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Acute respiratory failure in immunocompromised adults

Elie Azoulay, Djamel Mokart, Achille Kouatchet, Alexandre Demoule, Virginie Lemiale

Acute respiratory failure occurs in up to half of patients with haematological malignancies and 15% of those with solid tumours or solid organ transplantation. Mortality remains high. Factors associated with mortality include a need for invasive mechanical ventilation, organ dysfunction, older age, frailty or poor performance status, delayed intensive care unit admission, and acute respiratory failure due to an invasive fungal infection or unknown cause. In addition to appropriate antibacterial therapy, initial clinical management aims to restore oxygenation and predict the most probable cause based on variables related to the underlying disease, acute respiratory failure characteristics, and radiographic findings. The cause of acute respiratory failure must then be confirmed using the most efficient, least invasive, and safest diagnostic tests. In patients with acute respiratory failure of undetermined cause, a standardised diagnostic investigation should be done immediately at admission before deciding whether to perform more invasive diagnostic procedures or to start empirical treatments. Collaborative and multidisciplinary clinical and research networks are crucial to improve our understanding of disease pathogenesis and causation and to develop less invasive diagnostic strategies and more targeted treatment options.

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Introduction

A growing number of adults have immune dysfunction.[1] Up to 5% of the general population are cancer survivors,[2] transplantation is on the rise,[3] and immunosuppressant drugs are being used for more indications.[4] Moreover, intensive treatments now improve disease-free survival,[2] but also increase the risk of life-threatening events, many of which affect the lungs.[5–8]

Acute respiratory failure can be defined as a triad of clinical signs, radiographic findings, and gas exchange alterations. Most patients present with newly developing or worsening respiratory symptoms over a period of 7 days. Severe acute respiratory failure manifests as respiratory distress with severe tachypnoea, laboured breathing, and recruitment of accessory respiratory muscles. Various patterns of pulmonary infiltrates might be seen, the most common of which are diffuse bilateral infiltrates.[9] Patients with acute respiratory failure require oxygen therapy and most studies of acute respiratory failure included patients receiving ≥6 L/min of standard oxygen. However, depending on the country and number of available hospital beds, patients with acute respiratory failure can be managed on wards, in intermediate care units, or in intensive care units (ICUs). Overall, the need for ICU admission, need for invasive mechanical ventilation (IMV), or mortality increase with the required oxygen flow.[10] Thus, for patients that require 6 L/min of standard oxygen or more, need for intubation throughout the ICU stay and mortality before hospital discharge are up to 40%.[9–16] Delayed ICU admission has been associated with increased mortality.[13,14,17]

Immunocompromised patients with acute respiratory failure can be encountered by all clinicians in their daily practice. In this Review, we look at the epidemiology, outcomes, and diagnostic investigations in immunocompromised patients with acute respiratory failure, with emphasis on the broad range of causes that must be considered. We discuss the role for invasive and non-invasive tests in identification of the cause of acute respiratory failure, although the huge diversity of tests available for each cause, coupled with the scarcity of randomised controlled trials, creates major challenges. We also suggest an approach to the management of hypoxaemia based on the latest literature.

Epidemiology

The incidence of respiratory events varies across different groups of immunocompromised patients (table 1). Few studies have followed cohorts of patients with the main objective of collecting information about the incidence of pulmonary infiltrates or respiratory complications. Observational studies have shown that among haematological malignancies, lymphoproliferative disorders (acute lymphoblastic leukaemia and lymphoma) were associated with a moderate incidence of respiratory events (8–18%)[18] compared with acute myeloid leukaemia and myelodysplastic syndromes (22–84%; table 1).[19,20,38]

Key messages

- Acute respiratory failure occurs in up to 50% of haematology patients (primarily patients with acute myeloid leukaemia or allogeneic haemopoietic stem cell transplantation) and in up to 15% of patients with solid tumours (chiefly lung cancer) or solid organ transplants (chiefly of the heart or lung).
- Mortality is high and is associated with invasive mechanical ventilation and organ dysfunction; older age; frailty or poor performance status; delayed intensive care unit admission; and acute respiratory failure due to an invasive fungal infection or unknown cause.
- In addition to appropriate antibacterial therapy, initial management aims to restore oxygenation and predict the most probable cause on the basis of variables related to the underlying disease, the characteristics of acute respiratory failure, and the radiographic findings. The cause of acute respiratory failure must then be confirmed using the most efficient, least invasive, and safest diagnostic tests.
- In patients with acute respiratory failure of undetermined cause, a standardised diagnostic investigation should be done immediately at admission before deciding whether to perform more invasive diagnostic procedures or to start empirical treatments.
- Collaborative and multidisciplinary clinical and research networks are crucial both to improve our understanding of disease pathogenesis and causation and to develop less invasive diagnostic strategies and more targeted treatment options.

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Moreover, patients with prolonged neutropenia[6] and autologous or allogeneic stem cell transplant recipients[24–27] have higher incidences of respiratory events compared with other haematology patients. Solid tumours are associated with a lower incidence of respiratory events than haematological malignancies, with lung cancer having the highest rates (up to 50%), because endobronchial obstruction and atelectasis are risk factors for pneumonia.[30] However, in patients with breast cancer treated with radiation and paclitaxel, the crude rate of pneumonitis was 14·6% (95% CI 5·6–29·2).[31] Of note, in patients with cancer receiving immunotherapy (mostly with programmed death 1 and programmed death ligand 1 inhibitors), the incidence of pneumonitis can reach 4%.[32,39] Acute respiratory failure occurs in about 5% of kidney transplant recipients and 12–14% of heart or lung transplant recipients.[34,36] Overall, mortality among patients with acute respiratory failure is about 50%, depending on the underlying condition, nature, severity, and course of the respiratory failure, need for IMV, and associated organ dysfunctions.[13]

Factors associated with mortality

Several studies have assessed risk factors for mortality in immunocompromised patients with acute respiratory failure. These factors can be grouped into five categories: (1) factors reflecting the severity of the acute respiratory failure and associated organ dysfunctions, (2) factors related to delayed ICU admission, (3) factors related to the underlying disease and comorbid conditions, (4) factors related to the initial oxygenation and ventilation strategy, and (5) factors related to the cause of acute respiratory failure.

	Incidence of respiratory events	Need for ICU admission	Hospital respiratory mortality
Haematological malignancies			
Acute myeloid leukaemia[5,18–23]	22–84%	66%	45%
Acute lymphoblastic leukaemia[18,22,23]	7–18·5%	12–15%	38·5%
Lymphoproliferative diseases[5]	8%	8%	40-50%
Myelodysplastic syndrome[18]	29·4%	20%	17%
Autologous haemopoietic stem cell therapy[24,25]	3–28%	42%	3–55%
Allogeneic haemopoietic stem cell therapy[26,27]	24–30%	50%	51%
Prolonged neutropenia[6,28]	8–29·5%	11–16%	5–12%
Solid tumours			
Lung cancer[29,30]	26–50%	100%	11·2–60%
Other solid tumours[5,30,31]	0·7–10·3%	100%	6·1–55%
Patients on immunotherapy[32,33]	1·3–3·6%	1·3%*	..
Solid organ transplantation			
Lung transplantation[34]	14%	All	65%
Heart transplantation[35]	12·5%	All	76·5%
Kidney transplantation[36,37]	3·3–4·8%	All	16·4–22·5%

Data on patients with drug-related immunosuppression are sparse. *Refers to grade 3–4 toxicities. ICU=intensive care unit.

