Acute Respiratory Failure Before ICU Admission: A Practical Approach

10

Eleni Diamantaki, Athanasia Proklou, Emmanouil Pediaditis, Vasilis Amargianitakis, and Eumorfia Kondili

10.1 Introduction

Acute respiratory failure (ARF) occurs in up to half patients with hematologic and solid malignancies and is the leading cause of ICU admission in those patients. It is associated with poor outcome, with an overall mortality of 20–80% depending on the cause, the need for mechanical ventilation, the concomitant organ dysfunctions, the presence of graft-versus-host disease, and the goals of care [1, 2]. Delay in identification of the cause of ARF and the initiation of the appropriate therapy may further increase mortality. The most common cause of ARF in cancer patients is pulmonary infections, as a result of the immunosuppression posed by the underlying disease or the cancer therapy. Other frequent causes include cardiogenic and noncardiogenic pulmonary edema (acute respiratory distress syndrome [ARDS]), antineoplastic therapy (chemotherapy, radiation therapy)-induced lung injury, cancer-related medical disorders (such as venous thromboembolism, transfusion-related acute lung injury), and direct involvement of the respiratory system by malignancy and progression of underlying disease.

In cancer patients with ARF, the diagnostic strategy is to guide the immediate empirical treatment, most notably antimicrobial therapy as well as life-supporting interventions [3]. However, investigations must be obtained very rapidly to confirm or refute the initial diagnoses.

Differential diagnosis of ARF in cancer patients is a challenging process for the clinical physician. The cornerstone in the etiological diagnosis of ARF consists of a

E. Diamantaki, M.D. • A. Proklou, M.D., Ph.D. • E. Pediaditis, M.D.
V. Amargianitakis, M.D.
Department of ICU, University Hospital of Heraklion, Crete, Greece

E. Kondili, M.D., Ph.D. (✉)
Department of ICU, University Hospital of Heraklion, Crete, Greece

School of Medicine, University of Crete, Heraklion, Crete, Greece
e-mail: konde@med.uoc.gr

A.M. Esquinas et al. (eds.), *Mechanical Ventilation in Critically Ill Cancer Patients*,
https://doi.org/10.1007/978-3-319-49256-8_10

comprehensive clinical evaluation aimed at identifying the most likely causes and, therefore, at determining the appropriate diagnostic approach. A thorough physical examination provides key information on the respiratory manifestations (bronchial, interstitial, alveolar, vascular, or pleural symptoms), the severity of the ARF, and the time elapsed since respiratory symptom onset.

Both invasive and noninvasive diagnostic strategies can be used to identify the cause of ARF in cancer patients. The invasive strategy relies on fiberoptic bronchoscopy with bronchoalveolar lavage (FO-BAL), and the noninvasive strategy on imaging studies, on microbiological examination of blood and sputum, and on serological test.

It is already established that stable patients presenting with ARF and pulmonary infiltrates should undergo FB-BAL as microbiological and cytological examination of the BAL can be diagnostic in up to 50% of cancer patients with ARF [4]. However, in severely hypoxemic patients, FO-BAL has been described as inadvisable or contraindicated because of the risk of deterioration in respiratory status with a subsequent need for mechanical ventilation [5].

Imaging tests are of importance, in the identification of the cause of ARF. Chest X-ray should be performed in any patient presented with symptoms and signs of ARF, though it is neither specific nor sensitive in providing a specific diagnosis in particular in patients with febrile neutropenia. High-resolution computed tomography (HRCT) with sections at 1-mm intervals and, if needed, sections during expiration is more sensitive than chest radiography even in non-neutropenic patients. However, HRCT provides diagnostic orientation rather than a definitive diagnosis in cancer patients with ARF [6]. HRCT yields an overall sensitivity and negative predictive value of 90%, in identifying the cause of ARF in cancer patients with lung infiltrates, but low specificity and positive predictive value [7]. In some times HRCT may help to select the nature and site of endoscopic sample collection.

Recently lung ultrasound (LUS) has been introduced as diagnostic test in patients with ARF. LUS is a noninvasive and bedside-available imaging test, and many studies have shown that compared to chest X-ray, it has a higher diagnostic accuracy for pleural effusion, consolidation, pneumothorax, and interstitial syndrome and may be used as alternative to CT [8].

This chapter reviews the most common causes of ARF in oncologic patients and discusses the diagnostic and therapeutic approach before ICU admission.

