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Pneumonia in the neutropenic cancer patient

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Abstract

Purpose of review—Pneumonia is the leading cause of death among neutropenic cancer patients, particularly those with acute leukemia. Even with empiric therapy, case fatality rates of neutropenic pneumonias remain unacceptably high. However, recent advances in the management of neutropenic pneumonia offer hope for improved outcomes in the cancer setting. This review summarizes recent literature regarding the clinical presentation, microbiologic trends, diagnostic advances and therapeutic recommendations for cancer-related neutropenic pneumonia.

Recent findings—While neutropenic patients acquire pathogens both in community or nosocomial settings, patients' obligate healthcare exposures result in the frequent identification of multidrug resistant bacterial organisms on conventional culture-based assessment of respiratory secretions. Modern molecular techniques, including expanded use of galactomannan testing, have further facilitated identification of fungal pathogens, allowing for aggressive interventions that appear to improve patient outcomes. Multiple interested societies have issued updated guidelines for antibiotic therapy of suspected neutropenic pneumonia. The benefit of antibiotic medications may be further enhanced by agents that promote host responses to infection.

Summary—Neutropenic cancer patients have numerous potential causes for pulmonary infiltrates and clinical deterioration, with lower respiratory tract infections among the most deadly. Early clinical suspicion, diagnosis and intervention for neutropenic pneumonia provide cancer patients' best hope for survival.

Keywords

Neutropenia; pneumonia; leukemia; cancer; galactomannan

Introduction

Worldwide, pneumonia profoundly impacts all populations.(1–4) However, the impact of pneumonia on cancer populations is uniquely severe, accounting for more morbidity and mortality than any other infectious complication.(5–13) This review addresses the

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epidemiology, pathophysiology, microbiology, diagnostics, and therapeutics relevant to clinical care of pneumonia in neutropenic cancer patients, with particular emphasis on recent guidelines.

Epidemiology

Lower respiratory tract infections are strikingly common among cancer patients. Reports indicate that 13–31% of leukemia patients receiving chemotherapy (8–10, 12–14) and up to 80% of hematopoietic stem cell transplant (HSCT) recipients will experience at least one episode of pneumonia.(15, 16) The mortality attributable to pneumonia in these populations is very high with case fatality rates in leukemia patients ranging from 25%–80% (11, 17, 18) while the case fatality rate in HSCT recipients is as high as 90%.(8–10, 12–14, 18–23)

Pathophysiology and Host Factors

Both cancer and its treatment induce derangements of innate and adaptive immune function. Leukocyte depletion, dysregulated inflammation, impaired pathogen recognition, and graft-versus-host responses contribute to cancer patients' tremendous susceptibility to lower respiratory tract infections. 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.

Among the risks for cancer related pneumonia, neutropenia is the most prominent. Neutrophils are sensitive to alkylating agents and nucleoside analogs, resulting in dose dependent reductions in the absolute neutrophil count. Severe neutropenia, defined as a count $< 500/\mu\text{L}$, is associated with severe lung infections caused by bacterial and fungal organisms.(24) The rapidity of onset, duration, severity, and underlying physiologic process all impact susceptibility to neutropenic pneumonia.(7, 20, 25–30) Moreover, impairments of neutrophil phagocytosis and chemotaxis follow such common cancer-related insults as radiation, corticosteroids, hypovolemia, acidosis, and hyperglycemia.(31) Thus, functional neutropenia can also contribute to cancer-related pneumonia risk.

Microbiology and the Spectrum of Pathogens

The spectrum of pathogens to which neutropenic patients are susceptible is staggeringly broad (see Table 1). It is, therefore, helpful to consider the site of acquisition, because this impacts the spectrum of pathogens and their antimicrobial resistance patterns and therefore determines optimal treatment strategy.

