinase inhibitors increase risks for bacterial pneumonia through both neutropenia-dependent and -independent mechanisms, possibly including effects on antibody class switching [81, 82]. Anthracyclines, taxanes, topoisomerase inhibitors, and vinca alkaloids all appear capable of increasing risk of bacterial pneumonia via non-neutropenic mechanisms during treatment [83].

There are also a number of non-neutropenic defects that predispose patients to bacterial pneumonia, even after treatment has been completed. For example, agents such as fludarabine and alemtuzumab can cause long term lymphocyte dysfunction, in some cases lasting years beyond the treatment interval.

In recipients of allogeneic stem cell transplants, GVHD can predispose to bacterial pneumonias both through episodes of mucositis and chronic defects of cell-mediated immunity [13, 84]. Moreover, intensification of immunosuppressive therapies in response to GVHD flares notably enhances susceptibility to bacterial pneumonia.

Finally, hematologic malignancies can cause intrinsic immune defects that predispose patients to bacterial pneumonia. Specific defects depend on the cells affected by the malignancy. For example, excessive expansion of clonal leukemia populations can result in deficiencies of functional leukocytes, resulting in immune dysfunction through cytopenias. On the other hand, non-malignant leukocytes may be present at near normal levels in multiple myeloma, but immune defects may exist due to deficiencies of functional immunoglobulins and immunoglobulin class-switching.

Prevention of Bacterial Pneumonia in Cancer Patients

Minimizing pathogen exposures is foundational to preventing bacterial pneumonia in cancer patients. Optimized hand hygiene is central to nosocomial spread of pneumonia-causing organisms as well as avoidance of community-acquired pathogens, and no other single intervention has been demonstrated to be more effective [3]. The past four decades have also seen reduced pathogen transmission to neutropenic patients through development of protected hospital environments utilizing laminar airflow, ultraviolet light decontamination and specialized personal protective equipment.

Given the relevance of oropharyngeal aspiration to pneumonia, regular dental care is important in cancer patients. Periodontal disease following radiation, chemotherapy or malignancy-related immune dysfunction can all be associated with increased risk of preventable pneumonia.

The role of vaccinations in cancer patients has been an issue of intensive investigation, given the complex immunologic consequences of malignant diseases, chemotherapy and immunosuppression.

The only FDA-approved vaccinations available against bacterial pneumonia both target *Streptococcus pneumoniae*. The 23-valent polysaccharide vaccine (PSV23), principally activates mature B-cells which may be deficient or dysfunctional in patients with cancers such as lymphomas or myelomas. Interestingly, in this population, antibody responses to PSV23 positively correlate with hematologic response to chemotherapy [85]. The conjugated 13-valent pneumococcal vaccination (PCV13) depends more heavily upon T-cell responses, and remains more immunogenic in many immunocompromised cancer populations [86-88].

Two cancer populations of particular note when considering vaccination are those with asplenia and those receiving anti-CD20 therapy, as both generate poor humoral responses to vaccines. Some cancer patients require therapeutic splenectomy while others, including many patients with Hodgkin lymphoma, develop functional asplenia that results in both increased frequency and severity of pneumococcal disease [89]. These patients may generate reduced initial antibody titers to PCV13 vaccination, especially if given during cytoreductive therapy, and even apparently normal initial levels may decline below expected titers years after vaccination [90]. Anti-CD20 therapy such as rituximab disrupts B cell mediated antibody production, increasing the risk of invasive pneumococcal disease impairing responses to both PCV13 and PSV23 [87, 91].

The current CDC recommendation is that immunocompromised patients with cancer receive both the PCV13 followed by PSV23 at least eight weeks later [92]. Where feasible, patients typically initiate vaccination prior to initiation of chemotherapy, particularly if rituximab is anticipated. In those not vaccinated prior to receiving cytotoxic therapy, some experts recommend delaying vaccination up to 6 months after chemotherapy is completed to ensure greater efficacy. The effectiveness of the current recommendations in reducing disease burden remains unclear, potentially due to underutilization of vaccines in the cancer

population resulting from confusion about the utility of vaccination in patients who are receiving myeloablative treatments, even in tertiary cancer centers [93].