10.2 Acute Respiratory Failure (ARF) in Cancer Patient Causes

10.2.1 Pulmonary Infections

Pulmonary infections are very frequent and represent the most common cause of ARF in oncologic patients, and unless proven otherwise, ARF in cancer patients

must be considered as an infectious emergency. Several factors increase the risk of infection in those patients, including chemotherapy, corticosteroid-induced immunosuppression, multiple hospital admissions, and exposure to broad-spectrum antibiotics [9]. Causative pathogen depends on the underlying immune state. In patients with impaired humoral immunity, such as those with acute and chronic lymphocytic leukemia and multiple myelomas, *Streptococcus pneumoniae* and *Haemophilus influenzae* are the predominantly isolated organisms. In patients with impaired cell-mediated (T-cell) immunity as those with Hodgkin disease or those therapy with corticosteroids, the predominantly isolated organisms are *Pneumocystis jirovecii* pneumonia (PJP), followed by mycobacteria, *Cryptococcus*, *Legionella pneumophila*, and viral infections (mainly herpes virus and *Cytomegalovirus*). Neutropenic patients are usually infected by gram-positive cocci (*Staphylococcus aureus* and *Streptococcus pneumoniae*), gram-negative enteric bacilli (*Pseudomonas aeruginosa* and *Klebsiella pneumoniae*), or opportunistic fungi (mainly *Aspergillus*)—especially in the case of prolonged neutropenia [9, 10] . When evaluating pneumonia in patients with cancer, determining the level and the duration of immunosuppression, the previous exposure to antimicrobials (over the last month), the length of the illness, the presenting symptoms, and the radiographic pattern will better predict the suspected pathogens. Hereby we discuss the most common pulmonary infections in the immunocompromised patients.

10.3 Bacterial Pneumonia

In patients with bacterial pneumonia, clinical manifestation is the typical one occurring in non-oncologic patients with pneumonia, including acute onset of shaking chills, tachypnea, tachycardia, fever (which occurs in virtually all patients with bacterial pneumonia), and productive cough. However, in the setting of neutropenia, clinical diagnosis is often jeopardized by nontypical clinical findings [11] . Sputum production is seen in less than 60% of neutropenic patients, while in severe neutropenia (neutrophils <1000 cells/mm^3), purulent sputum is present in less than 8% of patients. Routine clinical examination often reveals rales and signs of consolidation. To determinate the cause of pneumonia, blood cultures should be performed routinely; however, the results may be of limited value. Similarly, sputum analysis is often low yield, and the results are difficult to interpret. Identifying the exact cause of pneumonia in patients with cancer often requires fiberoptic bronchoscopy with BAL as sputum is seldom produced. The overall diagnostic yield of BAL in neutropenic and non-neutropenic patients with suspected pneumonia is 49% and 63%, respectively [12]. Chest X-ray findings of bacterial pneumonia in cancer patients are nonspecific. The initial chest radiograph may be normal (mainly in neutropenic patients) or demonstrate lobar consolidation (usually missing in neutropenic patients) and diffuse interstitial infiltrates.

10.4 Pulmonary Aspergillosis

Aspergillus lung disease may present in four district clinical syndromes, i.e., allergic bronchopulmonary aspergillosis, aspergilloma, chronic-necrotizing pulmonary aspergillosis, and invasive aspergillosis. Invasive aspergillosis is a rapidly progressive and potentially fatal infection, which typically occurs in the setting of prolonged neutropenia, treatment with corticosteroids and broad-spectrum antibiotics, and underlying leukemia or lymphoma [13]. The clinical features include tachypnea, fever, dyspnea, nonproductive cough, pleuritic chest pain with or without a friction rub, progressive hypoxemia, and sometimes hemoptysis in patients with prolonged neutropenia or immunosuppression.

Often the only evidence of *Aspergillus* pneumonia is fever with pulmonary infiltrates that do not respond to antibiotics. Chest radiographic features are variable and may show patchy bronchopneumonia, multiple nodular densities, and peripheral, wedged-shaped infiltrates. CT scans may demonstrate the characteristic halo (an area of ground-glass infiltrate surrounding nodular densities) or the air-crescent sign [14].