Community acquired organisms

Genuine community acquired pneumonia (CAP), defined as development of pneumonia in patients that have not been hospitalized or resided in a nursing home for ≥ 14 days prior to the onset of symptoms, and who do not meet criteria for other risk groups,(32–34) is relatively uncommon among cancer patients, owing to their frequent healthcare exposures. (35) This is particularly true among neutropenic patients, since this typically reflects recent chemotherapy. Nonetheless, outpatient neutropenic individuals routinely encounter

community pathogens, so physicians must consider CAP organisms when approaching patients with neutropenic pneumonia.

The most frequent agent of bacterial CAP remains *Streptococcus pneumoniae*, including in the cancer setting.(36, 37) Other causes of CAP among neutropenic patients include *Staphylococcus aureus*, *Pseudomonas* spp., and nontypeable *Hemophilus influenzae*. Nonfermenting-Gram-negative bacilli (NF-GNB), such as *Stenotrophomonas maltophilia*, *Burkholderia* spp., *Chryseobacterium meningosepticum*, and *Alcaligenes* (*Achromobacter*) spp., are increasingly recognized as etiologic agents in both CAP and nosocomial pneumonias.(38–45) *Streptococcus pyogenes*, *Neisseria meningitidis*, and *Moraxella catarrhalis* are less frequent causes of CAP. Atypical pathogens such as *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella* spp. also cause CAP in this population. The community acquired viruses most frequently causing CAP in neutropenic patients include influenza viruses, parainfluenza viruses, human metapneumovirus, and adenoviruses.

While community acquired organisms cause pneumonia in neutropenic patients, it is crucial to recall that neutropenic patients do not respond to pathogens in similarly to non-neutropenic individuals. What might be an easily cleared inoculum for an immunocompetent patient may cause life threatening pneumonia in the setting of neutropenia. Guidelines for CAP management were developed for patients without immune dysfunction.(32, 46) Consequently, clinical scoring strategies to direct management of CAP, such as the Pneumonia Severity Index (PSI) and the CURB-65, may underestimate the severity of illness in the neutropenic population and should be used with caution.(35)

Nosocomial bacterial pathogens

By virtue of their health care interactions, most neutropenic outpatients are typically best categorized as having healthcare associated pneumonia (HCAP), rather than CAP. Formally, HCAP encompasses pneumonia that develops in outpatients who have been hospitalized for 2 days in the prior 90 days, received treatment in a hospital or hemodialysis clinic, resided in long-term care facilities, received intravenous antibiotics, chemotherapy or wound care in the prior 30 days.(47) This definition is contrasted with hospital acquired pneumonia (HAP), wherein pneumonia develops 48 hours after hospital admission, or ventilator associated pneumonia, which develops > 48–72 hours after endotracheal intubation.(47) The spectrum of pathogens causing HCAP substantially overlaps that of late onset HAP or VAP,(47, 48) and the available guidelines for management of these nosocomial infections overlap.(47)

The bacterial causes of nosocomial pneumonias in cancer patients without recent antibiotic exposure include *S. pneumoniae*, *S. aureus*, and *H. influenzae*. In those with cancer patients with neutropenia, additional pathogens to be considered are the Gram-negative enteric organisms, including *Pseudomonas* spp., *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter cloacae*, *S. maltophilia*, *Citrobacter* spp., *Serratia marcescens*, *Acinetobacter baumannii*-complex and *Proteus* spp.(15, 41, 43, 44, 49–52) Unfortunately, the rise in Gram-negative neutropenic respiratory infections has also yielded a corresponding increase in extended spectrum beta-lactamase producing Enterobacteriaceae. Mortality rates associated with drug resistant *P. aeruginosa* and MRSA are disproportionately higher than

those caused by other nosocomial bacterial pathogens.(53) Finally, sporadic outbreaks of *Legionella pneumophila* and *Nocardia* spp. have occasionally been reported by various transplant centers and should be considered depending on the context (54–56).

