How I manage pulmonary nodular lesions and nodular infiltrates in patients with hematologic malignancies or undergoing hematopoietic cell transplantation

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Contributions: JRW wrote the paper and JWH and MAJ edited and contributed to the text and tables.

Conflicts: The authors have no relevant conflicts.
Abstract

Pulmonary nodules and nodular infiltrates occur frequently during treatment of hematologic malignancies and after hematopoietic cell transplantation. In patients not receiving active immunosuppressive therapy the most likely culprits are primary lung cancer, chronic infectious or inactive granulomata, or even the underlying hematologic disease itself (especially in patients with lymphoma). In patients receiving active therapy, or who are otherwise highly immunosuppressed, there is a wider spectrum of etiologies with infection being most likely, especially by bacteria and fungi. Characterization of the pulmonary lesion by high resolution CT imaging is a crucial first diagnostic step. Other non-invasive tests can often be useful but invasive testing by bronchoscopic evaluation or acquisition of tissue by one of several biopsy techniques should be performed for those at risk for malignancy or invasive infection unless contraindicated. The choice of the optimal biopsy technique should be individualized, guided by location of the lesion, suspected etiology, skill and experience of the diagnostic team, the procedural risk of complications, and the patient status. Although presumptive therapy targeting the most likely etiology is justified in patients suspected of serious infection while evaluation proceeds, a structured evaluation to determine the specific etiology is recommended. Interdisciplinary teamwork is highly desirable to optimize diagnosis and therapy.
Introduction

Lung nodules and nodular infiltrates are common in patients treated for hematologic malignancy (HM) and in patients undergoing hematopoietic cell transplantation (HCT). Various case series suggest that 13-60% of patients develop a pulmonary infiltrate at some point in their treatment course, with the incidence varying considerably by different diseases and treatments (1-3). High resolution CT (HRCT) scans are the preferred method for evaluation of a lung infiltrate over radiography because they are more sensitive in detecting infiltrates earlier and they are more capable of better characterization of the infiltrates. In patients treated for acute leukemia or undergoing HCT, HRCT scans have a high degree of sensitivity (>85%), high negative predictive value (>85%) in detecting pneumonia and a gain of 5 days compared to chest radiography (4). Clinical management is often changed because of the HRCT findings (5).

In general, pulmonary infiltrates can be categorized by their radiographic pattern broadly into diffuse and nodular infiltrates. This distinction is useful because the differential diagnostic possibilities are quite different (Table 1). Nodular lesions may be further characterized as solitary micro- or macro-nodules with sharp or unsharp margins with or without halos, multiple nodules, masses, nodular infiltrates, and focal air-space disease. In reality, many patients have mixtures of multiple types of infiltrates simultaneously. A systematic approach to evaluation is necessary to determine the cause and develop a sensible management strategy. This report will address the management of pulmonary nodules and nodular infiltrates and mention diffuse infiltrates only for comparison.

What is the differential diagnosis?

Both infectious and non-infectious etiologies can be the cause of nodules and nodular infiltrates. The differential diagnosis varies according to the patient’s treatment and immune
status. We will separate consideration of those receiving active chemo- or immunosuppressive therapy who are very immunocompromised (eg, those undergoing induction chemotherapy for acute leukemia or those within the first 6 months after allogeneic HCT or even later if still receiving immunosuppressive therapy for chronic graft versus host disease (GVHD) from those not receiving active chemotherapy or off immunosuppressive therapy after HCT. The latter would also include those who present prior to treatment and after completion of their course of anti-neoplastic and/or immunosuppressive therapy, where host defenses are more intact.

Patients not receiving active chemo- or immunotherapy. Nodular lesions may be caused by the HM, especially in patients with Hodgkin or non-Hodgkin lymphoma, and much less so for patients with leukemia. Pulmonary nodular lesions are occasionally seen with plasmacytomases as extramedullary manifestations of multiple myeloma. There are case reports of acute myelogenous leukemia (AML) causing pulmonary nodules due to leukemia but these are infrequent. More commonly, pulmonary infiltrates in patients newly presenting with AML are diffuse and may be due to leukostasis in those with high leukocyte counts or even frank leukemic infiltration of tissues, pulmonary hemorrhage, and less commonly infection. Patients newly presenting with AML occasionally present with pulmonary infections. The types of infections that cause nodular infiltrates before start of chemotherapy have not been well described but in our experience are mostly bacterial. Both Gram positive organisms (especially staphylococci and streptococci) and Gram negative organisms (especially P. aeruginosa, E coli and Klebsiella spp.) are common (6). Fungal pneumonia is infrequent in newly diagnosed AML at initial presentation, and where seen, occurs predominantly in those with antecedent cytopenias or iron overload (7). However, consideration should be given to the possibility for endemic mycoses in certain high-risk geographic locations, such as coccidiomycosis in the southwest USA.
histoplasmosis and blastomycosis principally in the Ohio and Mississippi river basins and less commonly in other temperate zones.