Definitive diagnosis of invasive aspergillosis requires the demonstration of the organism in tissue. Visualization of the specific fungi using Gomori methenamine silver stain or calcofluor or a positive culture from sputum, needle biopsy, or bronchoalveolar lavage (BAL) confirms the diagnosis of invasive aspergillosis. However, a negative result does not exclude pulmonary aspergillosis.

10.5 *Pneumocystis Jirovecii* Pneumonia

The incidence of *Pneumocystis jirovecii* pneumonia (PJP) (formerly known as *Pneumocystis carinii*) is high among patients with lymphoproliferative malignancies and solid tumors and those receiving long-term corticosteroids or immunomodulation agents.

PJP typically presents as an acute or subacute pulmonary process with fever, nonproductive cough, dyspnea, shortness of breath, and severe hypoxemia.

Physical examination is often unrevealing except for fever and tachypnea. Chest examination is commonly normal; however, diffuse rales, and eventually signs of consolidation, may be present as the disease progresses.

Chest X-ray findings are nonspecific consisting of diffuse alveolar or interstitial infiltrates in 80% of the patients. High-resolution computed tomography (HRCT) represents the gold standard imaging modality in detecting parenchymal abnormalities. The most common HRCT finding is bilateral ground-glass opacities with apical predominance and peripheral sparing. The range of other HRCT findings includes a combination of ground glass and consolidative opacities, linear-reticular opacities, cystic abnormalities, multiple nodules, and parenchymal cavities.

The standard method for diagnosis of PJP relies on the microscopic visualization of *P. jirovecii* organisms in respiratory specimens. Bronchoalveolar lavage (BAL) combined with colorimetric and direct or indirect immunofluorescence stain of

BAL fluid is considered the method of choice with sensitivity and specificity more than 95%. An alternative is an examination of material obtained by induced sputum [15]. However, the sensitivity of this method is more dependent on the experience of the personnel performing the procedure and evaluating the samples, with high variation in the diagnostic sensitivity reported (ranged between 50 and 90%). Most recently highly sensitive molecular techniques, using semi- or fully quantitative polymerase chain reaction (PCR) targeting *P. jirovecii*-specific genes, have been introduced. A meta-analysis of PCR studies has shown a pooled sensitivity of 99% and specificity of 92% [16, 17].

10.6 CMV Pneumonia

CMV pneumonia has a high mortality rate of 15–75%, especially in patients that require mechanical ventilation. Cancer patients in risk are the bone-marrow transplant recipients [18]. Fever, nonproductive cough, and dyspnea are common presenting symptoms. Radiographic patterns in CMV pneumonia include lobar consolidation, focal parenchymal haziness, and bilateral reticulonodular infiltrates. CT may reveal ground-glass opacities, bronchial wall thickening, reticular opacities, and nodules.

The diagnosis of CMV pneumonia depends on isolation of the virus from patients with a positive finding on chest radiograph and appropriate clinical signs [19]. CMV may be isolated from the lung with bronchoalveolar lavage (BAL) or open-lung biopsy. In support of the diagnosis, CMV antigen or inclusions are found with histological examination. CMV isolated from clinical samples in the absence of clinical symptoms may represent viral colonization or subclinical replication disease.

10.6.1 Acute Respiratory Distress Syndrome (ARDS)

ARDS is a clinical syndrome characterized by the acute onset (within 7 days) of severe hypoxemia (defined by a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen [PaO_2/FiO_2] of less than 300 despite the application of PEEP or CPAP $\geq$ 5 cm H_2O) and the presence of bilateral alveolar or interstitial infiltrates that cannot be fully attributed to cardiac failure or fluid overload [20].

Even though the incidence of ARDS in the general population is estimated to be 13–24 cases per 100,000, the exact incidence of ARDS in patients with cancer remains unknown. In oncologic patients with or without neutropenia, ARDS may be related to infectious or noninfectious causes. Causes of primary ARDS include bacterial or opportunistic infections such as invasive pulmonary aspergillosis, *Pneumocystis jirovecii* pneumonia, and fungal and severe viral infections. Secondary ARDS is related to a systemic process such as severe sepsis or septic shock from extrapulmonary bacterial or fungal infections. In a recent retrospective study in up to 90% of ARDS, the causative was an infection, including one-third due to invasive fungal disease [21]. Mortality in oncologic patients with ARDS remains high

Table 10.1 The most common chemotherapeutic and immunosuppressive agents associated with pulmonary toxicity

Bevacizumab
Bleomycin
Busulfan
Cyclophosphamide
Docetaxel
Erlotinib
Everolimus
Gefitinib
Gemcitabine
Interferons
Irinotecan
Methotrexate
Mitomycin C
Nitrosourea
Oxaliplatin
Paclitaxel
Topotecan
Trastuzumab
Vinblastine

although a significant decrease has been recorded over the time. Risk factors for higher mortality include the need for mechanical ventilation, allogeneic bone-marrow transplantation, NIV failure, severe ARDS, and invasive fungal infection. ARDS treatment, although supportive, is considered significant, in both identifying and treating—if possible—the underlying cause [22, 23].