Fungi

While bacterial pathogens cause documented neutropenic pneumonias about twice as often as fungi,(13, 27) invasive pulmonary mycoses are associated with significant morbidity and mortality. *Aspergillus* is the most common fungal pneumonia in neutropenic patients, with *Aspergillus fumigatus* being the most frequently cultured of this genus, although *A. flavus*, *A. niger*, and amphotericin B-resistant *A. terreus* have also emerged as important pathogens. (57, 58) Risk factors for aspergillus pneumonia include both duration (> 1 week) and severity (<100 cells/ μ L) of neutropenia.(59–61) Non-*Aspergillus* molds such as *Fusarium* spp., *Pseudallesheria boydii*, *Scedosporium* spp., and the dematiaceous molds that are often not susceptible to conventional antifungal agents are also described in this population.(62, 63).

Widespread use of fluconazole prophylaxis appears to have induced a decline in pneumonias caused by endemic mycoses, such as *Histoplasma capsulatum*, *Blastomycetes dermatitidis*, and *Coccidioides immitis*. However, neutropenic pneumonias caused by zygomycetes (mainly mucorales) have increased in recent years, corresponding with increased use of voriconazole and declining use of amphotericin B (to which these organisms are more often susceptible).(63)

While *Pneumocystis jiroveci* pneumonia is typically seen in patients with CD4+ cell depletion, this organism must also be considered as a cause of neutropenic pneumonia, particularly in patients with severe hypoxemia.(64, 65) Because of the effectiveness of trimethoprim-sulfamethoxazole prophylaxis during the neutropenic period after HSCT, most *Pneumocystis* in HSCT patients is now seen among sulfa-allergic patients receiving less effective prophylaxis.(66)

Viruses

The incidence of CMV infection has declined in recent years due to aggressive prophylaxis and preemptive therapy, but active infections continue to cause severe morbidity, especially among seronegative HSCT recipients.(67–69) Detection of CMV viremia or antigenemia strongly suggests active disease, whereas detection of CMV in lower respiratory tract secretions may reflect viral shedding without active infection. Consequently, the observation of cytopathic changes can help in diagnosing CMV pneumonia. Respiratory syncytial virus (RSV) pneumonia is relatively uncommon in the neutropenic adult population, but is associated with very high mortality rates.(40, 70) Other less common causes of viral lower respiratory tract infections include varicella-zoster and human herpes virus 6.

Mycobacteria

Mycobacterium tuberculosis is a rare cause of neutropenic pneumonia, typically seen among foreign-born individuals receiving cancer care in non-endemic regions.(71) Most cases are reactivation episodes of latent infections rather than *de novo* infections. Conversely,

nontuberculous mycobacterial lower respiratory tract infections are widely reported among neutropenic patients.(72)

Polymicrobial

Polymicrobial isolates are common among patients with neutropenic pneumonia.(73) Because of the frequency with which multiple organisms are identified on respiratory samples, recent guidelines support the use of semi-quantitative or quantitative cultures in patients with suspected HCAP, HAP and VAP.(47) An unfortunate consequence of frequent polymicrobial infections is that a positive test for one pathogen does not necessarily allow withholding of empiric therapies for other pathogens.

Diagnostics

Evaluation of neutropenic cancer patients with suspected pneumonia requires careful clinical and microbiologic assessment, supplemented by selected molecular testing for particular pathogens.

Clinical assessment

The classical clinical signs of pneumonia in most populations include new pulmonary infiltrates, leukocytosis, fever, and purulent secretions. However, due to disordered host inflammatory responses in the neutropenic cancer patient, these clinical and radiographic hallmarks may be unapparent.(25, 40, 41, 47, 62) Thus, early CT scanning is warranted for neutropenic patients with unanticipated clinical deterioration, unexplained fevers or questionable infiltrates on conventional imaging.(40, 41, 62)

However, the differential diagnosis of pulmonary infiltrates is expansive and includes such noninfectious mimics as leukemic infiltrates, drug toxicity, and hydrostatic pulmonary edema. Thus, while infection remains the most frequent cause of these radiographic abnormalities in neutropenic patients,(13, 21, 22, 27, 45, 74) the potential diagnoses are numerous and the challenge is to identify those patients who are most likely to benefit from further investigations in addition to empiric antimicrobial therapy.(21, 22, 45, 74)