Table 1: **Incidence of respiratory events in various types of immunocompromised patients**

Hypoxaemia is the hallmark of respiratory failure. The clinical signs and tolerance of hypoxaemia are usually a function of respiratory symptom duration. For instance, an acute hypoxaemic episode can lead to respiratory distress within a few hours, whereas a subacute or non-acute lung insult of similar magnitude can result in deep hypoxaemia without signs of respiratory distress. Overall, degree of hypoxaemia reflects the extent of lung involvement. Hypoxaemia, measured directly as the PaO_2 on room air or assessed on the basis of the oxygen flow needed to achieve an peripheral capillary oxygen saturation (SpO_2) of 95% or the estimated or calculated ratio of partial pressure arterial oxygen and fraction of inspired oxygen (PaO_2/FiO_2 ratio), has been used for many years to risk-stratify patients and guide ICU admission decisions. Increased oxygen flow has been associated with the need for ICU admission,[10] need for IMV,[10,16] and hospital mortality.[17] Similarly, lower PaO_2/FiO_2 has been associated with mortality in patients with acute respiratory distress syndrome,[40] the need for non-invasive ventilation (NIV),[41] or failure of high-flow nasal oxygen therapy (HFNO).[42] Persistent tachypnoea has also been associated with failure of standard oxygen,[42] NIV,[41] or high-flow nasal cannula, requiring the implementation of another strategy (eg, intubation).[43] No study has evaluated the impact of hyperoxygenation in this setting.[44] Associated organ dysfunctions are best depicted by the Sequential Organ Failure Assessment (SOFA) score, which has consistently been identified as a determinant of mortality, with higher scores associated with increased mortality.[5,13,45] Delayed ICU admission has been associated with increased mortality in immunocompromised patients,[14] particularly in those with acute respiratory failure.[10,13,17] Benefits from earlier ICU admission might be the result of the careful clinical assessment, optimal oxygenation strategy, avoidance of potentially harmful investigations, and selection of the least invasive diagnostic tests in ICUs. The characteristics of the underlying immunosuppressive condition are not usually associated with hospital mortality following ICU admission,[46] although variations occur depending on ICU admission policies. A higher proportion of patients admitted to ICU with do-not-resuscitate or do-not-intubate status results in stronger associations between variables reflecting characteristics of disease status and mortality.[47,48] Performance status and comorbidities have been associated with increased mortality.[13,14,49,50] The effects of initial oxygenation and ventilation strategy on mortality are discussed later in this Review. Furthermore, as previously mentioned, several studies have assessed the association between the cause of acute respiratory failure and mortality. Mortality is lowest in patients with cardiac pulmonary oedema and highest in those with invasive fungal infections or no identified cause of acute respiratory failure.

Early assessment of pre-test probability of acute respiratory failure cause

One of the first and key steps in the early management of immunocompromised patients with acute respiratory

failure is to establish the probable cause of acute respiratory failure, at the bedside, based on clinical examination before undertaking tests. No standard combination therapy is suitable for all patients with acute respiratory failure; each patient must be considered individually. Clinicians should make every effort to identify the cause of acute respiratory failure in patients at high risk of intubation and mortality (eg, those with a higher SOFA score or more hypoxaemic). Bacterial infection is the main cause of acute respiratory failure, and up to 90% of patients receive antibacterial drugs soon after admission.[9] Cardiogenic pulmonary oedema must be considered in every patient. However, other diagnoses should be considered on a case-by-case basis. Thus, the basic diagnostic investigation is the same for all patients (panel 1). It includes tests for cardiogenic pulmonary oedema, sputum examination, and blood cultures to detect bacterial or fungal infections, induced sputum examination for *Pneumocystis*, viral multiplex PCR on nasopharyngeal aspirates or swabs, viral PCR on plasma or blood, an assessment of the likelihood that the underlying condition and its treatments will affect the lungs, and an analysis of the imaging data.

When performing the first clinical examination, the mnemonic DIRECT can be used to assess the cause of acute respiratory failure at the bedside.[51,52] D refers to respiratory symptom duration in days, I to the type of immunosuppression, R to the chest X-ray pattern, E to the clinician's experience of similar cases, C to the clinical findings, and T to high-resolution CT. In patients with myeloproliferative diseases such as acute myeloid leukaemia, myelodysplastic syndrome, or chronic myeloid leukaemia, most cases of acute respiratory failure that occur early after disease onset are related to leukaemic infiltrates (figure 1), although some patients might present with pneumonia or cardiogenic pulmonary oedema.[20,53,54] Acute respiratory failure of infectious origin is, however, more common at the earliest phase of lymphoproliferative disorders (figure 1), such as acute lymphoblastic leukaemia or lymphoma.[21,55] In patients with T-cell proliferations, opportunistic infections have been reported before cancer treatment initiation, exemplifying the role played by disease-related immunosuppression.[56] Later, during follow-up, infection is the main cause (figure 1), although treatment-related toxicities and disease relapse can also lead to acute respiratory failure. Clinicians can struggle with non-infectious causes whose diagnosis is believed to rely solely on biopsies, which are difficult to obtain in hypoxaemic patients with thrombocytopenia and haemostatic disorders, or on bronchoscopy and bronchoalveolar lavage, and have been reported as possibly deteriorating the respiratory status and increasing IMV needs. However, a multidisciplinary and collaborative approach allows earlier recognition of typical patterns of clinical and laboratory findings, for which no additional diagnostic procedures are needed (lung infiltration by the underlying condition, leukaemic infiltrates in patients with acute myeloid leukaemia, diffuse alveolar haemorrhage, cytarabine-related pulmonary toxicity, immunotherapy-related pneumonitis, etc). Patients with these patterns are often considered to have no known cause of acute respiratory failure until a multidisciplinary team makes the appropriate diagnosis. Similarly, conditions such as neutropenia or allogeneic haemopoietic stem cell transplantation are associated with both a high risk of respiratory events and specific acute respiratory failure causes such as exacerbation of previous lung injury during neutropenia recovery,[57] or non-infectious interstitial lung diseases following haemopoietic stem cell transplantation.[26,58]

Acute respiratory failure in the first few days after solid organ transplantation is probably related to either a

***Panel 1*: Basic diagnostic investigations to be applied to all immunocompromised patients presenting with acute respiratory failure**

Tests to diagnose or rule out cardiogenic pulmonary oedema
- Echocardiography
- Biomarkers such as natriuretic peptide or N-terminal pro b-type natriuretic peptide could be used in the emergency department to rule out cardiogenic pulmonary oedema for their good negative predictive value

Sputum examination to detect bacterial (and mycobacterial) infections

Blood cultures to detect bacterial or fungal infections

Urine antigen for *Legionella pneumophila* and *Streptococcus pneumoniae*
- Induced sputum examination for *Pneumocystis jirovecii* pneumonia. Both classic staining, immunofluorescence, and PCR can be useful on induced sputa

Induced sputum is performed after inhalation (during 15–20 min) of nebulised sterile hypertonic saline solution followed by coughing and expectoration of airway secretions. In patients with severe chronic obstructive pulmonary disease or asthma, pre-treatment with inhaled salbutamol and monitoring of lung function during the procedure are needed

Viral multiplex PCR on nasopharyngeal aspirates or nasal swabs to detect respiratory viruses (adenovirus, metapneumovirus, some types of coronavirus, parainfluenza virus types 1, 2, 3, and 4, influenza virus types A and B, respiratory syncytial virus A and B, rhinovirus A, B, and C, bocavirus, and enterovirus). This test also detects *L pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*

Viral PCR on plasma or blood to detect herpesviruses (including cytomegalovirus).