10.6.2 Drug-Induced Toxicity

Pulmonary toxicity of antineoplastic agents, known as drug-induced toxicity (DIT), is a common cause of respiratory failure in oncologic patients and should be included in the differential diagnosis of ARF in patients who are on or have been treated with antineoplastic agents. Table 10.1 shows the most common chemotherapeutic and immunosuppressive agents associated with pulmonary toxicity.

Up to 10% of patients treated with chemotherapy will develop DIT. The extent of lung injury depends on both physical and biological factors including the pharmacokinetic properties of the drug and the drug dose and whether it is used as single therapy or as combination with other chemotherapeutics, the prior exposure to radiation and high oxygen concentration, and the presence of preexisting lung disease [24].

DIT may manifest in a broad variety of pulmonary syndromes, including acute interstitial pneumonitis, nonspecific interstitial pneumonia, ARDS, capillary leak syndrome, hypersensitivity pneumonitis (HP), cryptogenic organizing pneumonia (COP), eosinophilic pneumonia (EP), alveolar hemorrhage, and fibrosis [25]. Symptoms are usually nonspecific including low-grade fever, nonproductive cough,

pleural pain, and shortness of breath and can manifest days or even years after the exposure. Routine clinical examination usually reveals rales and/or a pleural friction rub.

The diagnosis of DIT remains an exclusionary process, in particular when considering common or atypical infections, as well as recurrence of the underlying neoplastic process. Diffuse pulmonary infiltrates are the most common findings in chest X-ray, while high-resolution computed tomography (HRCT) findings are mainly dependent on the type of the drug-induced pulmonary syndromes and usually consist of pleural effusions, ground-glass opacities, traction bronchiectasis, and fibrosis. Pulmonary function tests in the majority of DIT cases may reveal a pattern of restrictive abnormality, with decreased values of DLCO. Bronchoscopy can be helpful in determining the presence of pneumonitis and for the differential diagnosis of lymphangitic carcinomatosis, vasculitis, alveolar hemorrhage, or pneumonia from infectious agents. Most drug-induced immunological reactions, such as HP, COP, and EP, may be excluded if BAL cytology is normal. In regard to the management in many instances, DIT may respond to withdrawal of the offending agent and the judicious application of corticosteroid therapy [26].

10.6.3 Acute Pulmonary Embolism

Venous thromboembolic disease (VTD) may be present both in the form of deep venous thrombosis (DVT) or pulmonary embolism (PE) and is one of the leading causes of morbidity and mortality in oncologic patients [27]. It is now well established that the incidence of VTD is higher in patients with cancer than in the general population and that the malignancies that are most frequently associated with thrombotic complications are those of the pancreas, brain, stomach, lung, and pleura [28].

The most common symptoms are shortness of breath, pleuritic or substernal chest pain, palpitations, cough, hemoptysis, and syncope. Even though hypoxemia is considered a typical finding in acute PE, up to 40% of the patients present with normal arterial oxygen saturation.

As the majority of preventable deaths associated with PE can be ascribed to a missed diagnosis and anticoagulation is associated with a risk of bleeding, it is crucial to exclude or confirm the diagnosis of PE to avoid unnecessary anticoagulation or promptly start such treatment if it is appropriate [29].

In patients with suspected PE, both the diagnostic and therapeutic strategies rely on well-established and extensively validated algorithms, which utilize the clinical stratification of severity (assessment of the risk of death), the clinical probability (pretest probability), the plasma D-dimer measurement, and imaging tests [30].

Stratification of severity is based on patient's clinical status at presentation, with high-risk PE being suspected or confirmed in the presence of shock or persistent arterial hypotension.

For patients with suspected PE, the pretest probability is determined by using validated clinical prediction rules, and two alternative classification schemes may

be utilized, i.e., the three category schemes (low, moderate, or high clinical probability of PE) and the two category schemes (PE likely or unlikely) [31].