Microbiologic assessment

Neutropenic pneumonia is most reliably diagnosed when a likely pathogen is recovered from a typically sterile site or when a non-commensal organism is isolated from respiratory secretions. Although practice patterns vary widely,(75) bronchoscopy with bronchoalveolar lavage (BAL) is the diagnostic tool of choice for obtaining lower respiratory samples from neutropenic cancer patients.(8, 76) BAL is safe for most cancer patients,(8) although traditional culture methods yield a definite pathogen in only 25–51% of cases.(8, 19, 76–79) The diagnostic benefit of BAL is likely greatest when performed early, particularly if it can be done prior to the initiation of antimicrobial therapy.(8, 76, 80) However, therapy should not be delayed so that a BAL can be done, since the detrimental effects of delays in treatment outweigh the modest gains recognized by having improved BAL sensitivity. When feasible, transbronchial biopsies (TBBx) may reveal angioinvasion by microbes (e.g., *Aspergillus* spp.), however culturing TBBx material has not been proved superior to BAL

and TBBx carries a higher risk of complications such that it is often precluded in neutropenic patients because of concurrent thrombocytopenia.

Interpretation of BAL culture data can be challenging, due to frequent colonization of the upper airway with nonpathogenic microorganisms.(41) Autopsy studies suggest that in the presence of sufficiently severe immunosuppression, many organisms that are usually considered as colonizers can cause significant disease. Thus, the clinician must carefully assess each patient to determine the appropriateness of responding to positive culture results. Conversely, sterile cultures do not exclude infection, particularly in the setting of prior antibiotic utilization.(40, 41) These diagnostic challenges have promoted the use of modern molecular techniques to enhance the sensitivity of BAL and to facilitate the discrimination of *bona fide* pathogens from irrelevant commensals. Such techniques include polymerase chain reaction (PCR) testing and antigen detection methods.(41, 45, 81)

Molecular Testing for Galactomannan as a Test for Invasive Aspergillosis

Early diagnosis of invasive Aspergillosis (IA) remains problematic, because microbiologic proof is often not possible.(82, 83) IA may be suggested by CT findings which may include nodular infiltrates, with or without cavitation, sometimes with patchy or segmental consolidation.(84) Peribronchial infiltrates and tree-in-bud patterns can also be seen, and radiographic findings vary with host factors and the degree of immunosuppression. As highlighted in Figure 1, while CT imaging may be suggestive of IA, the range of potential radiographic patterns overlaps with other causes of pneumonia. Thus, CT imaging is not sufficient to make a definitive diagnosis.

Because sputum and BAL cultures have limited sensitivity,(85–87) there has been increasing interest in molecular tests and immunoassays for diagnosing IA. The best characterized clinically available assay is the Platelia galactomannan (GM) assay, which has been approved by the US Food and Drug Administration (FDA) for use on serum and BAL.

GM is a heat-stable polysaccharide found in the cell wall of *Aspergillus* spp. Immunoassays have been developed to test for GM in serum and BAL to aid clinical diagnosis.(88–90). The FDA-approved GM EIA presents results as a ratio of the test sample optical density relative to a provided control optical density; optical density ratios ≥ 0.5 (the “optical index”) are considered positive. Once thought specific for *Aspergillus*, it is now clear that the galactofuranose side chain epitopes targeted by the EIA may react with *Fusarium* spp., *Penicillium* spp. and *Histoplasma capsulatum*.(91–93) False positive serum GM tests have been reported in patients receiving certain formulations of piperacillin-tazobactam,(94) however subsequent studies suggest that current preparations of piperacillin-tazobactam do not generate cross-reactivity.(95)

Several strategies of GM testing have been evaluated, including: 1) testing BAL and serum in patients with suspected disease and 2) screening serum of high risk patients without current evidence of disease. These strategies are reviewed below. Because cultures are frequently negative and tissue usually cannot be obtained, the reference standard for many of these studies has therefore been the EORTC/MSG consensus group standards which categorize cases as none, possible, probable or proven.(96, 97)

BAL GM and serum testing in patients with suspected disease—A meta-analysis of 30 studies found that BAL GM testing had a pooled sensitivity of 0.87 (95% CI 0.79–0.92) and pooled specificity of 0.89 (95% CI 0.85–0.92).⁽⁹⁸⁾ The pooled likelihood ratio positive was 8.0 (95% CI 5.7–11.1) and the pooled likelihood ratio negative was 0.15 (95% CI 0.10–0.23). Sources of heterogeneity identified included differences in study design (cohort vs case-control studies), study size, prior exposure to antifungals, and neutropenia status.

