Minimally Invasive Diagnostic Strategy in Immunocompromised Patients with Pulmonary Infiltrates

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Contents

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15.1 Introduction

Physicians in most medical specialties are seeing a growing number of patients with solid tumours and haematological malignancies. The implementation of routine screening policies has improved the early diagnosis of cancer, and treatment advances have been achieved, with the result that prolonged survival or complete recovery can be obtained in many patients. Intensive and prolonged treatment regimens introduced over the last decade have increased the overall survival rates among patients with various types of malignancies [1]. For instance, intensified and shortened cyclical chemotherapy for acute lymphoblastic leukaemia in adults has improved survival [2], advances in the understanding of multiple myeloma have led to the development of new drugs [3], targeted therapies have proved useful in patients with lymphoma and chronic myeloid leukaemia [4, 5], and growth factors that hasten neutropenia recovery have allowed higher-dose chemotherapy regimens that increase the chances for a cure [6]. However, treatment-related toxic and infectious complications have increased in lockstep with the expanding use of aggressive cancer treatments.

Pulmonary events are the leading complications in patients treated for cancer. These events are frequently severe, with diffuse pulmonary infiltrates, hypoxaemia, and secondary dysfunction of other organs (i.e., shock and kidney injury) [7]. ARF is the most common reason for admission of cancer patients to the intensive care unit (ICU) [8–10]. In cancer patients admitted to the ICU for ARF, the mortality rate is about 50% overall, 60–70% when invasive mechanical ventilation is needed, and 80–90% in recipients of allogeneic bone marrow or

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Table 15.1 Causes of pulmonary infiltrates in patients with solid tumors or hematological malignancies (Adapted from [16])

Infections
Bacterial infections
Common pyogenic bacteria
Streptococcus pneumoniae
Staphylococcus aureus
Haemophilus influenzae
Pseudomonas aeruginosa and Enterobacteriaceae
Intracellular bacteria
Legionella pneumophila
Chlamydia and *Mycoplasma pneumoniae*
Other bacteria
Actinomyces israelii
Nocardia spp.
Pneumocystis jirovecii
Invasive fungal Infections
Molds
Aspergillosis
Emerging mycotic infection: trichosporosis, fusariosis, zygomycetes
Yeasts
Lung involvement during candidemia
Endemic fungal infections
Histoplasmosis, coccidioidomycosise, blastomycosis
Viral infections (primary infections or reactivations)
Seasonal respiratory viruses
Influenzae, parainfluenzae, rhinovirus
Respiratory syncytial virus
Herpes virus
Cytomegalovirus, herpes virus, zoster virus and HHV6
Other viruses: adenovirus
Mycobacterial infections
Tuberculosis and atypical mycobacteria
Noninfectious causes
Cardiogenic pulmonary edema
Capillary leak syndrome
Lung infiltration
Drug-induced toxicity
Alveolar hemorrhage
Transfusion-related acute lung injury
Radiation-induced lung damage
Alveolar proteinosis
Diffuse alveolar damage
Bronchiolitis
Cryptogenic organized pneumonia
Second malignancy

stem cell transplants who require mechanical ventilation [11]. Non-invasive mechanical ventilation has improved survival in cancer patients requiring ventilation by reducing the need for endotracheal intubation [12–15].

A vast array of conditions can manifest as pulmonary infiltrates in patients with cancer (Table 15.1). Although the need for early treatment, most notably with antimicrobials, is universally recognized, debate continues about the best diagnostic strategy in cancer patients with pulmonary infiltrates [16]. Suggested diagnostic strategies cover an extensive spectrum ranging from empirical treatment without diagnostic investigations to diagnostic lung biopsy. However, most groups recommend diagnostic investigations. The main difference across strategies consists in whether fiberoptic bronchoscopy with bronchoalveolar lavage (FO-BAL) is performed (Table 15.2) [16]. The debate about the appropriateness of FO-BAL is particularly relevant in patients with hypoxemic ARF, among whom 40% experience respiratory status deterioration when FO-BAL is performed [17–19]. This risk must be weighed against the increased risk of death that is independently associated with failure to identify the cause of pulmonary infiltrates in patients with cancer [11, 20–22].