Other PCR tests: although the results of most PCR methods lack specificity for the detection of *Aspergillus* sp, PCR allows early detection of other fungi (eg, *Mucorales*) or parasites (eg, *Toxoplasma gondii*)

Biomarkers
- Procalcitonin has limited predicitive value in immunocompromised patients
- Serum *Aspergillus* galactomannan is useful for the detection of both invasive aspergillosis and histoplasmosis
- Serum 1,3 β-D-glucan for all fungal infections except mucormycosis

Echography-guided pleurocentesis (check platelet count and haemostasis)

Biopsy or puncture of extra-pulmonary involvement (skin, joints, peripheral lymph nodes, sternal puncture, buccal smear, etc)

Imaging data, including chest X-ray, lung and pleural echography, and high-resolution CT scan (without first-line contrast media unless there is a clinical suspicion of pulmonary vascular disease)

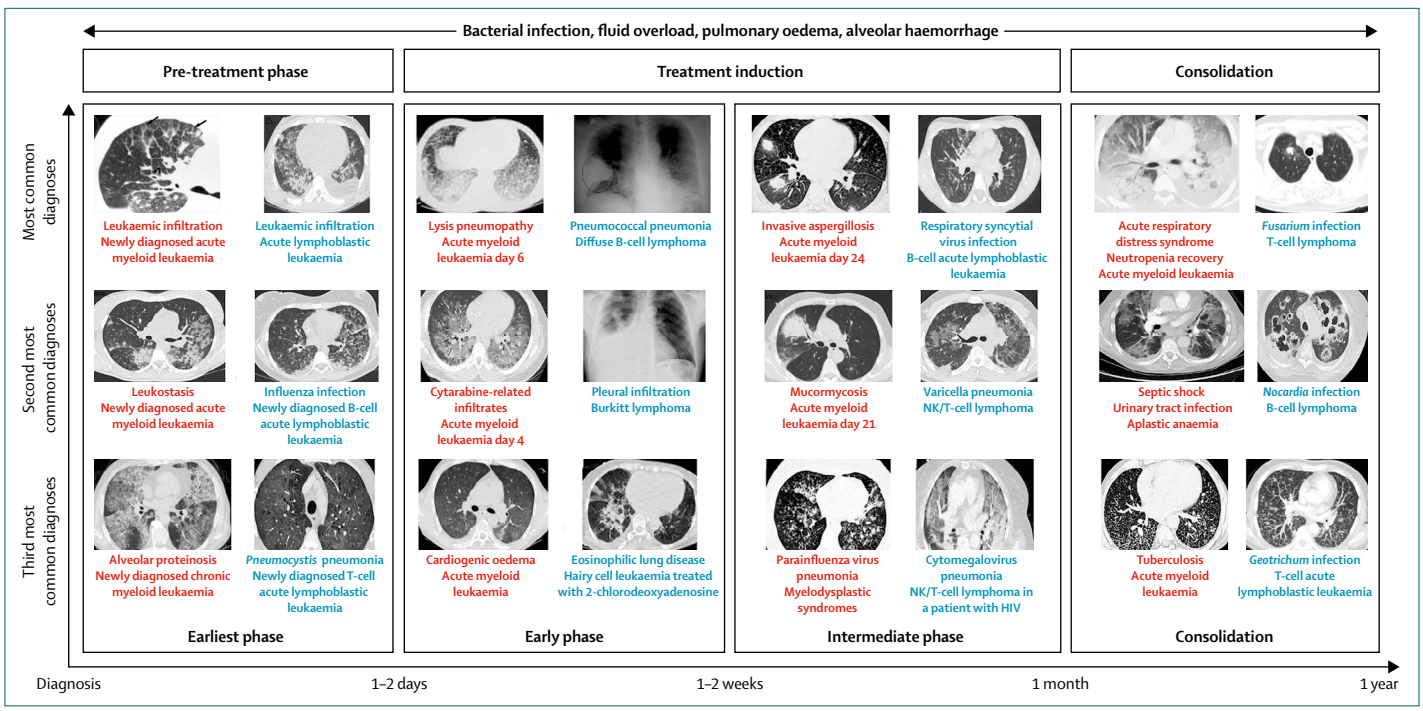

Figure 1: **Causes of acute respiratory failure by time since diagnosis of haematological malignancy**
CT scans with red text refer to myeloid malignancies and those with blue text to lymphoid malignancies. The x-axis indicates time since diagnosis of the malignancy. For each scenario, the three most common diagnoses (in decreasing order) are reported at each timepoint and for each condition.

surgical complication or to decompensation of a chronic respiratory or cardiac comorbid condition.[34,36,59,60] Invasive candidiasis might occur quite early after transplantation.[37] However, most opportunistic infections are reported more than 3 months after transplantation and depend heavily on adherence to prophylactic regimens by the patient.[35,37,61–66] Of note, with the use of intensive immunosuppression in patients experiencing acute humoral or interstitial rejection[67] and with the use of immunosuppressant drug combinations to ensure graft tolerance, clinicians must carefully assess the individual risk for each possible cause and perform a complete diagnostic investigation.[68]

In each individual case, the type of immune deficiency must be assessed to allow appropriate adjustment of the initial anti-infectious treatment (figure 2) and to avoid treatment delays. Imaging studies, particularly high-resolution CT, are another important bedside tool for determining the cause of acute respiratory failure.[69] This Review does not detail the radiological findings in immunocompromised patients with acute respiratory failure. Patterns of lung involvement are an important piece of the puzzle but are not predictive of a specific cause.[69] However, a combination of positive and negative high-resolution CT findings suggest specific causes of lung infiltrates.[70] Different components of the DIRECT mnemonic contribute to determining the pre-test clinical probability for each individual diagnosis (figure 3). A given clinical situation can be related to different causes of acute respiratory failure, because contextual elements and clinical findings vary across patients. However, the administration of antifungal drugs or anti-*Pneumocystis* therapy should not be delayed if the pre-test probability of the disease is substantial.

Avoiding situations in which the acute respiratory failure cause remains undetermined

Non-invasive diagnostic tests offer an alternative to bronchoscopy and bronchoalveolar lavage, which carry a risk of respiratory deterioration requiring IMV.[51] However, bronchoalveolar lavage might be required when non-invasive respiratory samples are either not feasible or of poor quality. Performing bronchoalveolar lavage with the support of NIV or high-flow nasal cannula can help patients tolerate the procedure. Also, first-line bronchoalveolar lavage must be considered in situations in which patients have a possible diagnosis of diffuse alveolar haemorrhage, *Pneumocystis jirovecii* pneumonia, or drug-related pulmonary toxicity, or when lung infiltrates might be involved in the underlying disease (vasculitis, lymphoma, etc). The diagnostic yield of non-invasive tests has, however, increased since the introduction of more sensitive diagnostic tests, such as PCR. However, these tests are more sensitive than specific, and the clinical relevance of a positive PCR is sometimes uncertain. In patients with cancer, the standard diagnostic investigation done immediately at ICU admission includes a physical examination, a pre-test probability assessment using DIRECT, sputum (if possible) and induced sputum

Immunological deficiency	Neutrophils	Monocytes/dendritic cells/ macrophages	B lymphocytes	T lymphocytes	Humoral (antibody) immunity
Diseases	Acute leukaemia; myelodysplastic syndrome; aplastic anaemia; chemotherapy and drug-related neutropenia	Hairy cell leukaemia; aplastic anaemia; allogeneic bone marrow transplant; malignant histiocytosis; acute myeloid leukaemia; chronic myeloid leukaemia; solid tumours; haemophagocytic lymphohistocytosis	Multiple myeloma; B-cell lymphoma; chronic lymphocytic leukaemia	T-cell leukaemia; T-cell lymphoma; Hodgkin disease	Multiple myeloma; chronic lymphoid leukaemia
Treatments	Chemotherapy-induced neutropenia	Steroids; basiliximab; antithymocyte globulin; tacrolimus; mycophenolate mofetil; belatacept	Chemotherapy; steroids; asplenia; rituximab	Steroids; fludarabine; cyclophosphamide; methotrexate; azathioprine; alemtuzumab; mycophenolate mofetil; cyclosporine; mTOR inhibitors (sirolimus); tacrolimus; 2-chlorodeoxyadenosine; daratumumab	Ibrutinib; rituximab; daratumumab; cyclophosphamide
Most frequently encountered infections	• Gram-negative bacteria • Gram-positive bacteria • *Candida* • *Aspergillus* • *Nocardia*	• Non-tuberculous mycobacteria • *Salmonella, Listeria, Legionella, Histoplasma, Brucella* • Herpes simplex virus, varicella zoster virus, parainfluenza virus, respiratory syncytial virus • *Candida parapsilosis* • *Staphylococcus aureus, Enterococcus faecalis, Pseudomonas aeruginosa*	• Encapsulated bacteria (*Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae*) • *Giardia lamblia, Campylobacter, Salmonella* • *Mycoplasma* • Enterovirus • Recurrent infections	• Herpes simplex virus, cytomegalovirus, Epstein-Barr virus • *Pneumocystis, Aspergillus, Cryptococcus* • Mycobacterial infection • Skin candidiasis • Diarrhoea (rotaviruses, adenoviruses, *Cryptosporidium*, microsporidia, etc) • John Cunningham virus	• Encapsulated bacteria (*S pneumoniae, S pyogenes, H influenzae*) • *Mycoplasma, Ureaplasma urealyticum* • Other infections related to associated T-cell defects

Figure 2: **Risk for specific pathogens according to the type of haematological malignancy or treatment**
This figure illustrates the most frequently encountered types of infection according to the main disease-related or treatment-related immunological deficiency. It focuses mainly on secondary immunosuppression in adults, as data for primary immune deficiencies are scarce.