In addition, the optical density ratios that were used to define positive GM assays varied between studies, and this variation in threshold values had a moderate influence on heterogeneity. The optimal threshold value for defining positive results is an area of ongoing debate. In a retrospective study of 251 consecutive patients undergoing BAL GM testing, a threshold 0.8 had a sensitivity of 86.4% and a specificity of 90.7%, resulting in a positive predictive value (PPV) of 81% and a negative predictive value (NPV) of 93.6%.⁽⁹⁹⁾ Adjusting the threshold to 3.0 resulted in a specificity of 100%, while lowering the threshold to <0.5 resulted in a very high sensitivity.

On balance, the available evidence for routine use of BAL GM in neutropenic patients with pneumonia is inconclusive. A recent prospective observational cohort study of 568 patients with hematologic malignancies found that BAL GM had a 50% sensitivity, 73% specificity, 16% PPV, and 93% NPV for proven or probable IA.⁽⁸⁴⁾ With the posterior probability of disease ranging from 7%–16%, it would be difficult to justify using GM testing in this clinical context to decide on whether to start or stop antifungal therapy. However, depending on the threshold used and the pretest probability, BAL GM might be useful in select cases.

Screening with GM in patients without clinical evidence of disease—A meta-analysis identified 27 studies that evaluated surveillance with serum GM testing for IA in high risk populations that used the EORTC/MSG consensus group or similar criteria as the reference standard.⁽¹⁰⁰⁾ The EORTC/MSG consensus group categorize IA cases as none, possible, probable or proven.^(96, 97) Using proven IA as the outcome, serum GM had a pooled sensitivity of 0.71 (95% CI 0.68–0.74) and specificity of 0.89 (95% CI 0.88–0.90).⁽¹⁰⁰⁾ If the outcome was proven or probable IA the pooled sensitivity was 0.61 (95% CI 0.59–0.63) and specificity was 0.93 (95% CI 0.92–0.94). Overall these findings were consistent with moderate accuracy, despite significant study heterogeneity. Subgroup analysis revealed significant test characteristic variability depending on whether the outcome was proven vs proven and probable, the patient population, the reference standard, and the threshold values used for defining positive (Tables 2 and 3). GM testing performed best in patients with hematologic malignancies and HSCT. Overall accuracy of GM testing improved somewhat when a higher threshold was used to define positive results.⁽¹⁰⁰⁾

On balance, the available evidence for the use of weekly or twice weekly screening with GM testing for high risk patients remains inconclusive. There are no large prospective randomized trials using this screening strategy and it is not clear whether antifungal therapy could be withheld if the results were negative and clinical suspicion was high. Cost-effectiveness is also an issue. Important variables to consider include the underlying disease, the pretest probability of disease, what optical density threshold should be used, the relative

magnitude of the consequences of false positive and false negative tests, and whether or not the information obtained will be actionable.

Therapeutic Strategies

The value of the information obtained from any of the above diagnostic tests is contingent on having effective therapeutic alternatives. Because of the broad range of potential pathogens, therapeutic strategies must integrate a variety of potential tools, including antibiotics, antifungals, antivirals, and host directed therapies.

Antibiotic therapies

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 neutropenic patients, thus it is common practice to initiate empiric and/or preemptive antimicrobial therapy when neutropenic pneumonia is suspected. (41, 101, 102) No consensus exists for the optimal time to first antibiotic dose, but one recent study suggests that neutropenic fever outcomes are better when antibiotics are delivered within 104 minutes of presentation.(30) Most clinicians would endorse the earliest possible dosing, with a possible exception when bronchoscopic evaluation is immediately available. 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, but this delay should not be longer than 2 hours. Antibiotics should not be held for hours or days in anticipation of bronchoscopy, as the harm from delaying therapy outweighs the benefits of improved test performance.