Nodules in patients not highly immun0- or myelosuppressed may also be caused by the same types of processes that cause pulmonary nodules in non-immunosuppressed patients. In non-compromised patients, approximately half of nodules are caused by malignancy, chiefly primary lung cancer (usually solitary nodules) or less commonly metastases (usually multiple nodules) (8-10). The other half are mostly due to infectious granulomata from mycobacteria or fungi and much less commonly from other infrequent benign etiologies such as hamartomas, sarcoidosis, or arteriovenous malformations. The differential diagnosis of pulmonary nodules in patients who are not immunocompromised has been reviewed in multiple publications (8-11). Radiographic features described below can be useful in distinguishing the likelihood of benign or malignant etiology. If there are no manifestations of acute infection, the crucial differential diagnosis should emphasize the exclusion of a malignant process (12) and its evaluation may proceed in a manner similar to that for the non-compromised patient (described below).

After completion of antineoplastic therapy, pulmonary nodular lesions may represent residua of infections that occurred earlier during active therapy. Of course, in patients treated for lymphoma, the principal concern is recurrent disease. In the patient undergoing allogeneic HCT, secondary cancers must also be considered. There is a bimodal distribution of types of secondary cancers after HCT. During the first 6-12 months, the major concern is EBV-associated post-transplant lymphoproliferative disorders (PTLD) (13). Risk factors for PTLD include T cell depletion of the stem cell graft, use of anti-thymocyte globulin (ATG), use of a mismatched or unrelated donor, cord blood stem cell source, and GVHD (14). The greater the number of risk factors the greater the likelihood that PTLD will occur. Epithelial cancers of
various types occur at a higher rate than in the general population in survivors after allogeneic HCT and the risk begins to increase appreciably 10 years after transplant and thereafter climbs. Recently an increased risk for lung cancer has been noted (15). Lung cancer has also been noted to occur at increased rates in survivors of Hodgkin and non-Hodgkin lymphoma and chronic leukemia, but this issue has been less well studied (16-19). Other potential non-infectious causes of nodular lesions include toxicity from the antineoplastic therapy which more commonly cause diffuse fibrosis but in some instances can cause micronodular lesions (20-21).

Patients receiving active chemo- or immunotherapy. Infections account for most nodular infiltrates in patients receiving active chemo- or immunotherapy or have severe compromise in immunity. Bacterial and fungal infections most commonly account for nodular infiltrates, whereas viruses, *P. jiroveci*, and Legionella most commonly account for diffuse infiltrates.

Bacterial pneumonia during neutropenia can be caused by both Gram positive and Gram negative organisms. Early after HCT staphylococcus and Gram negative pathogens are problematic, with a spectrum of pathogens similar to that for newly diagnosed AML as noted above. Later the likely bacterial pathogens are different: in patients with chronic GVHD after allogeneic HCT, encapsulated bacteria are particularly problematic as causes of sinopulmonary infections (22). Nocardia is another bacterial pathogen that causes pulmonary nodular infiltrates late after HCT (23). Mycobacterial infections are also important but less frequent bacterial pathogens. In advanced countries atypical mycobacteria are more common while in underdeveloped countries, *M. tuberculosis* is more likely (24). However, in inner city settings in the US and various regions elsewhere in the world, *M. tuberculosis* infections are becoming more common. Accordingly, in geographic areas with high rates of *M tuberculosis* infections, strong consideration should be given to this diagnostic possibility.
Invasive fungal infections, especially by mold pathogens, are particularly common, especially in patients with deep prolonged neutropenia during AML therapy. The onset is frequently later during neutropenia, typically occurring beyond 2 weeks of neutropenia (25). Approximately 45% of nodular infiltrates in AML treatment are due to aspergillosis (26). In our experience, at least half of nodular infiltrates in AML therapy and HCT are due to fungi, with 80% of the pulmonary fungal infections caused by aspergillosis, the remainder due to other molds, such as the agents of mucormycosis, and less frequently, fusarium, and scedosporium species.