Patient presentation	Diagnostic options after application of DIRECT
Acute respiratory failure, severe hypoxaemia and diffuse alveolar-interstitial infiltrates within 7 days of a new haematology diagnosis	• If untreated hairy cell leukaemia, consider intra-cellular pathogens (*Legionella*, influenza, filamentous fungi) as possible source of infection • If hyperleukocytic acute myeloid leukaemia (200 000 cells per L) treated for 3 days, consider acute lysis pneumopathy • If untreated acute myeloid leukaemia, consider leukaemic infiltrates such as infiltration or leukostasis
Acute respiratory failure 14 months after kidney transplantation. No extra-pulmonary symptoms. Fever. Diffuse ground-glass opacities	• If no prophylaxis, very high probability of *Pneumocystis jirovecii* pneumonia • If patient receiving sirolimus, brochoalveolar lavage rules out infection and discloses hypercellularity with lymphocytosis. Consider drug-related pulmonary toxicity • If the patient is compliant with *Pneumocystis* prophylaxis, but did not receive the flu vaccine, consider severe influenza if during flu season
Acute onset of respiratory distress with fever and hypotension in an immunocompromised patient. Focal or diffuse alveolar consolidation	• If patient has myeloma and hypo-gammaglobulinaemia, give priority to bacterial infection • If γδ-T-cell lymphoma with diagnostic splenectomy 2 years ago, give priority to bacterial infection • If lung cancer patient with neutropenia, give priority to bacterial infection
Acute respiratory failure in a patient with ischaemic cardiopathy treated with PD-1 inhibitors for metastatic melanoma for 4 months. Bilateral ground-glass opacities on CT	• Rule out cardiogenic pulmonary oedema, do echocardiography and diuretic test • If patient taking aspirin and anticoagulants, exclude overdose and diffuse alveolar haemorrhage. Perform BAL • Perform bronchoscopy and BAL to document T-lymphocytic alveolitis. Start steroids
Severe respiratory distress in a patient with long-term steroids and infliximab for severe Crohn's disease. CT scan discloses ill-defined consolidations and cavitations in both lungs	• Tuberculosis must absolutely be confirmed and treated. Diagnostic investigation should include the search for extra-pulmonary tuberculosis • Search for *Nocardia* and include trimethoprim-sulfamethoxazole in the initial treatment • Although rare, disseminated aspergillosis has been reported in such patients

Figure 3: **Five clinical vignettes for which the application of the DIRECT mnemonic leads to different diagnostic probabilities**
Diagnoses such as bacterial infection, pulmonary oedema, and alveolar haemorrhage need to ruled out or treated in every case. BAL=bronchoalveolar lavage.

examinations, nasopharyngeal aspirates or swabs, blood cultures, serum and urine antigen assays, imaging studies, and biomarker assays. These non-invasive tests perform as well as bronchoscopy and bronchoalveolar lavage.[9,71] In solid organ transplant recipients, however, bronchoalveolar lavage has a higher diagnostic yield,[36] although the risk–benefit ratio has not been assessed in this population. Moreover, with the advent of omics to assist in the diagnosis of infections,[72] as well as sophisticated immunology and molecular biology methods and advances in imaging techniques to establish the diagnosis of non-infectious conditions, a reappraisal of the diagnostic yield of non-invasive tests in immunocompromised patients is warranted.

Nevertheless, despite an optimal early diagnostic investigation, the cause remains undetermined in 10–15%

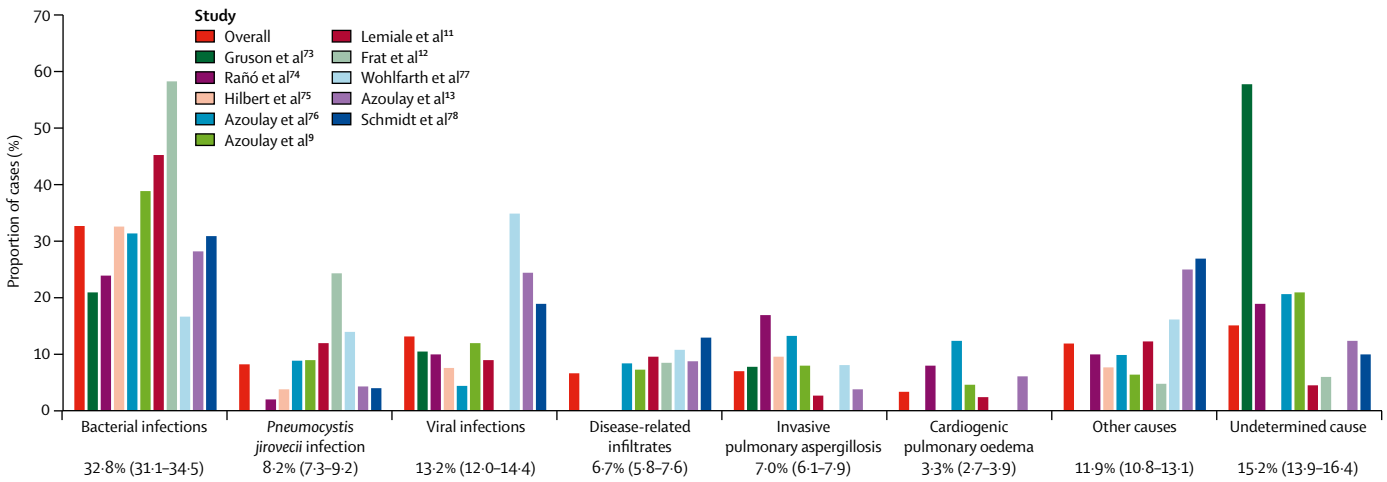

Figure 4: **Causes of pulmonary infiltrates in immunocompromised patients with acute respiratory failure**
Mean percentage is reported in the first column in red for each cause, with 95% confidence intervals reported underneath. The study by Gruson and colleagues[73] included only bone marrow transplant recipients and the studies by Wohlfarth and colleagues[77] and Schmidt and colleagues[78] included only patients with severe acute respiratory distress syndrome treated with extra-corporeal membrane oxygenation.