This review focuses on the diagnostic strategy for cancer patients with pulmonary infiltrates. We will start by briefly reviewing our DIRECT approach designed to increase the likelihood of appropriate anti-infectious therapy being given within 2 h after ICU admission (Fig. 15.1). We do not recommend a strategy based solely on the DIRECT approach, because identifying the cause of the pulmonary infiltrates increases the chances of survival. We describe the two

Table 15.2 The diagnostic strategy without bronchoscopy in cancer patients with pulmonary infiltrates (Adapted from [16])

Radiography Chest radiography Thin-section high-resolution computed tomography Echocardiography or pleural ultrasonography
Sputum Bacteria Tubercle bacillus Fungi (aspergillus)
Tests for *Pneumocystis jirovecii* (MGG staining and immuno-fluorescence)
PCR for *Pneumocystis jirovecii*
Blood cultures
Serum tests Serology: Chlamydia, Mycoplasma, Legionella Herpes consensus PCR test Circulating aspergillus antigen Circulating cytomegalovirus antigen
Nasopharyngeal aspiration Tests for viruses (PCR and immunofluorescence)
Urine tests Cytology, bacteriology *Legionella* antigen
Biological markers Brain natriuretic peptide (BNP) or ProBNP Creactive protein Fibrin Procalcitonin

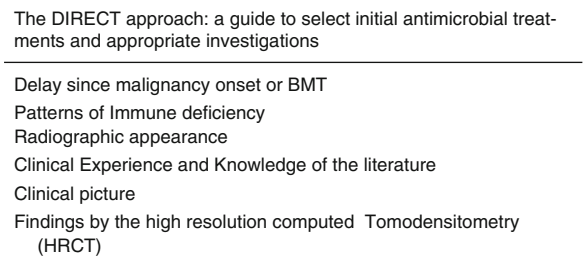

Fig. 15.1 The DIRECT approach for selecting the initial antimicrobial treatment (Adapted from [16]). This approach does not obviate the need for diagnostic investigations

main strategies for identifying the cause of pulmonary infiltrates, i.e., with and without FO-BAL. Because the diagnostic efficiency of FO-BAL was evaluated recently [16], we will focus on the strategy that does not include FO-BAL. In our ICU experience, although FO-BAL combined with other investigations fails to identify the cause of ARF in 10–15% of patients [11, 23], severe hypoxemia and associated organ dysfunctions limit the feasibility of lung biopsy in many cases. However, studies have found lung biopsy to be highly efficient, and we raise this point in the last section of this review, which identifies areas for future research that may help us to improve the management of these very vulnerable patients.

15.2 The DIRECT Approach: A Guide for Selecting the Initial Antimicrobial Treatment and Investigations

We recently proposed a clinical approach designed to help clinicians make hypotheses about the cause of pulmonary infiltrates in patients with haematological malignancies or solid tumours (Fig. 15.1) [16]. This empiric approach is being evaluated prospectively. In the next paragraphs, we describe this strategy and provide one or two examples for each situation. The main goal of the DIRECT approach is to target diagnostic and therapeutic efforts toward those conditions that are most likely to be present in the individual patient, instead of running through the entire list of causes of pulmonary infiltrates in cancer patients. By identifying the two or three diagnoses that are plausible in a given patient, the DIRECT approach may help to initiate appropriate treatment within a few hours after admission.

D stands for *D*elay and refers to three time intervals that should be taken into account: (1) time from the diagnosis of malignancy, (2) time from respiratory symptom onset and (3) where relevant, time from allogeneic bone marrow transplantation (BMT). For example, pulmonary leukaemic infiltration or leukostasis occurs in patients with high counts of circulating blast cells, i.e., at the earliest stage of acute leukaemia or during relapses [24]. Gradually worsening dyspnea over the last 4 weeks is more likely to indicate pulmonary infiltration by the malignancy or congestive heart failure and pulmonary oedema than bacterial infection or *Pneumocystis* pneumonia (PCP). In allogeneic BMT recipients, cytomegalovirus pneumonia may occur during graft-versus-host disease (GVHD) but is unlikely to explain pulmonary infiltrates during the first 30 days after transplantation [25].

I indicates the type of *I*mmune deficiency. This point is crucial when making hypotheses about the

type of infection responsible for pulmonary infiltrates. Patients with lymphocyte abnormalities (e.g., acute or chronic lymphocytic leukaemia or lymphoma) are at risk for viral or fungal infections [e.g., herpes simplex virus (HSV), PCP, and emerging fungal infections], diseases affecting monocytes and macrophages (e.g., hairy cell leukaemia, chronic myelomonocytic leukaemia, and chronic myeloid leukaemia) are associated with intracellular bacterial infections (e.g., *Legionella*, *Mycoplasma*, and tuberculosis), and neutrophil abnormalities (e.g., absolute or relative neutropenia, myelodysplastic syndrome, and chronic myeloid leukaemia) increase the risk for bacterial and fungal infections. In addition, hypogammaglobulinaemia in patients with chronic lymphocytic leukaemia or myeloma is specifically associated with infection by encapsulated bacteria. However, all these patterns need to be re-evaluated using new technologies to assess the cellular defects. In addition, the increasing use of intensive and prolonged cancer chemotherapy regimens and of targeted therapies (e.g., rituximab and alemtuzumab) can be expected to change the patterns of immune deficiency seen in cancer patients and, therefore, qualitative studies are needed.