It is also important to recognize that nodular lesions may be due to more than one organism. Mixed mold infections (most commonly aspergillosis and mucormycosis) can occur. Also, aspergillosis can be accompanied by coinfection by bacteria or viruses. This growing recognition of mixed infections emphasizes the need for establishing a specific diagnosis.

Non-infectious causes must also be kept in mind, although they are less common. Non-infectious conditions include primary lung cancer, metastases from other epithelial cancers, lymphomas, EBV-associated post-transplant lymphomas after HCT, and pulmonary thromboembolism. Rare conditions such Wegener’s granulomatosis, sarcoidosis, and pulmonary arteriovenous malformation, should also be considered.

Occasionally infections and non-infectious entities that usually cause diffuse infiltrates (mentioned in Table 1) can also cause nodular infiltrates, especially micronodules, or even consolidation. Thus, one should be mindful of these possibilities as well.

How do I make the diagnosis?
Can Imaging distinguish various etiologies? The HRCT scan is the best imaging technique to evaluate pulmonary infiltrates (27-29). A variety of studies in non-immunocompromised patients have noted size, location, calcification pattern, change in size over time, edge characteristics, internal characteristics, number of nodules, attenuation, and contrast enhancement as features that provide important information (29). Lesions <1 cm are infrequently due to neoplasm. Larger nodules are more likely to be malignant. Masses (lesions >3 cm) are highly likely to be malignant. Malignant lesions are more likely to be in the upper lobes, whereas non-malignant etiologies are more evenly distributed. Calcification is very suggestive of a benign granulomatous etiology if it has an organized diffuse, central or laminar pattern. Lesions stable for more than 2 years are rarely malignant. Spiculated edges are suspicious for malignancy. Satellite nodules surrounding a central larger nodule are suggestive of granulomatous disease. An air-bronchogram within a nodule is suggestive of malignancy. Cavitation may be seen in both malignant and non-malignant entities. Ground glass opacification is suggestive of malignancy such as adenocarcinoma in situ or minimally invasive adenocarcinoma of the lung. Figure 1 offers illustrative images of nodular lesions commonly observed.

Using such considerations, in non-compromised patients, lesions can categorized as demonstrating low, indeterminant, or high probability of malignancy. Those lesions judged to be high risk should undergo resection. Those at low risk (small <8 mm, benign calcification pattern, stable over time, no smoking history) can be followed over time (30). Those judged to be indeterminant require further evaluation.

PET scans have been shown to be quite useful in the evaluation of the solitary pulmonary nodule (SPN) in the non-immunocompromised patient (31-33). PET scans may be of particular
value in lesions of indeterminant significance (34), since malignancies typically have high
uptake (>2.5 SUV). PET scans have been found to be quite useful in lymphoma patients to
distinguish active disease from inactive scar (35). However, PET has not been found to be useful
for small lesions <1 cm due to false negative results. Those at high risk require resection or
biopsy. Infectious etiologies may also have high signal uptake by PET (36). Imaging using MRI
and PET technologies has been poorly studied in the evaluation of new nodules and nodular
infiltrates during active chemo- or immunotherapy in the hematologic malignancy and HCT
setting where infection is highly likely (37-38).

A number of studies have evaluated imaging findings as they relate to specific etiologies
in patients treated for HM or undergoing HCT. For bacterial pneumonias, air-space
consolidation is most common, but small centrilobular nodules and ground glass opacities are
also common; large nodules also are seen but are less common (20%) (39-41). The halo sign
appears to be the most useful radiologic sign for distinguishing aspergillosis from bacteria (40).