	N	Cause of immunosuppression	Intubated (%)				Mortality (%)				Underwent bronchoalveolar lavage (%)	Undetermined cause (%)
			All	O_2	NIV	HFNO	All	O_2	NIV	HFNO		
Antonelli et al[79]*	40	Solid organ transplants	33·7	70	20	..	35	50	20	..	27·5	0
Hilbert et al[75]*	52	All types	61·5	66	46·1	..	53·8	80·8	50	..	32·7	..
Azoulay et al[9]	203	Oncology and haematology patients	85·0	..	57	..	56	9	48·1	..	72	20·7
Lemiale et al[16]	380	Haematology patients	24·7	20	32	..	32	26	44	..	..	24·7
Lemiale et al[80]*	374	All types	41·4	45	38·2	..	25·7	34·4	30·9	..	38	4·5
Mokart et al[81]	178	Oncology and haematology patients	48·0	50	45·9	75	46	55	56	25	..	25
Frat et al[12]†‡	82	All types	46·3	43	65	31	29·3	27	46	15		4·9
Coudroy et al[82]	115	All types	44·0	..	55	35	30	..	40	20	..	..
Lemiale et al[11]†	353	All types	40·2	38	..	45	22·6	20·7	..	25·9	38·2	4·5
Azoulay et al[13]	1611	All types	40·9	41	41	41	36·5	32·7	36·9	38·4	60	12·9
Tu et al[83]	38	Solid organ transplants	34·2	..	50	20	22·7	..	22·2	5	..	..
Total	3426	..	45·0	47	45	41	35	37	40	21	45	12

Only studies published in English from Jan 1, 1998, to April 30, 2018, were taken into account. Studies that comprised only postoperative patients and studies on palliative NIV were not included. NIV=non-invasive ventilation. HFNO=high-flow nasal oxygen therapy. *Randomised controlled trials. †Post-hoc analysis of randomised controlled trials. ‡Indicates day-90 mortality; all other studies reported hospital mortality.

Table 2: **Studies reporting intubation and mortality in immunocompromised patients receiving standard oxygen, non-invasive ventilation, or high-flow nasal oxygen therapy**

of patients with acute respiratory failure (figure 4; table 2). Failure to identify the cause of acute respiratory failure was independently associated with mortality in several studies.[5,13,76,84] In some patients, the cause of acute respiratory failure is identified late, and the impact of a late diagnoses and correspondingly late treatment has not been assessed. The association between absence of a documented cause and mortality raises several questions (table 3). The association might be related in part to patients who die within a few hours with intractable hypoxaemia and multiple organ dysfunction before diagnostic tests can be performed. When providing expert opinion, careful attention should be directed to the clinical situation, underlying disease, comorbid conditions, and ongoing long-term treatments, as well as to the response to treatments given for the current acute respiratory failure episode. Figure 5 shows first-line diagnostic strategy according to clinical and radiographic presentation. The expert will also have the (sometimes difficult) task of determining which tests are actually performed, obtaining their exact results (as opposed to a classification as positive or negative), and potentially obtaining results that might not yet have been made available to the bedside physicians.

We are aware that lung biopsy is often not feasible, due to haemodynamic instability, deep hypoxaemia, or

	Unidentified, unsuspected, and untreated condition	Unidentified, suspected, but suboptimally treated condition	Undocumented coinfection in which one pathogen remains untreated	Infectious and non-infectious condition, of which one is unidentified or untreated	Identified aetiology mistakenly considered as irrelevant finding
Actual underlying cause	Pneumonitis while taking checkpoint inhibitors	Lung infiltration by lymphoma	Tuberculosis in a kidney transplant recipient	*Pneumocystis* pneumonia in a patient with lung cancer	Invasive aspergillosis
Incorrectly presumed cause	Positive nasal swab (rhinovirus) in a patient treated for melanoma; no clinical sign of viral infection	Patient treated for bacterial infection based on high plasma C-reactive protein and procalcitonin	The only positive result is a positive PCR for cytomegalovirus (2 logs)	Patient receiving steroids for radiation pneumonitis without prophylaxis	Patient believed to have an undetermined acute respiratory failure cause
Procedure that should have been performed	CT scan suggested hypersensitivity pneumonia; bronchoalveolar lavage cell analysis was not performed	CT-guided lung biopsy (the diagnosis of lymphoma was made based on node and bone marrow biopsies)	CT findings suggested tuberculosis with 3 apical cavitated nodules in the right upper lobe	As hypoxaemia worsened and ground-glass opacities extended, bronchoalveolar lavage should have been considered	Galactomannan at 0·50 and sputum positive for *Aspergillus fumigatus*, both considered irrelevant
Missed treatment	Steroids; drug withdrawal	Chemotherapy	Antituberculosis drugs	Trimethoprim and sulfamethoxazole	Antifungal agents

Table 3: **Hypothetical examples of causes of increased mortality when the cause of acute respiratory failure is not identified**

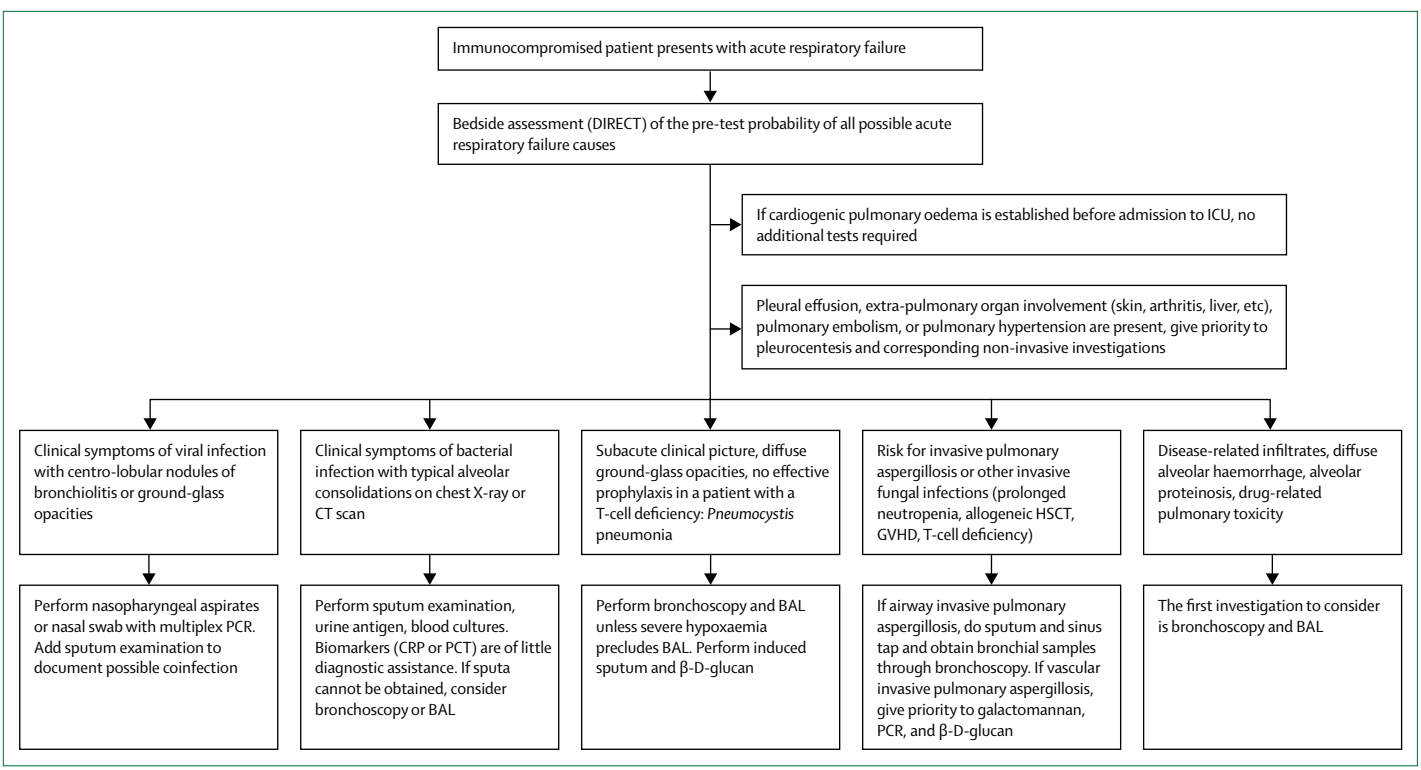

Figure 5: **First-line diagnostic strategy according to clinical and radiographic presentation**
ICU=intensive care unit. HSCT=haemopoietic stem cell therapy. GVHD=graft versus host disease. CRP=C-reactive protein. PCT=procalcitonin. BAL=bronchoalveolar lavage.