Regarding the specific for PE diagnostic tests, computed tomography pulmonary angiography (CTPA) remains the gold standard diagnostic method in patients with suspected PE, with 83 and 98% sensitivity and specificity, respectively. Plasma D-dimer testing has a high negative predictive value for excluding PE, though its positive predictive value remains low [32].

Hereby describe the diagnostic and therapeutic workup should be followed in patients with suspected PE, based on the proposed algorithms [30, 33].

In patients with suspected PE and presented with shock or hypotension, bedside transthoracic echocardiography represents the most useful initial diagnostic approach. An echocardiography evidence of right ventricular dysfunction is sufficient to prompt immediate reperfusion without further testing. Following patient's stabilization, a CTPA should be performed to confirm the diagnosis.

In hemodynamically stable patients, the first step in the diagnostic and therapeutic algorithm is the determination of the pretest probability. In patients with a low/intermediate clinical probability, the first-line test is the measurement of plasma D-dimers, and a negative D-dimer test rules out the diagnosis of PE. In the case of a positive D-dimer test, a CTPA should be performed. In patients with high clinical probability, CTPA represents the first-line test.

10.6.4 Transfusion-Related Acute Lung Injury (TRALI)

Patients with cancer, particularly those with hematologic malignancies and those undergoing a major surgical operation, are subjected to multiple transfusions of fresh frozen plasma, platelets, and packed red blood cells, and thus they are at a risk for developing transfusion-related acute lung injury (TRALI). The diagnosis is mainly based on clinical criteria, and several definitions of TRALI have been introduced in the last decades (Table 10.2). Accordingly, the syndrome is characterized by the presence of hypoxemia and bilateral infiltrates occurring during or within 6 h of a transfusion, in the absence of cardiac failure or volume overload [34].

Although any blood component can cause TRALI, plasma-rich units are more likely to be the culprits. The precise mechanisms of the capillary leak syndrome in TRALI have not been fully elucidated, but currently, two main hypotheses have been proposed. The first hypothesis supports the activation of recipient's neutrophils by passively transporting leukoagglutinating antibodies. The activated neutrophils, in turn, are carried to the lungs and activate the complement leading to endothelial damage, capillary leak, and lung injury [35]. The second hypothesis supports that neutrophils accumulate and are primed in the patient's pulmonary microvasculature as a result of preexisting systemic inflammation. Activation of these neutrophils by lipids or other mediators contributes to endothelial damage in susceptible patients.

Signs and symptoms include tachypnea, frothy pulmonary secretions, hypotension (less commonly hypertension), fever, tachycardia, and cyanosis. Routine

Table 10.2 Current criteria for the diagnosis of TRALI

American-European Consensus Conference Definition of ALI
Acute onset
Bilateral pulmonary infiltrates evident on chest radiograph
Hypoxemia, defined as $PaO_2/FiO_2 \leq 300$
No evidence of left atrial hypertension (i.e., no congestive heart failure or PAOP ≤18, if available)
National Heart, Lung, and Blood Institute Definition of TRALI
No ALI before transfusion
Signs or symptoms of TRALI during or within 6 h of transfusion
In patients with an alternative ALI risk factor, TRALI is still possible
Massive transfusion should not exclude the possibility of TRALI
European Haemovigilance Network Definition of TRALI
Respiratory distress during or within 6 h of transfusion
No signs of circulatory overload
Radiographic evidence of bilateral pulmonary infiltrates

clinical examination reveals diffuse rales. The differential diagnosis should include the transfusion-associated circulatory overload (TACO) and respiratory distress due to anaphylactic transfusion reactions.

The mainstay of treatment for TRALI remains supportive care with supplemental oxygen in all reported cases and mechanical ventilator support in up to two-thirds of patients. If the suspected blood product is still being transfused, it should be discontinued immediately. In contrast to ARDS from other causes, the majority of the patients recover completely, with improvement of hypoxia and resolution of pulmonary infiltrates that occur within 96 h of the transfusion.