The optimized strategy to best protect HSCT patients remains an area of intensive investigation. Multi-society guidelines from 2009 [11] recognize that PSV23 elicits inadequately immunogenic responses in the first year after HSCT, so three doses of the more immunogenic, but less broad, PCV are recommended in that interval. A fourth vaccination with PSV23 may provide enhanced breadth of coverage, though PCV may be preferred for the fourth dose in patients with chronic GVHD. The timing of the vaccination also remains controversial, as initiation of pneumococcal vaccination 3 months after HSCT may provide confer early protection, but may not provide similarly durable antibody responses or reliable PSV23 boost compared to vaccination started 9 months after HSCT.

Diagnosis of Bacterial Pneumonia in the Cancer Patient

While the clinical syndrome of pneumonia is well characterized in the general population, this diagnosis may be challenging in the cancer patients. Most of the cardinal clinical features of pneumonia represent host response elements that may be impaired or absent in immunocompromised cancer patients. Conversely, when present, cough, fever and radiographic infiltrates may be manifestations of the malignancy itself or complications of therapy. Nevertheless, the correct diagnosis of pneumonia and identification of an infecting pathogen are both associated with better outcomes. Thus, a high clinical suspicion and appropriate testing are essential. Further, given the severe immune impairment and frequent health care exposures experienced by cancer patients, it important to consider the possibility that pneumonias may be caused by uncommon, atypical or opportunistic organisms.

Imaging Studies—While plain chest x-rays (CXRs) are often rapidly available and can reveal some lower respiratory tract infections, they are nonspecific and have a poor negative predictive value, particularly in hematologic malignancy and HSCT patients. In one recent study, radiologist-interpreted CXR predicted the correct type of infection in immunocompromised patients with pneumonia only 34% of the time [94]. CT is more sensitive than CXR in detection and characterization of pneumonia. When performed with high resolution formatting, in particular, CT is better able to discern bilateral and apical disease, and to discriminate between typical patterns suggestive of bacterial infection than CXR [95]. In another study of adults with febrile neutropenia, 48% of patients with a CT suggestive of pneumonia were found to have a CXR that was interpreted as normal [96]. Offsetting enthusiasm for early and frequent CT in cancer patients is the fact that radiographic studies subject patients to radiation exposures, potentially to organs that also receive therapeutic radiation. Ultra-low dose CT has been investigated as a tool to maintain adequate image quality while reducing radiation dose to cancer patients. A recent study in patients with febrile neutropenia suggests that this approach may preserve reasonable diagnostic accuracy [97].

Certain CT patterns, such as lobar consolidation or peribronchial nodules, have been described as characteristic of bacterial pneumonias [98], as shown in Figure 2A-C. However, CT patterns are frequently nonspecific, particularly in patients with impaired immune

function, and cannot be relied upon for a microbiologic diagnosis [98, 99]. Moreover, the patterns observed in cancer patients with bacterial pneumonia overlap substantially with competing non-infectious diagnoses, as suggested by the CT patterns shown in Figure 2D-F.

Positron emission tomography using fluorine-18 fluorodeoxyglucose (PET-FDG) has been proposed as a means to predict infection in cancer patients with infiltrates, though no study has clearly defined standard uptake values that are confirmatory of infection or changed management [100-102].

Diagnostic Bronchoscopy—Although CT lacks specificity, it is frequently helpful in directing bronchoscopic investigations. In cancer patients with suspected pneumonia and from whom high quality sputum samples cannot be obtained, flexible bronchoscopy with bronchoalveolar lavage (BAL) is the diagnostic tool of choice. Depending on the patient population investigated and technique used, the diagnostic yield for a pathogen or non-infectious cause of infiltrates (e.g., malignant cytology) is reported between 15% and 55% [103-106]. Diagnostic yield may be enhanced by rigorous adherence to BAL protocol [106]. Further, BAL performance in the first four days of symptoms in HSCT patients with suspected pneumonia is associated with improved diagnostic yield and mortality [107]. The role for bronchial washings remains unclear, and the addition of protected specimen brushing (PSB) and protected lavage (PBAL) has not been shown to improve the diagnosis of pneumonia in patients with hematologic malignancies [108].