Initial antimicrobial therapy for febrile neutropenia in patients with pulmonary infiltrates cover the broad range of pathogens described above, with particular emphasis on antimicrobial activity against multi-drug resistant strains of *S. aureus* and *P. aeruginosa*.(22, 25, 41, 102) Antibiotic selection should be based on culture data, pneumonia severity, local antibiotic sensitivity profiles, and patient immune status.(32–34, 46) Empiric antibiotics for early HAP (i.e., within seven days of admission) should include coverage of *S. pneumoniae*, MRSA, *H. influenzae*, and Enterobacteriaceae. Initial regimens for patients with late HAP, HCAP or VAP should ensure enhanced coverage for multi-drug resistant GNB.(22, 41, 102) 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.(25, 48, 102)

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.(25) De-escalation should be undertaken with caution in patients with poor clinical response to antimicrobial therapy, persistent neutropenia, or ongoing immunosuppressive therapy.(25, 41, 102)

Antifungals—Early initiation of effective antifungal coverage is associated with improved outcomes in neutropenic pneumonia.(103) Suspected invasive fungal infections in neutropenic patients requires coverage for *Aspergillus* spp. Amphotericin B remains a

treatment option for life threatening aspergillosis, as well as cryptococcosis, systemic candidiasis, histoplasmosis, blastomycosis, coccidioidomycosis, and zygomycosis. However, given the toxicities associated with amphotericin, increasing amphotericin resistance in *A. terreus*, and the *in vitro* evidence of superior fungicidal activity of newer azoles, either voriconazole or liposomal amphotericin B are recommended as primary therapy.(41, 58, 104–107) For inadequate responders, recommended salvage therapy consists of caspofungin, micafungin or posaconazole.(58, 106, 108) Antifungal combinations are frequently prescribed for neutropenic patients with suspected mycoses. No consensus exists regarding preferred antifungal combinations,(58, 105) though initial strategies combining voriconazole plus caspofungin or amphotericin have been suggested to be superior to single agent therapy in neutropenic patients.(105, 109)

Antivirals—CMV and HHV-6 lower respiratory tract infections are treated with Ganciclovir or foscarnet.(41, 68, 69, 110, 111) The evidence on combining antiviral agents with intravenous immunoglobulin remains inconclusive.(110, 111) Even with aggressive therapy, mortality rates remain high with these viral infections.(67) Mortality rates among those with RSV pneumonia approaches 80%, and initiation of treatment with aerosolized ribavirin and intravenous immunoglobulin initiated at the stage of upper respiratory infection is recommended to avoid progression.(70) Intravenous ribavirin has also been used successfully in patients with life-threatening human metapneumovirus disease.(112) Neuraminidase inhibitors, such as oseltamivir, are routinely prescribed for neutropenic patients with documented influenza infections, regardless of whether they have confirmed lung involvement.(25)

Host directed therapies

Despite broad spectrum antimicrobial strategies, mortality rates remain high in neutropenic patients. These antimicrobial failures arise, at least in part, from the continuing immune defects associated with the neutropenia. Consequently, a number of groups have investigated means by which the immune defects might be restored, allowing pathogen clearance. One focus is correction of the underlying neutropenia. Evidence supports the efficacy of colony stimulating factors, but they are not generally recommended as a treatment for established infection,(25) although in the setting of invasive fungal infections reconstitution of the immune system appears essential for resolution.(58) More recently, transfusion of donor granulocytes and administration of recombinant T_H1 cytokines have been studied, but this approach, while promising, is still investigational.(113–115) However, some authors argue that severely ill neutropenic patients may benefit from granulocyte transfusion.(116)