In patients with invasive aspergillosis (IA), one large study, in mostly HM and HCT
therapy, found that 94% had one or more macronodules (at least 1 cm in diameter) (42). In 79%
of cases, the nodules were multiple, and in 60%, there were multiple bilateral nodules. Halo
signs (dense nodules surrounded by ground glass perimeter) were found in 61%. Other findings
noted with IA were consolidation (30%), infarct-shaped nodules (27%), cavities (20%), and air-
crescent signs (10%). The nodular lesions of IA are often peripherally located (43). The
presence of dense, well circumscribed nodule, air crescent sign, or cavity have been adopted as
specific radiologic criteria that along with appropriate clinical setting and with supporting
microbiology criteria establish the diagnosis of IA in consensus guidelines (44). In earlier
studies serial HRCT scans were performed in patients with IA: halo signs were most likely to be
found early in infection, air-crescent signs much later, typically found at time of neutrophil recovery (45-46). Although IA is the most likely cause of halo lesions in this population, it is important to note that the halo is now known to not be specific for IA: other pathogens, such as *P. aeruginosa*, the agents of mucormycosis and other less common molds can also give rise to halo infiltrates (47). Mucormycosis can present with pulmonary nodules or nodular infiltrates similar to IA. There may be some distinguishing findings on CT scan. Comparing IA and mucormycosis, the presence of more than 10 nodules, pleural effusion, or sinus involvement, and a history of prior voriconazole use (an antifungal active against aspergillus species but not mucormycosis) were conditions more likely to be found with mucormycosis than with IA (48-49). Important to note is that while pulmonary nodules are highly likely in IA, other less-specific radiologic manifestations can also be caused by IA, including consolidation, ground-glass infiltrates, and occasionally pleural effusion (50). The reversed halo (circular focus of ground glass density within a ring of dense consolidation) was initially described as highly suggestive of mucormycosis and subsequently also IA, but other infectious and non-infectious etiologies may also present with this radiologic picture (47, 51).

In studies of patients with AML who were neutropenic and patients who underwent HCT with lung opacities >5mm, both IA (52) and bacterial pneumonia (53) were manifest frequently by both nodules and air-space consolidation in similar proportions (404. The halo sign was rarely seen in bacterial pneumonia, but cavities and air crescent signs were present in both. A recent study suggests a role for CT pulmonary angiography in the diagnosis of pulmonary mold infections, exploiting the fact that such infections are angioinvasive (54)
Can other non-invasive techniques be helpful? Gram stain and culture of sputum should be performed if sputum is being expectorated; unfortunately, the patient who is neutropenic is frequently unable to expectorate sputum. Bacterial and fungal blood cultures should be performed; when positive, they are helpful; however, most have negative blood cultures. Mycobacterial blood cultures should also be considered in the evaluation of nodular lesions in non-neutropenic patients.

There are 2 commercial serum assays to assist in the diagnosis of invasive fungal infections. The serum galactomannan (GM) and beta glucan tests are useful in detection of invasive fungal infections. The serum GM test has been widely studied in the AML and HCT settings. Galactomannan is a constituent of the cell wall of Aspergillus species and its presence in serum is strongly suggestive of IA. Its sensitivity and specificity have been found to be >80% in AML and HCT patients in the detection of IA (55). It is important to note that the test is recommended to be performed twice weekly prospectively in patients at risk and the sensitivity and specificity of a single test result drawn at the time of a lung infiltrate is less. There are both false positives and negatives reported. The most common reason reported for false positive results is the concomitant use of piperacillin-tazobactam (56). There are suggestions recently that this may be less problematic, but more data are needed on this point. The use of anti-mold prophylaxis attenuates the value of the galactomannan assay (57). There is also some cross-reactivity with penicillium (a rare pulmonary pathogen in the US and Europe) and other endemic fungi such as histoplasma and blastomyces, potential pathogens in certain geographic regions (58-59).

Beta glucan is also a cell wall constituent and its presence in the blood occurs in invasive fungal infections. The serum glucan test is highly sensitive, but less specific than the
galactomannan test, being positive in invasive infections by candida, aspergillus, fusarium, trichosporon, and pneumocystis species. It has been best studied in candida fungemia (60).

Neither of these fungal serologic tests can detect the agents of mucormycosis. Although fungal PCR assays for various fungi are under study, none are commercially available.

Even given the limitations of the two commercial serum fungal assays, we recommend their use. When positive, we launch an investigation in search of further confirmation of an invasive fungal infection. Even when negative, if either the clinical scenario and/or imaging suggest fungal pneumona; we recommend proceeding to invasive techniques in search of an invasive fungal infection or to establish a specific alternative diagnosis.