Transbronchial biopsy is principally beneficial in aiding the diagnosis of neoplasms or non-infectious pneumonitis [109]. Not only is this procedure often precluded in cancer patients by thrombocytopenia, but convincing evidence is lacking that culture of biopsy tissue results in reliable culture information. Thus, this intervention is recommended in only select patients with cancer and suspected pneumonia.

Serial dilution culture remains the standard clinical practice for bacterial pathogen detection, due to the breadth of organisms that can be identified by this strategy, the ability to quantify pathogen burden, and the ability to subculture for antimicrobial susceptibility testing. Table 1 identifies select bacterial pathogens that are frequently detected in patients with chemotherapy-induced neutropenia by this technique. However, PCR-based pathogen detection has the potential to supplement and, theoretically, supplant culture-based methods in patients with cancer. PCR-based strategies obviate the obligate delays for pathogen growth, potentially improving the time-to-correct antibiotics. Since cancer patients are typically receiving empiric antimicrobials by the time of BAL, standard growth techniques may be impaired, but PCR assays can detect genomic material even from nonviable bacteria [110]. Further, multiplex detection of resistance cassettes can allow prediction of antibiotic susceptibility and may allow detection of difficult to culture pathogens, including anaerobes [111]. However, the use of standalone PCR detection for bacteria is currently impeded by local laboratory capability and practical challenges of testing sufficiently comprehensive PCR probe sets.

Nonbronchoscopic diagnostics—Data from general (noncancer) populations indicate that urine antigen testing for bacterial pathogens including *S. pneumoniae* and *Legionella*

spp. provides enhanced sensitivity for the diagnosis of bacterial pneumonias over culture-only strategies. Moreover, like PCR testing on respiratory secretions, urinary antigen testing can be performed in minutes, potentially improving time-to-diagnosis and time-to-correct antibiotics [112, 113]. Notably, there appears to be a strong correlation between urine antigen levels and markers of host response, including procalcitonin levels, C-reactive protein levels and lobar infiltrates on CXR. Thus, there may be some dependency of urine antigen levels upon the host responses, so further testing is required to confirm that the sensitivity is comparable in immunocompromised cancer populations.

Biomarkers to aid the diagnosis of bacterial pneumonia in immunocompromised cancer patients have been long sought. Serum concentrations of procalcitonin, interleukin-6, C-reactive protein, serum amyloid proteins, and others have been investigated for their utility in the diagnosis of fevers of unknown origin [114]. While increases in these markers have been observed in critically ill patients, none has demonstrated discriminatory capacity for bacterial pathogens in this population [115]. Procalcitonin levels in pleural fluid may offer some advantage in distinguishing parapneumonic or tuberculous effusions from malignant effusions [114, 116].

Management of Bacterial Pneumonia in the Cancer Patient

Antibiotic therapy—The value of the above diagnostic tests is contingent upon the availability of effective therapies. Because of the broad range of potential pathogens and innumerable host factors, therapeutic strategies must be directed by the patient's immune status and exposure history, both to pathogens and antimicrobials.

Treatment should generally not be withheld while diagnostic interventions are undertaken. Delays in appropriate antimicrobial therapy increase the risk of secondary complications and infection-associated deaths in immunocompromised cancer patients, thus it is common practice to initiate empiric or pre-emptive antibiotic therapy when pneumonia is suspected [3, 18, 117, 118]. No consensus exists for the optimal time to first antibiotic dose, although one recent study suggests that neutropenic fever outcomes are better when antibiotics are delivered within 104 minutes of presentation [119]. While the earliest possible antibiotic dosing is generally recommended, possible exceptions include when bronchoscopic evaluation is immediately available [3]. In that case, it may be reasonable to hold empiric antibiotic therapy until completion of the brief procedure, potentially enhancing the diagnostic yield of the collected microbiologic cultures. This delay should generally be no longer than 2 h. Antibiotics should not be held for multiple hours or days in anticipation of bronchoscopy, as the harm from delaying therapy outweighs the benefits of improved test performance [120-122].