thrombocytopenia or other severe haemostatic abnormalities. Data on surgical lung biopsies in this setting are, therefore, scarce (table 4). Nevertheless, valuable information can be gleaned from studies reporting surgical lung biopsy or autopsy data in immunocompromised patients with acute respiratory failure of unknown cause. Overall, lung biopsy had a diagnostic yield above 60%, with complications in 10% of patients, despite careful patient selection for the procedure. Lung biopsy had a lower diagnostic yield in patients receiving IMV. Invasive fungal infections and malignant or potentially steroid-sensitive lung infiltrates were the most common causes of acute respiratory failure (table 4). The diagnostic yield of surgical lung biopsy for unexplained pulmonary infiltrates was assessed in a retrospective study of 62 haematology patients.[95] The exact diagnosis was established in 67% of patients, with invasive aspergillosis and malignancy being the main causes. The biopsy result prompted a treatment change in 40% of patients, and complications occurred in 11% of patients. The diagnostic yield was lower in patients

	Lung biopsy		Invasive fungal infections	Mycobacterial infections	Need for steroids or chemotherapy	Comments
	Surgical	Post-mortem				
White et al (2000)[85]	63	0	8 (13%)	6 (9·5%)	47 (75%)	Complication rate 13%; lower diagnostic yield in neutropenic patients and patients on IMV; higher diagnostic yield if focal infiltrates
Gossot et al (2001)[86]	21*	0	0	0	8 of 29 (26%)	0 of 9 biopsies of residual mass in patients with lymphoma
Dai et al (2001)[87]	7	0	1 (14%)	0	3 (43%)	..
Kim et al (2002)[88]	31	0	17 (55%)	1	12 (39%)	All patients underwent lung biopsy for suspected invasive pulmonary aspergillosis
Sharma et al (2005)[89]	71	0	12 (17%)	14 (20%)	19 (27%)	All were adult bone marrow transplant recipients (39 allogeneic)
Zihlif et al (2005)[90]	62	0	14 (23%)	0	31 (50%)	Complication rate 11%; lower diagnostic yield in patients on IMV
Gupta et al (2010)[91]	213	0	32 (15%)	13 (6%)	85 (40%)	Large or cavitary lesions or lung masses were more likely to yield a specific diagnosis
Sharma et al (2013)[92]	34†	0	15 (44%)	NA	NA	..
Gay et al (2013)[93]	11	10	0	5 (24%)	5 (24%)	Only haematology patients
Uhlving et al (2015)[94]	44		13 (29·5%)	NA	4 (9%)	Allogeneic bone marrow transplant recipients with biopsy-verified bronchiolitis obliterans

IMV=invasive mechanical ventilation. NA=not applicable. *8 CT-guided biopsies. †All CT-guided.

Table 4: **Studies reporting the results of surgical or post-mortem lung biopsies**

with acute respiratory failure who were receiving IMV at the time of biopsy than in non-intubated patients. In a cohort of 63 haematology patients, the diagnostic yield of lung biopsy was 62% and the therapeutic yield 57%.[73] The diagnostic yield was lower in patients on IMV and in those with neutropenia, but was higher in patients with focal infiltrates. Invasive aspergillosis was also a common biopsy finding in this study. Complications occurred in 13% of patients.[73] The 15% prevalence of invasive aspergillosis is in line with data on acute respiratory distress syndrome in patients with cancer[40] and with autopsy findings in patients with acute respiratory distress syndrome.[90] In 21 haematology patients, including 10 in whom the lung biopsies were obtained post-mortem, inflammatory and malignant infiltrates were the most common diagnoses.[85] A retrospective autopsy study of 7 haemopoietic stem cell transplant recipients showed that fungal infections, potentially steroid-responsive lung involvement, and malignant infiltrates were under-diagnosed.[96] Complications associated with lung biopsies occurred in about 10% of patients who were highly selected based on platelet count, performance status, and goals of care. Given the lower diagnostic yield of lung biopsy in ICU patients, the risk–benefit ratio is not favourable; therefore, lung biopsy is rarely performed in critically ill immunocompromised patients with acute respiratory failure and lung infiltrates of unknown cause. However, minimally invasive CT-guided lung biopsies and trans-bronchial cryobiopsies are increasingly done.[88,89,92,93,97,98] Studies to assess the timing of these minimally invasive diagnostic techniques in this setting are warranted. The diagnostic yield should be better defined as the identification of a new diagnosis that was not detected by any other less invasive technique and that resulted in a change in treatment. Moreover, the risk–benefit ratio needs to be re-assessed. If these minimally invasive biopsy techniques are evaluated in a randomised controlled trial, control patients should receive empirical treatment for the most common lung biopsy diagnoses, namely, invasive fungal infection or steroid-responsive lung disease (panel 2).

Oxygenation and ventilation strategies

The initial oxygenation and ventilation strategy aims to restore safe oxygenation, reduce the respiratory rate, alleviate the dyspnoea and respiratory distress, and improve patient comfort.[99] Over the past two decades, studies have consistently shown higher mortality in immunocompromised patients who required IMV. Priority has, therefore, been given to avoidance of IMV by use of non-invasive oxygenation or ventilation devices (figure 6). However, failure of NIV[13,41,100] or HFNO[13] was associated with higher mortality,[13] and two older studies even suggested that early IMV was associated with improved survival.[101,102] Furthermore, because respiratory disease severity or associated organ dysfunctions are usually worse in intubated patients, determining whether the excess mortality in patients on IMV is due to the IMV itself or to the greater severity of the acute illness is difficult. In other words, a focus on avoiding intubation might not be effective, because the need for IMV might identify a group of patients with high disease severity.

Overall, five initial oxygenation methods are available for patients with hypoxaemic acute respiratory failure (figure 6). Guidelines from the European Respiratory Society and American Thoracic Society advocate the use of NIV.[101] This recommendation is based mainly on a 2001 single-centre trial in 52 patients,[75] in which mortality was 81% in the group assigned to standard oxygen, the highest ever reported in this setting (table 2). Another seminal trial in solid organ transplant recipients[103] also

Panel 2: **Unresolved issues and future directions in acute respiratory failure in patients with solid or haematological malignancies, solid organ transplant recipients, and patients taking immunosuppressive drugs**

Update data on the prevalence of pulmonary involvement in immunocompromised patients
- Develop and implement multinational patient registries
- Analyse the severe forms of drug-related toxicity from targeted therapy, immunotherapy, and other new drugs
- Collect longer-term follow-up data to assess the true morbidity of acute respiratory failure

Define the best standard of care for immunocompromised patients with acute respiratory failure
- Monitor times to intensive care unit (ICU) admission, to treatment implementation, and to diagnosis
- Manage respiratory failure and associated organ dysfunctions according to the latest guidelines
- Find a balance between aggressive and non-beneficial care, and implement full-code intensive care in patients with a substantial hope of survival

Educate all stakeholders to avoid delays in ICU management
- Provide information on outcomes according to oxygen needs
- Explain how delayed ICU admission leads to increased mortality
- Encourage clinicians to assess the pre-test probability of each acute respiratory failure cause and start the corresponding treatments early

Develop a minimal early diagnostic investigation that applies to all patients, combined with targeted diagnostic strategies for patients at risk for specific diseases
- Search for bacterial and fungal infections (sputum examination, blood cultures), viral infection (multiplex PCR on nasopharyngeal aspirates or swabs), and cardiogenic pulmonary oedema; evaluate the extent to which the underlying condition and its treatments may affect the lungs; obtain imaging data in all patients
- Apply specific clinical algorithms and perform targeted non-invasive or minimally invasive diagnostic tests in patients at risk for specific diseases (*Pneumocystis* pneumonia, invasive aspergillosis, mycobacterial disease, etc)
- Identify situations in which more invasive tests may be required