10.6.5 Cardiogenic Pulmonary Edema

Cardiogenic pulmonary edema (CPE) should always be included in the differential diagnosis of acute respiratory failure in oncologic patients, in particular when chemotherapy with cardiotoxic drugs has been preceded. The etiology of pulmonary edema is multifactorial and includes increased hydrostatic pressure from high-volume infusions and/or multiple transfusions, cardiotoxic effects of chemotherapy, and renal impairment. Anthracyclines (e.g., doxorubicin, daunorubicin, epirubicin, idarubicin), taxanes (paclitaxel and docetaxel), and alkylating agents (cyclophosphamide, ifosfamide, melphalan) are chemotherapeutics drugs with well-established cardiotoxicity [36]. Even though a universally accepted definition does not exist, the American Society of Echocardiography and the European Association of Cardiovascular Imaging define cancer therapeutic-related cardiac dysfunction as a decrease in the left ventricular ejection fraction (LVEF) of >10%, to a value <53% confirmed by repeat imaging [37].

The diagnostic and therapeutic approach in CPE in cancer patients is the same as in any other patients [38]. In most cases, clinical manifestation consists of

hypoxemia, tachycardia, tachypnea, shortness of breath, orthopnea, and profuse diaphoresis. Hypotension may present and indicate severe LV systolic dysfunction and the possibility of cardiogenic shock. Pink, frothy sputum may be present in patients with severe disease. In regard to routine clinical examination, auscultation of the lungs usually reveals fine, crepitant rales (most commonly heard at the lung bases), but rhonchi or wheezes may also be present, while cardiovascular findings are notable for S_3, accentuation of the pulmonic component of S_2, and jugular venous distention.

Apart from clinical examination, laboratory and imaging tests are of great importance for establishing the diagnosis of CPE. Plasma levels of the B-type natriuretic peptide (BNP) and its amino-terminal fragment N-terminal proBNP (NT-proBNP) have been shown to be useful, in addition to clinical judgment, for the etiological diagnosis in patients with acute onset of dyspnea, and should be measured in all patients with ARF and suspected CPE. BNP has a high negative predictive value, and being lower than the recommended cutoff value of 100 pg/mL in patients with suspected CPE makes the diagnosis unlikely [39]. A bedside echocardiogram in a patient with CPE remains the cornerstone in determining the etiology of pulmonary edema. Echocardiography can be used to evaluate LV systolic and diastolic function, as well as valvular function, and to assess for pericardial disease.

Chest X-ray may be proved as a useful diagnostic test for CPE. Pulmonary venous congestion, pleural effusion (particularly bilateral and symmetrical), interstitial or alveolar edema, and cardiomegaly are the most specific findings for CPE. However, it should mention that in up to 20% of patients, chest X-ray maybe nearly normal.

More recently, lung ultrasound (LUS) has been introduced as a simple, non-invasive diagnostic method in patients with suspected CPE. In cases in which there is a moderate to high pretest probability of acute CPE, LUS can be useful in strengthening a working diagnosis. Findings of B-lines on ultrasonography have been reported to have a sensitivity of 94.1% and a specificity of 92.4% for acute CPE [40].

References

1. Azoulay E, et al. The prognosis of acute respiratory failure in critically ill cancer patients. Medicine. 2004;83:360–70.
2. Aygencel G, et al. Prognostic factors in critically ill cancer patients admitted to the intensive care unit. J Crit Care. 2014;29(4):618–26.
3. Azoulay E, et al. Diagnostic strategy in cancer patients with acute respiratory failure. Intensive Care Med. 2006;32:808–22.
4. Azoulay E, et al. Diagnostic strategy for hematology and oncology patients with acute respiratory failure: randomized controlled trial. Am J Respir Crit Care Med. 2010;182:1038–46.
5. Azoulay E, et al. Diagnostic bronchoscopy in hematology and oncology patients with acute respiratory failure: prospective multicenter data. Crit Care Med. 2008;36:100–7.
6. Collins J. CT signs and patterns of lung disease. Radiol Clin North Am. 2001;39:1115–35.
7. Mandeep K, et al. Role of HRCT in detection and characterization of pulmonary abnormalities in patients with febrile neutropenia. Lung India. 2013;30:124–30.