A novel alternative strategy to prevent and possibly treat pneumonias in the setting of neutropenia may be induction of innate antimicrobial responses from lung epithelial cells. Lung epithelial cells are long lived and relatively resistant to chemotherapy.(117, 118) In addition to their barrier function, recent investigations have demonstrated that these cells also possess the capacity to detect pathogens, to modulate local immune responses, and to generate direct antibacterial responses through the production of antimicrobial peptides and reactive species.(119–123) 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 neutropenic. (124–131) One such treatment, known as PUL-042, is in clinical trials. Preclinical studies demonstrate that in animal models PUL-042 protects against Gram-positive, Gram-negative, fungal and viral pathogen challenges. The real value of this approach is that it offers a new host-directed strategy for combatting infection in the neutropenic cancer patient that can be complementary to traditional antibacterial and antifungal therapeutics.

Conclusion

Neutropenic pneumonia remains a challenge for the clinician and a threat to the patient. The clinical approach requires integration of traditional microbiologic techniques as well as targeted molecular diagnostics. BAL and serum GM are now more widely available and may be a useful adjunct in select patients, depending on the pre-test probability of IA. It remains uncertain how large an impact GM testing can have, given that the posterior probabilities of disease are often not that different and that empiric treatment is often required. Therapeutic strategies still must rely on early recognition and initiation of broad spectrum antibacterial and antifungal therapy in appropriate patients. New host directed therapies that help to reconstitute the immune system and others that stimulate epithelial innate immunity are under investigation in clinical trials. These may serve to supplement more traditional approaches in the future.

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Key Points

- Pneumonia in the cancer patient accounts for more morbidity and mortality than any other complication.
- Initial broad spectrum antibacterial coverage including resistant gram negatives and MRSA is warranted in high risk neutropenic cancer patients, with antifungals for those that have persistent fevers or risk factors.
- Serum and BAL GM testing is now more widely available for clinical use and may be beneficial in select patients with neutropenic fever and suspicion of pneumonia.
- Host directed therapies that enhance innate epithelial immunity and that reconstitute the immune system are undergoing clinical investigation.

Figure 1.

Figure 1a. 50 year old woman with relapsed refractory B-cell lymphoma, neutropenic, with fevers, presenting with consolidation in the lingula. Galactomannan index was 1.98.

Figure 1b. 60 year old man with history of Hodgkins lymphoma with autologous bone marrow transplant, 3 years later developed myelodysplastic syndrome with progression to acute myeloid leukemia, presented with neutropenic fevers following. Nodular and ground glass opacities are present bilaterally. BALF was positive for Aspergillus.

Figure 1c. 68 year old woman with acute myeloid leukemia with neutropenia after induction chemotherapy. Numerous bilateral pulmonary nodules were seen, most prominent in the RLL superior segment. BALF was positive for aspergillus.

Figure 1d. 50 year old woman with acute myeloid leukemia, received induction chemotherapy, had prolonged neutropenia, and developed fevers with bilateral nodular and ground glass opacities. Note the largest nodular density in the right lower lobe has a central low attenuation zone consistent with necrosis. This is seen more easily in the right hand panel.

Figure 1e. 54 year old man who presented with fevers and ground glass opacities to his local physician. After he failed to respond to antibiotics he was admitted to a local hospital and diagnosed with acute myeloid leukemia. He was transferred to receive induction chemotherapy. At the time of presentation patient had bilateral ground glass opacities as shown above, BAL was positive for Aspergillus.

Table 1

Pathogens of special concern in neutropenic pneumonia.