Initial antimicrobial therapy for febrile cancer patients with pulmonary infiltrates should ensure coverage of multidrug-resistant strains of *S. aureus* and *P. aeruginosa* [15, 123-126]. Coverage for atypical organisms is also appropriate in cancer patients admitted with community-acquired pneumonia, with the selection of macrolide, fluoroquinolone or doxycycline therapy largely dependent on the agent(s) chosen for drug-resistant pathogens and upon prior prophylactic regimens [127, 128]. All antibiotic choices should consider culture data, pneumonia severity, local antibiotic sensitivity profiles, prior antibiotic

exposures, and patient immune status [129]. Empiric antibiotics for early hospital-acquired pneumonia (early HAP, within 7 days of admission) should include coverage of *S. pneumoniae*, MRSA, *H. influenzae* and *Enterobacteriaceae*. Initial regimens for patients with late hospital-acquired pneumonia (late HAP), health care-associated pneumonia (HCAP) or ventilator-associated pneumonia (VAP) should ensure enhanced coverage for multidrug resistant Gram-negative bacilli [117, 120, 125, 130]. Secondary antibiotic selections for patients with refractory HAP, HCAP or VAP should be determined by institutional pathogen susceptibility profiles and on prior patient antimicrobial exposures [124, 125, 130, 131].

Early de-escalation of broad empiric therapy may be considered in patients who demonstrate prompt clinical response and in whom granulocyte recovery has occurred, especially if a susceptible pathogen has been identified [132, 133]. De-escalation should be undertaken with caution in patients with poor clinical response to antimicrobial therapy, persistent neutropenia or ongoing immunosuppressive therapy [134].

Therapies to augment host defenses—Despite broad-spectrum antibiotic strategies, mortality rates remain unacceptably high in cancer patient with bacterial pneumonia, particularly among neutropenic patients. Often, antibiotic failures arise, at least in part, from the continuing immune defects associated with the primary disease. Consequently, means to mitigate immune defects of cancer patients and improve pathogen clearance have become an area of intensive investigation.

A major research focus has been correction of granulocytopenia. Preparations of G-CSF (filgrastim, lenograstim and pegfilgrastim) and GM-CSF (sargramostim and molgramostim) are commercially available. Both classes demonstrate efficacy in reducing the duration of neutropenia, though a less favorable side-effect profile of GM-CSF limits its use primarily to post-HSCT immune reconstitution [135, 136]. While evidence suggests colony-stimulating factors may be safely used to prevent some bacterial pneumonias in cancer populations [137], they are not generally recommended as a treatment of established bacterial infections. Current guidelines recommend administration of G-CSF if the risk of developing febrile neutropenia is greater than 20% based on patient-specific risk factors [136].

Infusion of donor granulocytes has also been proposed as an adjunct therapy in cancer patients with febrile neutropenia. While this strategy holds promise, it remains investigational and interpretation of the associated studies is challenging due to heterogeneity of the populations and protocols [138]. However, some authors argue that severely ill neutropenic patients may benefit from granulocyte transfusion [137].

In addition to efforts to increase the absolute number of leukocytes in cytopenic patients, multiple groups have investigated manipulation of existing leukocytes through administration of recombinant cytokines. Exogenous interferon-gamma has demonstrated success in reducing some bacterial infections in patients with congenital neutropenia, and more recent studies suggest efficacy in patients with opportunistic infections following HSCT [139]. Postulated mechanisms for this effect include induction of surface molecules such as MHC Class II, Fc receptor gamma and integrins, increased phagolysosomal

superoxide production, and prolonged half-life of granulocytes. Administration of interleukin (IL)-12 has also been proposed as a means to protect against lung infections [140], potentially via interferon-gamma- and tumor necrosis factor (TNF)-dependent mechanisms.

Induction of innate antimicrobial responses directly from lung epithelial cells offers a novel alternate strategy to prevent, and possibly treat, pneumonias in cancer patients. Lung epithelial cells are long lived and relatively resistant to chemotherapy [141, 142]. Beyond their well-known barrier function, these cells also demonstrate a substantial capacity to detect pathogens, to modulate local immune responses and to generate directly bactericidal responses through the production of antimicrobial peptides and reactive species [26, 143]. Advances in the understanding of the molecular mechanisms involved in recognition and signal transduction have allowed development of inhaled therapeutics that induce protective innate immune responses from the lung epithelium in animals. In animal models of pneumonia, this provides protection from lethal pathogens even when there is concurrent neutropenia [142, 144, 145]. Preclinical animal studies of one such treatment, PUL-042, demonstrate protection against Gram-positive, Gram-negative, fungal and viral pneumonias, and clinical trials are ongoing [142, 145, 146]. Augmentation of innate immune responses offer several hypothetical advantages in terms of rapidity of effect, breadth of pathogen specificity, and lack of known antimicrobial resistance, but efficacy has not been established in humans.