R indicates the chest *R*adiograph findings.

E refers to *E*xperience and knowledge of the literature. For example, although diffuse alveolar haemorrhage can theoretically cause pulmonary infiltrates in immunosuppressed patients, this complication seems virtually confined to BMT recipients [26, 27]. Similarly, pulmonary aspergillosis, although possible in every cancer patient, occurs chiefly in patients with prolonged neutropenia (e.g., acute leukaemia patients), long-term steroid therapy [28, 29], and BMT [30].

T refers to findings by high-resolution computed *T*omography (HRCT).

15.3 Bronchoscopy and Bronchoalveolar (FO-BAL) Lavage in Cancer Patients with Pulmonary Infiltrates

In the late 1980s, FO-BAL became the most widely used investigation for identifying the cause of pulmonary infiltrates in immunosuppressed patients [31–36]. FO-BAL superseded lung biopsy, as it was easier, simpler, and less invasive. These advantages were reported to be particularly helpful in patients at very high risk of death if treated with mechanical ventilation [37]. The results of 18 studies (in 1,537 patients) indicated that FO-BAL provided the diagnosis in about half the patients and led to treatment modifications in one-third (Table 15.3). These data were confirmed by a recent retrospective study [38], including 175 haematological patients admitted to the ICU for ARF and showing a 10% rate of life-threatening complications after FO-BAL. Moreover, the diagnostic yield was only 50%, and the therapeutic impact was significant in only 17% of the patients [38].

Data from 764 BMT recipients in 15 studies showed that FO-BAL supplied the diagnosis in 55% of cases, but caused the respiratory status to deteriorate in up to 40% (Table 15.4) [17–19].

The limited diagnostic efficiency of FO-BAL in immunocompromised patients may be related to several factors. First, most patients are already on antimicrobial therapy at the time of FO-BAL. Therefore, bacterial pneumonia is usually documented clinically but not bacteriologically, although FO-BAL may detect resistant pathogens that require adjustment of the antimicrobial regimen. Second, BAL fluid analysis is often confined to tests for infections, and most studies fail to report the appearance of the alveolar cells, which may suggest drug toxicity, or the presence of malignant cells, indicating pulmonary infiltration. Third, most studies were conducted in the 1990s, before the introduction of new tools for diagnosing infections with viruses, parasites, and fungi [39]. However, the diagnostic yield of FO-BAL was not better in recent studies [11, 40]. Last, FO-BAL may be less efficient in patients with cancer than in those with AIDS because of pathophysiological differences in the development of pulmonary invasion by *Aspergillus* or *Pneumocystis* [30, 41–45]. For instance, a study of PCP in cancer patients showed marked inflammation and scarce *Pneumocystis* bodies, indicating that negative BAL fluid findings did not rule out PCP [43].

15.4 Diagnostic Strategy Without Bronchoscopy

Table 15.2 lists the investigations used in the diagnostic strategy without FO-BAL. Routinely performing all these tests may be an alternative to FO-BAL in most

Table 15.3 Studies of fiberoptic bronchoscopy with bronchoalveolar lavage in patients with malignancies and pulmonary infiltrates (Adapted from [16])

Reference	*n*	Diagnosis	Diagnostic impact	Therapeutic impact
Stover et al. [96]	97	HM	66	–
Martin et al. [109]	100	HM	30	–
Xaubet et al. [110]	96	HM	49	31
Campbell et al. [111]	22	HM	55	–
Pisani et al. [112]	150	HM	39	–
Maschmeyer et al. [113]	46	Neutropenia	30	–
Cordonnier et al. [100]	56	Neutropenia	53	24
Cazzadori et al. [114]	142	HM	36	–
Von Eiff et al. [40]	90	HM	66	65
White et al. [3]	68	HM	31	24
Ewig et al. [28]	49	HM	31	16
Gruson et al. [18]	41	Neutropenia	63	28
Hilbert et al. [22]	24/46	HM	62	71
Murray et al. [2]	27	HM	33	28
Azoulay et al. [4]	203	HM	49.5	45.1
Pagano et al. [115]	127	HM	53	14
Jain et al. [82]	104	HM	56	–
Hohenadel et al. [81]	95	HM	30	–
Total	1537		46.2	34.6

cancer patients with pulmonary infiltrates (Fig. 15.2 and 15.3). We review available data on the use of each of these investigations in cancer patients. Imaging findings are discussed in another chapter 12. We will focus on laboratory methods to diagnose pulmonary infiltrates.