Invasive techniques to establish the diagnosis. Invasive testing by bronchoscopic evaluation or acquisition of tissue by one of several biopsy techniques is usually needed to establish the diagnosis and should be done unless contraindicated. Studies have shown that in highly immunosuppressed patients with HM or undergoing HCT, adjustments in antimicrobial therapy are frequently made as a result of invasive testing (6, 12, 61, 62). The optimal type of invasive modality should be individualized. Factors that should guide the appropriate choice of procedure are location of the lesion, characteristics of the lesion, clinical presentation, the suspected etiology, the skill of the diagnostic team, risk of complications, and the patient’s ability to undergo the procedure. Several diagnostic approaches are available.

Invasive procedures for evaluation of SPN’s in the non-immunocompromised patient include transthoracic needle aspirate (TTNA), flexible bronchoscopy (FB), or surgical resection by video-assisted thoracoscopic surgery (VATS) or open thoracotomy. Each procedure has
strengths and limitations and there are additional considerations for their usefulness in the HM and HCT patient population (Table 2).

**Transthoracic needle aspirate (TTNA).** TTNA has a high yield for the evaluation of the SPN in the non-compromised patient, approaching 80-90%, and thus is generally preferred for tissue biopsy (63-64). TTNA is particularly useful in more peripherally located lesions. The yield is high for malignancy, but much lower for benign lesions (63-65). Bleeding and pneumothorax are the major risks. Pneumothorax occurs in 15-24% of instances and requires a chest tube in 6-7% (65,66). Thus, TTNA would be ill advised in patients with poor lung reserve. Studies in HM and HCT patients indicate a lower yield in the range of 50-78%, where the likelihood of malignant etiologies is less (12, 53, 67). The complication rate is also higher, with complications occurring in up to 38% with chest tube being required in up to 16% (Table 2) (12, 53, 67). TTNA is more likely to yield a definitive diagnosis with larger (>1 cm) and cavitary lesions and is probably of more benefit in patients with lymphoma, where malignancy is more likely than with AML.

**Flexible bronchoscopy (FB).** FB has had a more limited role in the evaluation of the SPN in the non-compromised patient with lower yields in the range of 10-50% (63), but it can be useful in the evaluation of central airway lesions or mediastinal adenopathy. Navigation guided bronchoscopy techniques have been evaluated in recent years and have been found to have higher yields, approximately 70% in a pooled analysis (68). However, FB with bronchoalveloar lavage (BAL) is a common approach for evaluation of nodular and diffuse infiltrates in HM and HCT patients. The reason is the low likelihood of serious complication such as hemorrhage or pneumothorax. The presence of symptoms, location more centrally, presence of bronchus sign on CT, and visualization during bronchoscopy are associated with higher yields (69). Major
complication rates have been low in non-compromised patients ranging between <1% to as high as 38% (63, 70-71), with severe complications typically 10% or less.

The yield of FB in patients with HM or undergoing HCT prior to the advent of non-culture based diagnostics varied widely in the range of 15-60% (61, 62, 72-74). The yield was found to be substantially higher when performed promptly at the onset of pulmonary infection rather than later (87% vs 35%) (61). Changes in therapy were made as a result of the FB in 51-65% of patients (61, 62). The diagnostic yield was higher in patients with focal infiltrates compared to diffuse infiltrates (64% vs 47%) (61).

FB is associated with low major complications in the HM and HCT setting: <2-27% overall and <1-8% major (6, 61, 62, 74, 75). In general, FB has a lower risk for pneumothorax compared to TTNA. Bronchoscopic transbronchial biopsy (TBBx) has the potential to increase the yield (75), but also increases the risk of hemorrhage and pneumothorax and its utility remains controversial in this area. TBBx should generally be avoided in patients with significant thrombocytopenia. One study noted a yield of 55% for TBBx and 20% for BAL in patients with HM (75). In another study of non-HIV immunosuppressed patients, of whom 46% had a HM, the diagnostic yield of BAL was 38%, TBBx was 38%, and both combined was 78% (76). Other studies, however, have not noted a significant improvement in diagnostic yields by including TBBx. In one HCT study, the diagnostic yield of FB with TBBx improved in only 8% of patients compared with BAL alone (61). Another HCT study noted that TBBx provided additional specific information in <10% of cases when added to BAL (77). In a study of neutropenic patients with infiltrates, TBBx added information in only 1 of 9 patients (78). The aforementioned studies did not include non-culture based diagnostics. It is important to note as mentioned, there may be a higher risk of life threatening complications with FB in patients
treated for HM or undergoing HCT in the ICU with severe respiratory complications: in one study, 12/121 (10%) of patients had a life-threatening complication from FB (79). The high complication rate was compounded by low diagnostic yields for infectious etiologies: only 23% in patients with AML and 41% in patients with lymphoid malignancies.