Conclusions

Bacterial pneumonias remain a frequent and challenging complication in patients with cancer. The clinical approach requires integration of traditional microbiologic techniques as well as targeted molecular diagnostics. Successful management strategies depend on early recognition, consideration of numerous cancer-related host factors, and prompt initiation of broad-spectrum antibacterial agents. Newer host-directed therapies that help to reconstitute or augment the immune system are under active investigation in clinical trials. These may serve to supplement more traditional approaches in the future.

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Key Points

- ◆ Bacterial pneumonias in cancer patients cause significant morbidity and mortality, particularly among those with treatment-induced cytopenias.
- ◆ Cancer- 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 non-specific but may aid in diagnoses. Bronchoscopy with bronchoalveolar lavage is recommended in patients at high risk for bacterial pneumonia with new infiltrates on chest imaging.
- ◆ Early initiation of antibiotic therapy is recommended for cancer patients suspected of having bacterial pneumonia, ensuring coverage of pathogens commonly encountered in the health care setting.
- ◆ Investigations into novel preventative strategies and therapies to augment host defenses are ongoing.

Figure 1. Host factors that promote bacterial pneumonia susceptibility in cancer patients

Although cancer patients' medical encounters expose them to uncommon, virulent and drug-resistant pathogens, much of the increased risk of pneumonia in this population derives from complex and often concurrent impairments of host defense. Shown are frequent defects in cancer patients' pneumonia defenses, caused by insults both in and outside the lungs. CNS, central nervous system.

Figure 2. Radiographic presentations of bacterial pneumonia in cancer patients

CT images of cancer patients with documented bacterial pneumonias. (A) Multifocal lobar consolidation in a patient with acute myelogenous leukemia and *Legionella micdadei* pneumonia. (B) Diffuse ground-glass infiltrates in a patient with chronic myelomonocytic leukemia and *Raoultella planticola* pneumonia. (C) Peribronchial nodules (and small, chronic pleural effusions) in a patient with myelodysplastic syndrome and *Stenotrophomonas maltophilia* pneumonia. (D) Multidrug-resistant *Klebsiella pneumoniae* pneumonia presenting as a single mass in a patient with aplastic anemia. (E) Diffuse, mixed alveolar and interstitial infiltrates in a patient with myelodysplastic syndrome and *Pseudomonas aeruginosa* pneumonia. (F) Methicillin-resistant *Staphylococcus aureus* pneumonia presenting as new nodules on a background of pre-existing nodules in a patient with renal cell carcinoma metastatic to the lungs.

Table 1

Bacterial Pneumonia Pathogens Commonly Associated with Chemotherapy-Induced Neutropenia

Gram-positive Bacteria
<i>Nocardia</i> spp.
<i>Rhodococcus equi</i>
<i>Streptococcus pneumoniae</i> †
<i>Streptococcus pyogenes</i>
<i>Staphylococcus aureus</i> †*
Gram-negative Bacteria
<i>Acinetobacter baumannii</i> -complex
<i>Alcaligenes/Achromobacter</i> spp.
<i>Burkholderia</i> spp.
<i>Citrobacter</i> spp. *
<i>Enterobacter cloacae</i> †
<i>Escherichia coli</i> *
<i>Klebsiella pneumoniae</i>
<i>Moraxella catarrhalis</i>
<i>Neisseria meningitidis</i>
Nontypeable <i>Hemophilus influenzae</i> †
<i>Proteus</i> spp. *
<i>Pseudomonas</i> spp. †*
<i>Stenotrophomonas maltophilia</i> *
<i>Serratia marcescens</i>
Atypical Bacteria
<i>Chlamydia pneumoniae</i>
<i>Legionella</i> spp.
<i>Mycoplasma pneumoniae</i>

† routinely consider in initial selection of antibiotics

* increased risk for antimicrobial resistance