8. Lichtenstein DA, et al. Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. Chest. 2008;124:117–25.
9. Hubel K, et al. Suppressed neutrophil function as a risk factor for severe infection after cytotoxic chemotherapy in patients with acute nonlymphocytic leukemia. Ann Hematol. 1999;78:73–7.
10. Vento S, et al. Lung infections after cancer chemotherapy. Lancet Oncol. 2008;9:982–92.
11. Godbole G, et al. Respiratory tract infections in the immunocompromised. Curr Opin Pulm Med. 2013;19:244–50.
12. Gruson D, et al. Utility of fiberoptic bronchoscopy in neutropenic patients admitted to the intensive care unit with pulmonary infiltrates. Crit Care Med. 2000;28:2224–30.
13. Kosmidis C, et al. The clinical spectrum of pulmonary aspergillosis. Thorax. 2015;70:270–7.
14. Chabi ML, et al. Pulmonary aspergillosis. Diagn Interv Imaging. 2015;96:435–42.
15. Cooley L, et al. Consensus guidelines for diagnosis, prophylaxis and management of Pneumocystis jirovecii pneumonia in patients with haematological and solid malignancies. Intern Med J. 2014;44:1350–63.
16. Fan LC, et al. Evaluation of PCR in bronchoalveolar lavage fluid for diagnosis of Pneumocystis jirovecii pneumonia: a bivariate meta-analysis and systematic review. PLoS One. 2013;8(9):e73099.
17. Lu Y, et al. PCR diagnosis of Pneumocystis pneumonia: a bivariate meta-analysis. J Clin Microbiol. 2011;49:4361–3.
18. Ariza-Heredia EJ, et al. Cytomegalovirus diseases after hematopoietic stem cell transplantation: a mini-review. Cancer Lett. 2014;342:1–8.
19. de la Hoz RE, et al. Diagnosis and treatment approaches to CMV infections in adult patients. J Clin Virol. 2002;25(Suppl 2):S1–12.
20. ARDS Definition Task Force, Ranieri VM, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012;307:2526–33.
21. Azoulay E, et al. Acute respiratory distress syndrome in patients with malignancies. Intensive Care Med. 2014;40:1106–14.
22. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301–8.
23. Neto S, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. JAMA. 2012;308:1651–9.
24. Esteban E, et al. Pulmonary toxicity in patients treated with gemcitabine plus vinorelbine or docetaxel for advanced non-small cell lung cancer: outcome data on a randomized Phase II study. Invest New Drugs. 2008;26:67–74.
25. Sadowska A, et al. Antineoplastic therapy induced pulmonary toxicity. Expert Rev Anticancer Ther. 2013;13:997–1006.
26. Chang AY, et al. Pulmonary toxicity induced by mitomycin C is highly responsive to glucocorticoids. Cancer. 1986;57:2285–90.
27. Stein PD, et al. Incidence of venous thromboembolism in patients hospitalized with cancer. Am J Med. 2006;119:60–8.
28. Wun T, et al. Epidemiology of cancer-related venous thromboembolism. Best Pract Res Clin Haematol. 2009;22:9–23.
29. Posch F, et al. Treatment of venous thromboembolism in patients with cancer: a network meta-analysis comparing efficacy and safety of anticoagulants. Thromb Res. 2015;136:582–9.
30. (ESC), The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014;35:3033–80.
31. Ceriani E, et al. Clinical prediction rules for pulmonary embolism: a systematic review and meta-analysis. J Thromb Haemost. 2010;8:957–70.
32. Di Nisio M, et al. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. J Thromb Haemost. 2007;5:296–304.

33. Käberich A, et al. Risk-adapted management of acute pulmonary embolism: recent evidence, new guidelines. Rambam Maimonides Med J. 2014;5(4):e0040.
34. Triulzi DJ, et al. Transfusion-related acute lung injury: current concepts for the clinician. Anesth Analg. 2009;108:770–6.
35. Sayah MD, et al. Transfusion reactions: newer concepts on the pathophysiology, incidence, treatment and prevention of transfusion related acute lung injury (TRALI). Crit Care Clin. 2012;28:363–72.
36. Aaron C, et al. The prevention, detection and management of cancer treatment-induced cardiotoxicity: a meta-review. BMC Cancer. 2015;15:366.
37. Plana JC, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2014;15:1063–93.
38. Ponikowski P, et al. Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Eur J Heart Fail. 2016;18(8):891–975.
39. Waldo SW, et al. Pro-B-type natriuretic peptide levels in acute decompensated heart failure. J Am Coll Cardiol. 2008;51:1874–82.
40. Al Deeb M, et al. Point-of-care ultrasonography for the diagnosis of acute cardiogenic pulmonary edema in patients presenting with acute dyspnea: a systematic review and meta-analysis. Acad Emerg Med. 2014;21:843–52.