Evaluate omics technologies on non-invasive samples
- Apply genomics, metagenomics, proteomics, metabolomics, and transcriptomics on samples that can be collected easily from patients with tachypnoea and hypoxaemia
- Use clinical algorithms and evaluate their ability to confirm the diagnosis in high-risk patients or to rule out the diagnosis in low-risk patients
- Assess whether the use of these technologies can result in improved clinical outcomes

Provide convincing data regarding the superiority of non-invasive ventilation or high-flow nasal oxygen therapy
- When standard oxygen alone alleviates respiratory distress and maintains SpO_2 ≥95%; or when standard oxygen fails to achieve these clinical goals
- Clarify whether patients who are intubated after failed non-invasive ventilation or high-flow nasal oxygen therapy would have had better outcomes if they had received earlier intubation and lung-protective ventilation
- Define consensual intubation criteria, as the need for invasive mechanical ventilation is an important outcome measure

Develop a multinational network to improve the management of immunocompromised patients with acute respiratory failure
- To define a non-invasive diagnostic and therapeutic strategy that is readily feasible at many locations and to demonstrate, using cohort studies and randomised controlled trials, how this strategy translates into improved outcomes
- To validate clinical algorithms that help identify patients at low *vs* high risk for a given disease
- To develop and implement multicentre basic and translational research
- To promote education, update guidelines, and establish patient-centred outcome measures

documented NIV benefits, but these results were obtained within 3 weeks following surgery. The European Respiratory Society and American Thoracic Society guidelines have been challenged by recent findings. A multicentre, randomised controlled trial in 374 patients in 28 centres in France and Belgium compared NIV with oxygen.[11] This trial showed neither benefits nor harms from NIV, in sharp contrast with a post-hoc analysis of the trial by Frat and colleagues,[12] which compared outcomes in 82 immunocompromised patients treated with HFNO, NIV, or standard oxygen. In this trial, the IMV and mortality rates were higher in the NIV group compared with the HFNO and standard oxygen groups. These results are consistent with studies reporting an increased risk of failure and mortality in patients receiving NIV for severe acute respiratory distress syndrome.[41,75,79] Thus, these data raise concerns about the use of NIV in immunocompromised patients with hypoxaemic acute respiratory failure.

When first introduced, HFNO seemed a promising alternative to NIV. HFNO is easy to use and delivers humidified warmed oxygen, thereby allowing high flows by improving tolerability and comfort.[104] HFNO improves oxygenation, lowers the respiratory rate, inspiratory effort,

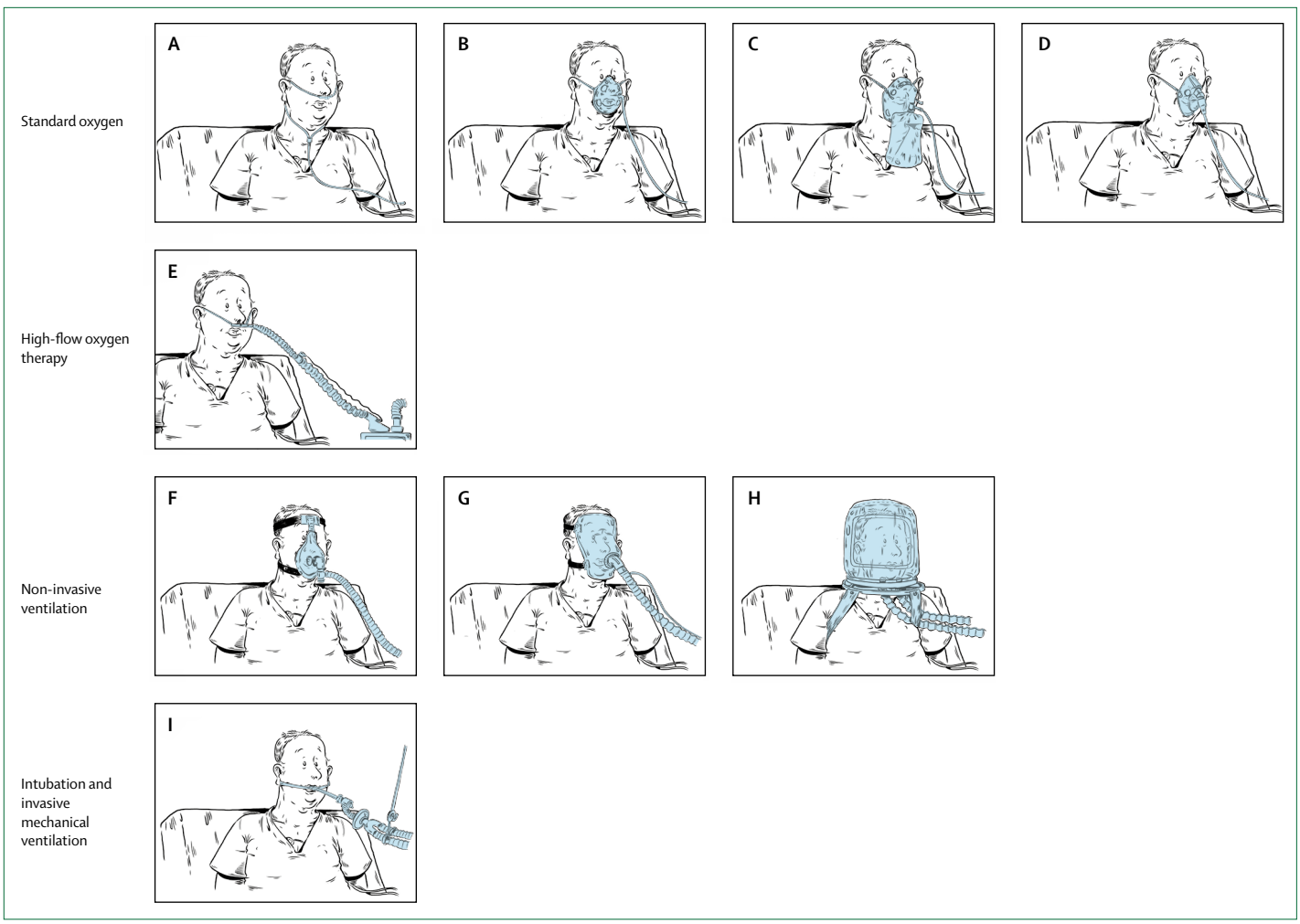

Figure 6: **Nine oxygenation and ventilation methods**
Standard oxygen can be administered through a wide array of devices. Low-flow oxygen systems comprise a nasal cannula (or nasal catheters; A) providing supplemental oxygen at flows below the total minute ventilation, leading to oxygen dilution with ambient air and lowering the inspired oxygen concentration. A standard nasal cannula delivers an inspiratory FiO_2 of 0·24–0·44 at supply flows 1–8 L/min, depending on respiratory rate and tidal volume. A humidification device is recommended for flows >4 L/min. Reservoir masks (B) can deliver FiO_2 values of 0·40–0·60 at 5–10 L/min. The reservoir system (~100–300 cm^3) stores oxygen. A flow rate >5 L/min must be set to ensure the washout of exhaled gas and avoid CO_2 retention. The non-rebreathing facemask (C) may deliver up to 0·90 FiO_2 at flow settings >10 L/min. It should be used only for short periods, as humidification is difficult and there is also a risk of CO_2 retention if the mask's reservoir bag is allowed to collapse on inspiration. Lastly, the Venturi system (D) mixes oxygen with room air (humidification is not necessary) and provides an accurate and constant FiO_2 despite variations in respiratory rate and tidal volume. It is employed when concern arises about CO_2 retention or when the respiratory drive is inconsistent. High-flow oxygen therapy through nasal prongs or cannulas (high-flow nasal oxygen therapy; E) supplies an exact FiO_2 (up to 1) at a flow equal to or greater than the patient's inspiratory flow demand. Nasal oxygen is administered at a flow rate of up to 60 L/min. It is warmed to body temperature and saturated to full humidity by molecular humidification. Non-invasive positive-pressure ventilation provides ventilator support without an endotracheal tube, using an oronasal (F) or total face (G) mask or a helmet (H). The main non-invasive ventilation mode used in hypoxaemic acute respiratory failure is pressure support; continuous positive airway pressure and bi-level positive airway pressure are used less often. Finally, invasive mechanical ventilation (I) uses a tracheal tube inserted into the trachea under general anaesthesia and a neuromuscular-blocking drug. The tube is then secured to the face or neck and connected to a ventilator. In patients with hypoxaemic acute respiratory failure, intubation and invasive mechanical ventilation are used after failure of standard oxygen and, in some cases, of the aforementioned non-invasive options. FiO_2= fraction of inspired oxygen.