Use of non-cultural microbial testing can also increase the yield of BAL. The use of BAL GM testing (26, 80) has been associated with substantially increased yield in patients with IA. In one trial BAL GM in patients with hematologic diseases had a sensitivity of 91% compared with culture and microscopy (50-55%) (26). Other studies have also noted the utility of BAL GM for diagnosis of IA (81). In a meta-analysis of BAL GM, summary estimates of the BAL-GM assay for proven or probable IA were as follows: sensitivity 90%; specificity 94%; positive likelihood ratio 14.87; and negative likelihood ratio 0.10 (82). The estimates of the BAL-GM assay for proven IA were sensitivity 94% and specificity 79% (82). Analysis of beta glucan in BAL specimens in diagnosing fungal pneumonia in humans has not been evaluated as yet. Although not as yet used routinely in clinical practice, PCR-based testing of BAL specimens for IPA is being investigated (83, 84).

Although the yield of FB in the diagnostic yield of focal lesions has been reported to be lower than TTNA in earlier studies, the use of CT guidance and the incorporation of newer diagnostic assays are pushing diagnostic yields of FB higher and make the need for adding a transbronchial biopsy to BAL unnecessary in many cases. Biopsy seems to be of best use in the diagnostic evaluation of lesions suspected to be malignancy, leukemic infiltrates, post-transplant lymphoproliferative disorder, toxic pneumonitis, or cryptogenic organizing pneumonia (COP, previously known as bronchiolitis obliterans organizing pneumonia, BOOP) and is likely superior to BAL when those conditions are suspected (85). In our view, the greater safety of FB
along with comparable yield has shifted the preference from TTNA and surgical lung biopsy to FB in most situations in the highly immunosuppressed HM and HCT setting, particularly where infection is most likely.

**Video-assisted thoracoscopic surgery (VATS) or open thoracotomy.** If the lesion cannot be diagnosed by either FB with BAL/TBBx or TTNA, VATS and open lung biopsy are options. Open lung biopsy offers the opportunity to examine a large piece of tissue and would be expected to give the greatest likelihood of establishment of the diagnosis (63). It is accompanied by considerable morbidity and occasionally mortality, and is not a good option for patients with poor lung reserve and thrombocytopenia. Notwithstanding, the diagnostic yield in patients with HM has varied considerably in different reports, generally about 60% (52, 53, 86, 87). However, it is associated with considerable morbidity and risk for serious complications. Its morbidity and particular danger in those with thrombocytopenia and reduced lung reserve makes it much less appealing in most instances. VATS has supplanted the more extensive open thoracotomy lung biopsy in many instances due to fewer complications and shorter recovery time while preserving similar rates of yield (88, 89). VATS is not suitable for centrally located lesions or large lesions >3 cm. Thoracotomy would be indicated for such lesions.

The choice of the diagnostic intervention must balance risk with likelihood of clearly establishing the diagnosis. In general, the involvement of a multidisciplinary team consisting of pulmonologist, radiologist, infectious disease specialist, and, if needed, thoracic surgeon, can facilitate reaching the best decision as to the optimal invasive procedure.

**What are sensible evaluation/treatment strategies?**
Patients not receiving active chemo- or immunotherapy. Drawing on lessons from non-compromised patients, after detection of a SPN in patients not on active therapy, there are 3 choices: 1) observe, 2) biopsy, or 3) surgical resection. The overarching principle is to aggressively pursue diagnosis and resection if the likelihood of cancer is substantial. Consensus guidelines have been developed to provide a structured approach in non-compromised patients (28, 30, 63). In patients with HM, particularly patients with lymphoma, who have completed therapy, malignancy similarly is more likely than infection (12). Figure 2 offers a diagnostic algorithm to consider.