Gram positive bacteria	Gram negative bacteria	Viruses
<i>Streptococcus pneumoniae</i>	<i>Pseudomonas</i> spp. *	Influenza A/B viruses
<i>Streptococcus pyogenes</i>	<i>Klebsiella pneumoniae</i> *	Parainfluenza 1–3 viruses
<i>Staphylococcus aureus</i> *	<i>Escherichia coli</i> *	Human metapneumovirus
<i>Nocardia</i> spp.	<i>Enterobacter cloacae</i> *	Adenoviruses
<i>Rhodococcus equi</i>	<i>Stenotrophomonas maltophilia</i> *	Cytomegalovirus
	<i>Citrobacter</i> spp. *	Respiratory syncytial virus
Fungi	<i>Serretia marcescens</i> *	Varicella-zoster virus
<i>Aspergillus</i> spp. *	<i>Acinetobacter baumannii</i> -complex	Human herpes virus 6
<i>Fusarium</i> spp.	Nontypeable <i>Hemophilus influenza</i>	
<i>Pseudallesheria boydii</i>	<i>Proteus</i> spp. *	Mycobacteria
<i>Scedosporium</i> spp.	<i>Burkholderia</i> spp.	<i>Mycobacterium tuberculosis</i>
<i>Histoplasma capsulatum</i>	<i>Chryseobacterium meningosepticum</i>	Nontuberculous mycobacteria
<i>Blastomycetes dermatitidis</i>	<i>Alcaligenes/Achromobacter</i> spp.	
<i>Coccidioides immitis</i>	<i>Neisseria meningitidis</i>	Atypical organisms
<i>Mucor</i> spp. *	<i>Moraxella catarrhalis</i>	<i>Mycoplasma pneumoniae</i>
<i>Rhizopus</i> spp. *		<i>Chlamydomypha pneumoniae</i>
<i>Pneumocystis jiroveci</i>		<i>Legionella</i> spp

* particular risk for antimicrobial resistance, depending on local exposure patterns

Table 2

Comparison of test performance characteristics in studies using galactomannan serum EIA as a surveillance test for invasive aspergillosis with the outcome being proven disease according to the reference standard

Groups being compared	Sensitivity	Specificity	Youden Index	Mean D	Q*
<i>Type of underlying disease in study</i>					
Hematologic malignancy	0.70	0.92	0.54	3.13	0.83
Hematopoietic stem cell transplant	0.82	0.86	0.73	3.02	0.82
Solid organ transplant	0.22	0.84			
<i>Reference standard</i>					
Studies using EORTC/MSG criteria	0.64	0.89	0.43	2.30	0.75
Studies using Other criteria	0.79	0.89	0.70	3.46	0.84
<i>Cutoff values for defining positive GM assay</i>					
Studies using EIA cutoff 0.5	0.27	0.79	0.10	0.50	0.67
Studies using EIA cutoff 1.0	0.79	0.87	0.50	1.99	0.78
Studies using EIA cutoff 1.5	0.68	0.92	0.65	3.56	0.84

Data abstracted from reference (109). Youden Index, Mean D, and Q* are measures of overall test accuracy. Youden Index = sensitivity + specificity - 1; D is a log odds ratio of the odds that a person with IA will have a positive test result divided by the odds that a person who does not have IA will have a positive test result. Q* is the upper left most point on the receiver-operating characteristics curve.

Table 3

Comparison of test performance characteristics in studies using galactomannan serum EIA as a surveillance test for invasive aspergillosis with the outcome being proven or probable disease according to the reference standard*

Groups being compared	Sensitivity	Specificity	Mean Youden Index	Mean D	Q*
<i>Type of underlying disease in study</i>					
Hematologic malignancy	0.58	0.95	0.54	3.13	0.83
Hematopoietic stem cell transplant	0.65	0.65	0.73	3.02	0.82
Solid organ transplant	0.41	0.85			
<i>Reference standard</i>					
Studies using EORTC/MSG criteria	0.60	0.93	0.43	2.30	0.75
Studies using Other criteria	0.74	0.89	0.70	3.46	0.84
<i>Cutoff values for defining positive GM assay</i>					
Studies using EIA cutoff 0.5	0.79	0.86	0.63	3.19	0.89
Studies using EIA cutoff 1.0	0.65	0.94	0.54	2.85	0.80
Studies using EIA cutoff 1.5	0.48	0.95	0.59	3.93	0.92

Data abstracted from reference (109). Youden Index, Mean D, and Q* are measures of overall test accuracy. Youden Index = sensitivity + specificity – 1; D is a log odds ratio of the odds that a person with IA will have a positive test result divided by the odds that a person who does not have IA will have a positive test result. Q* is the upper left most point on the receiver-operating characteristics curve.