and work of breathing, and reduces minute ventilation at a constant $PaCO_2$.[105] HFNO also increases end-expiratory lung volume and dynamic lung compliance.[105] These physiological effects are even more pronounced when increasing flow rates are delivered.[106] However, in a randomised controlled trial in 310 unselected patients with hypoxaemic acute respiratory failure and a PaO_2/FiO_2 ratio ≤300 mm Hg,[107] the number of patients requiring intubation was not significantly reduced with HFNO compared with NIV or standard oxygen. However, the number of ventilator-free days on day 28 was significantly higher with HFNO, and the hazard ratio for day-90 mortality was lower with HFNO.

Five studies evaluated the feasibility and safety of HFNO in immunocompromised patients with acute respiratory failure. In a retrospective single-centre study of 45 patients with haematological malignancies (half were bone marrow transplant recipients,[108] half had recently received systemic chemotherapy, and 42% were neutropenic), HFNO allowed recovery without intubation

in one-third of the patients. The hospital mortality rate was 13·3% when HFNO was successful and 86·7% when HFNO failed. The HFNO failure rate was only 15% in a single-centre study of 183 patients with solid tumours,[109] but was 80% in a study of 56 haematology patients.[110] A phase 2 trial in 30 patients with advanced cancer and persistent dyspnoea compared HFNO with biphasic positive airway pressure.[111] Oxygen saturation improved only with HFNO, whereas both treatments provided similar improvements in dyspnoea and respiratory rate. In 37 lung transplant recipients with acute respiratory failure, HFNO proved feasible and safe and decreased the absolute risk of intubation by 29·8%, with a number-needed-to-treat to avoid one intubation of 3.[34]

Although no results from trials specifically assessing HFNO in immunocompromised patients with hypoxaemic acute respiratory failure are available, six studies compared HFNO with other oxygenation or ventilation strategies in this setting (table 2). In a retrospective cohort of 178 patients with cancer and acute respiratory failure,[112] 76 (43%) patients received NIV plus HFNO, 74 (42%) NIV plus standard oxygen, 20 (11%) HFNO alone, and 8 (4%) standard oxygen alone. The combination of NIV and HFNO was associated with lower mortality rates (37% *vs* 52% in the other patients, p=0·04) and was independently associated with higher day-28 survival. In a post-hoc analysis of data from the iNVIctus randomised controlled trial of early NIV in immunocompromised patients with acute respiratory failure,[11] neither the intubation rate nor day-28 mortality differed significantly between the HFNO arm and the standard oxygen arm.[113] In the post-hoc analysis of the trial by Frat and colleagues,[12] outcomes were compared across standard oxygen, NIV, and HFNO. Although NIV was associated with increased need for intubation and higher mortality, neither parameter differed significantly between the 30 patients assigned to standard oxygen and the 26 patients assigned to HFNO. In a retrospective study of 115 immunocompromised patients with acute respiratory failure,[81] the proportion of patients that required intubation (55% *vs* 35%) and mortality (40% *vs* 20%) were higher with NIV than with HFNO. In the Efraim multicentre, multinational, prospective cohort study of 1611 immunocompromised patients,[13] 915 patients were not intubated on ICU admission and received standard oxygen, HFNO, NIV, or NIV plus HFNO. Hospital mortality was not affected by the initial oxygenation or ventilation management. There was a non-significant trend towards reduced intubation in patients given HFNO. In a retrospective study of 38 kidney recipients,[80] the number of ventilator-free days on day 28 was significantly higher in the HFNO group than in the NIV group. The results of two trials of HFNO focusing specifically on immunocompromised adults with acute respiratory failure (NCT02739451 and NCT02978300) are expected to be available in a few months.[82] HFNO has not yet been properly evaluated regarding its ability to assist diagnostic procedures such as bronchoscopy with bronchoalveolar lavage and bronchial or transbronchial biopsies.

Changes in the initial oxygenation and NIV strategy are unlikely to translate into improved survival. The response of patients to standard oxygen, HFNO, or NIV should be carefully assessed. If the initial strategy of standard oxygen, NIV, or HFNO lowers the respiratory rate and minute ventilation then it should be continued and continuously revaluated. If the tachypnoea and high respiratory drive persist, the risk of intubation is very high and it is reasonable to evaluate the potential benefits of avoiding delayed intubation and adding self-inflicted lung injury to the initial pulmonary insult.[83] Early intubation has been associated with improved survival in haematology patients.[101,102] Studies of early intubation in patients with a persistently high respiratory drive despite the initial oxygenation strategy are warranted.

Conclusion

In summary, acute respiratory failure is a common and often fatal event in immunocompromised patients that raises major diagnostic and therapeutic challenges. In the near future, with the use of more intensive therapeutic regimens designed to cure cancer, induce transplant tolerance, or control autoimmune and inflammatory diseases in ever older and frailer patients, the incidence of acute respiratory failure against a background of immunodeficiency can be expected to increase. Moreover, the expanding use of targeted therapies and immunotherapies will lead to a growing burden of toxicity and infection during the increasing life spans of these populations. Our knowledge of the effects of acute respiratory failure needs to be improved by longer-term follow-up studies. Multinational registries must be developed to analyse the effect of new drugs and update clinicians on future trends in the incidence of acute respiratory failure and in the use of intensive care for patients with acute respiratory failure. Targets for improving survival, such as early ICU admission and the early identification or treatment of the cause of acute respiratory failure, require evaluation in large randomised controlled trials. Patients with substantial life expectancy and who agree to undergo ICU management should be offered unrestricted access to diagnostic and therapeutic strategies. The greatest challenges are the identification of patients at high risk for specific diagnoses, earlier treatment of acute respiratory failure causes, and selection of the least invasive diagnostic tests. The non-invasive approach is promising but still needs to be refined and updated. Combining clinical algorithms and sophisticated tests, such as genomics, metagenomics, proteomics, or transcriptomics, on non-invasive samples to document or rule out infections will be a major advance only if the results include survival benefits, shorter ICU and hospital stay lengths, reduced costs, and improved patient-reported outcomes. Given that the initial oxygenation and NIV strategy is unlikely to be associated with survival, assessing the patient's

Search strategy and selection criteria

We searched Medline and PubMed for reviews and original articles on pulmonary involvement in immunocompromised adults published in English between Jan 1, 1998 and April 30, 2018, using the terms ("respiration disorders"[Mesh]) AND "immunocompromised host"[Mesh]), ("pneumonia"[Mesh]) AND ("immunocompromised host"[Mesh]), and ("respiratory insufficiency"[Mesh]) AND "immunocompromised host"[Mesh]). We also searched using individual terms such as "leukaemia", "lymphoma", "solid tumours", "cancer", "haematology", "malignancies", "transplantation", "immunosuppressant drugs", "systemic vasculitis", "connective tissue diseases", and "primary immunodeficiency". Although most of the studies we retrieved were published within the specified period, we did not exclude earlier reports. Furthermore, we searched the reference lists of the articles identified by this search strategy and our own personal files. We used original reports when available. Patients with HIV infection are not in the scope of this Review.

response to standard oxygen, HFNO, or NIV within 1–4 h following ICU admission might be the best approach. Patients who improve, whether quickly or slowly, can then be differentiated from those with persistent tachypnoea, high respiratory drive, and increasing oxygen needs, for whom avoiding late intubation might have lung-protective effects.

Declaration of interests
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