Patients receiving active chemotherapy or immunotherapy. Infections due to aggressive bacteria and fungi are key concerns. Prompt initiation of antimicrobial therapy is crucial. While evaluation is underway, presumptive therapy with broad spectrum antibiotics is warranted and should generally follow the recommendations for healthcare associated pneumonia (90) or one of the consensus guidelines (91-92), modified by local antibiotic susceptibility patterns. We also recommend presumptive anti-mold therapy until the etiology is established while the evaluation proceeds. Early diagnosis and timely initiation of therapy has been shown to improve treatment outcomes for IA (42, 93) and mucormycosis (94). Some clinicians focus on the use of broad spectrum antibiotics and antifungal therapy and do not pursue invasive diagnostic procedures unless the patient does not respond to the initial therapy. The downside for this approach is the uncertainty of the diagnosis, the need to subject the patient to therapy that he/she may not need along with its attendant costs and toxicities, and the possibility that the empirically chosen treatment may not target the true pathogen(s). We do not favor presumptive therapy as a substitute for invasive procedures but rather believe that both are important.
The development of sensitive non-cultural diagnostics has improved the yield of BAL (26, 80, 82, 85, 95). The use of HRCT to guide the optimal site for collection of BAL specimens has also been contributory to improved yields. Moreover, the delay in establishing a diagnosis not covered by the presumptive therapy is likely to result in poorer treatment outcome since delays are associated with lower responses (42, 61, 93, 94). Further, delayed investigation is associated with lower diagnostic yields (61). A study of early (within 4 days of presentation) versus late bronchoscopy in HCT patients found a 2.5 fold higher yield compared to later bronchoscopy (61) and greater mortality in patients subjected to late FOB. The yield was highest (75%) when bronchoscopy was performed within 24 hours of presentation. For these reasons, we urge performance of an invasive procedure at presentation rather than waiting to determine response to initial therapy, pursuing an invasive diagnostic only in those who are not responding (Figure 1).

**How should I assess the response to therapy?**

The first diagnostic decision is important but it may not be the last diagnostic decision since the results of the tests and the subsequent clinical course to therapy may dictate the need for a second diagnostic intervention. For patients with small lesions at low risk for active infection or malignancy in which the initial decision was to observe, additional scanning at 2-3 months is advisable.

For those who were found to have an active infection, response to therapy dictates the type and frequency of additional subsequent testing. If clinically responding, repeat imaging should be done periodically until the infection is resolved. It is important to note that infiltrates may take several weeks to 1-2 months to fully resolve and thus radiology by itself should not
dictate the need for further diagnostic interventions. It is well recognized that the infiltrates in patients with IA worsen over the first week of therapy even though with continued therapy, the patients respond (45). The patient with IA who is not clinically improving is the most challenging situation (96, 97). The patient may have clinical and or radiologic deterioration even while microbiologically responding. In large part this is related to the changing immune status of the patient. For example, neutrophil recovery or withdrawal of immunosuppressive therapy may exacerbate inflammatory responses leading to larger pulmonary infiltrates, persistent or worsening fever and clinical manifestations, the so-called immune reconstitution syndrome. For patients with IA, it has been proposed that serial GM testing can be helpful in distinguishing those truly not responding and those who are responding in the face of clinical worsening (98). Early data are promising for this approach but further study is needed.

If there is doubt as to whether the patient is responding or not, the diagnostic tests should be repeated. This is important since some infections are mixed and sometimes the initial assessment may not be conclusive. For example, in a patient who is documented to have IA at initial assessment but is not clinically responding and the radiography is not improving, consideration for a mixed infection by a respiratory virus, cytomegalovirus, bacteria (especially staphylococcus and pseudomonas), or another mold, such as the agents of mucormycosis, should be entertained and investigation to exclude these is warranted.

Summary

Lung nodules and nodular infiltrates are often caused by malignancy or aggressive bacterial or mold infections. The principal goal of evaluation in patients not highly myelo- or immunosuppressed is to distinguish malignant from non-malignant causes, where relapse of the
HM or a new primary lung cancer are major concerns. For patients receiving active chemo- or immunotherapy, acute infection is the chief concern. Where possible, a specific diagnosis should be established to optimize outcomes. The choice of the diagnostic intervention must balance risk with likelihood of clearly establishing the diagnosis. In general, the involvement of a multidisciplinary team consisting of an oncologist, pulmonologist, radiologist, infectious disease specialist, and, if needed, thoracic surgeon, can facilitate reaching the best decision as to the optimal invasive procedure and treatment strategy.
References

84. Tuon FF. A systematic literature review on the diagnosis of invasive aspergillosis using polymerase chain reaction (PCR) from bronchoalveolar lavage clinical samples. Rev Iberoam Micol 2007; 24:89-94.
88. Jiménez MF; Spanish Video-Assisted Thoracic Surgery Study Group. Prospective study on video-assisted thoracoscopic surgery in the resection of pulmonary nodules: 209 cases from the

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### Table 1. Major etiologies of pulmonary infiltrates

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<th>Non-infectious</th>
<th>Diffuse infiltrates</th>
<th>Nodules/Nodular infiltrates</th>
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<td><strong>Pulmonary edema</strong></td>
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<td>Chronic/inactive infectious granulomata</td>
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<td><strong>Mycoplasma</strong></td>
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<td>Aspergillus</td>
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<tr>
<td></td>
<td></td>
<td>Mucormycosis agents</td>
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<tr>
<td></td>
<td></td>
<td>Other molds</td>
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<td></td>
<td></td>
<td><em>Pneumocystis jiroveci</em></td>
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<tr>
<td></td>
<td></td>
<td>Toxoplasmosis</td>
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<td></td>
<td></td>
<td>Strongyloidiasis</td>
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</tbody>
</table>

**Figure 1.** Radiographs of different types of nodular lesions.

a. Solitary nodule.  b. Nodule with surrounding groundglass halo.  c. masslike consolidation with surrounding halo of ground-glass opacity.  d. Peripheral pleural based nodule with pleural effusion.  e. Large central irregular speculated density with surrounding ground-glass opacity and
smaller more peripheral speculated lesion. f. Cavitary nodule with sequestrum (air crescent sign).
b.

c.
Figure 2. Diagnostic algorithm

Respiratory symptoms

↓

HRCT

Nodular lesion

Patient on active treatment

Bacterial or fungal infection likely

FB with BAL including GM

If no response, consider repeating or another invasive diagnostic test

Malignancy not likely [small <8 mm, benign calcification pattern, stable over time, no smoking history, not treated for lymphoma]

Observe

Patient not on active treatment

Assess likelihood of malignancy

Malignancy likely [larger, change in size, calcification pattern not characteristic of benign lesion, smoking history, receiving treatment for lymphoma]

Perform biopsy (bronchoscopic TBBx, TTNA, or VATS excision) depending on size and location
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Non-compromised</th>
<th>Hematologic malignancy &amp; HCT</th>
<th>Non-compromised</th>
<th>Hematologic malignancy &amp; HCT</th>
<th>Limitations and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchoscopy with BAL</td>
<td>10-50% (62)</td>
<td>15-60% (90% for IPA if use non-cultural diagnostics) (60, 61, 72-74)</td>
<td>Major complications &lt;1-35%, severe 10% (62, 70, 71)</td>
<td>Most complications minor (&lt;2-28%); major complications (&lt;1-8% ) (6, 60, 61, 74, 75); 10% life-threatening complications if respiratory compromise (67)</td>
<td>Higher yields with guided bronchoscopic techniques Not suitable for patients with poor lung reserve</td>
</tr>
<tr>
<td>Transthoracic needle biopsy</td>
<td>80-90% (62,63)</td>
<td>50-78% (25, 46, 66)</td>
<td>Bleeding, pneumothorax (15-24%, chest tube (6-7%) (64, 65)</td>
<td>15-38% with 6-16% requiring chest tube (25, 46, 66)</td>
<td>Lesions optimally should be peripheral Better with larger lesions (&gt;1 cm) Not suitable for patients with poor lung reserve and thrombocytopenia</td>
</tr>
<tr>
<td>Open biopsy/excision</td>
<td>“gold standard” (62)</td>
<td>16-60% (45, 46, 85,86)</td>
<td>Considerable morbidity and mortality</td>
<td>13-21%; 30 day mortality 2-45% (45, 46, 85,86)</td>
<td>Not suitable for patients with poor lung reserve and thrombocytopenia</td>
</tr>
<tr>
<td>Video-assisted biopsy</td>
<td>Comparable to open lung biopsy (62,87)</td>
<td>Not adequately studied</td>
<td>10% morbidity, &lt;1% mortality (87, 88)</td>
<td>Not adequately studied</td>
<td>Not suitable for central or large (&gt;3 cm) lesions, lesions &lt; 1 cm, deeper in lung parenchyma Ground glass lesions may require localization procedure</td>
</tr>
</tbody>
</table>
How I manage pulmonary nodular lesions and nodular infiltrates in patients with hematologic malignancies or undergoing hematopoietic cell transplantation

John R. Wingard, John W. Hiemenz and Michael A. Jantz