15.4.1 Laboratory Tests for Diagnosing Infectious

15.4.1.1 Bacterial Infections

Bacterial pneumonia in immunocompromised patients is usually due to gram-negative bacilli or *Staphylococcus aureus*. Selection pressure due to the use of broad-spectrum antibiotics explains the emergence of resistant gram-negative strains. As discussed above, FO-BAL often fails to establish the exact diagnosis. Moreover, identified organisms may indicate colonisation rather than infection. In a population of allogeneic BMT recipients, no pathogen was isolated in 70% of the patients, and some of the isolated microorganisms (such as *Candida* spp., coagulase-negative staphylococci, and enterococci) were probably mere contaminants [46].

As shown by studies of FO-BAL, conventional microbiological testing may fail to identify the cause of lower respiratory tract infection. In patients on broad-spectrum antibiotics at the time of sample collection, gram staining and culturing have low sensitivity, and cultures require time. Furthermore, these methods fail to distinguish colonisation from infection. Serological testing is slow and often lacks both sensitivity and specificity. In most cases, the causative pathogen is not found, despite optimal investigations. Methods that rapidly identify the causative pathogen would help physicians to select the best treatment strategy. Such methods are already available for

Table 15.4 Studies of fiberoptic bronchoscopy with bronchoalveolar lavage in bone marrow transplant recipients with pulmonary infiltrates (Adapted from [16])

Author	*n*	Type of patients	Diagnostic impact	Therapeutic impact	Complications
Springmeyer et al. [20]	22	Auto-allo	58	–	13
Corodonnier et al. [17]	52	Allo	50	–	0
Cordonnier et al. [9]	69	Allo	66	–	–
Milburn et al. [19]	40	Allo	80	76	0
Springmeyer [78]	15	Auto-allo	89	–	40
Heurlin et al. [116]	18	Auto-allo	61	–	–
Weiss et al. [80]	47	Auto-allo	47	–	12
Campbell et al. [79]	27	–	74	63	11
AbuFarsakh et al. [117]	77	Auto-allo	42	–	–
White et al. [93]	68	Auto-allo	31	24	15 (7% MV)
Dunagan et al. [1][a]	71	Auto-allo	38	42	27 (4% MV)
Glazer et al. [118]	79	Auto-allo	67	62	–
Gruson et al. [39]	38	Auto-allo	42	–	–
Gruson et al. [18]	52	Auto-allo	38	28	17
Huaringa et al. [108]	89	Auto-allo	42	–	–
Total	764	Auto-allo	55	49	0–40%

[a]32% Mechanical ventilation

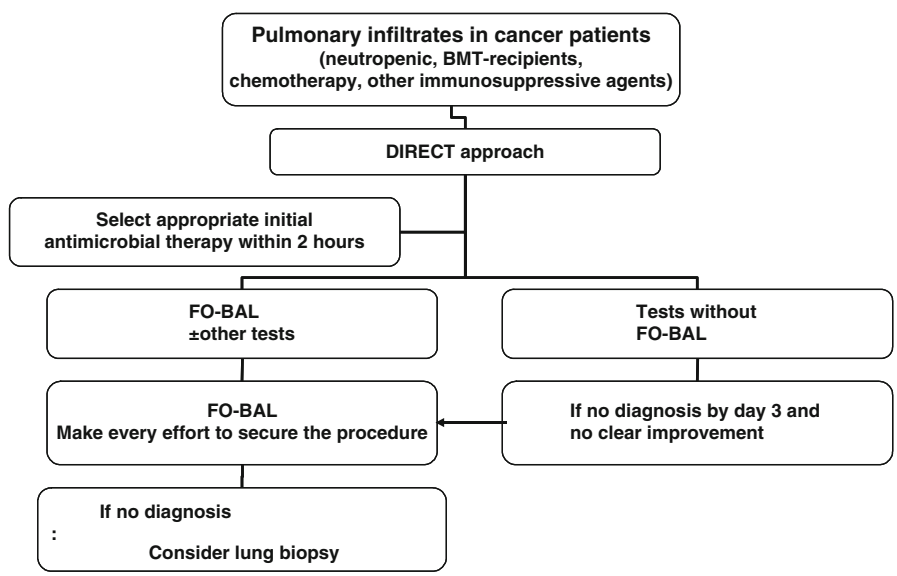

Fig. 15.2 Diagnostic strategy for cancer patients with pulmonary infiltrates

Legionella pneumophila and *Streptococcus pneumoniae* and are being developed for other bacteria. It seems, however, that the incidence of these pathogens may have been overestimated in haematological patients.

Legionella pneumophila

Antibodies to *Legionella pneumophila* were first detected using indirect immunofluorescence or microagglutination tests. Since then, numerous ELISAs based on different antigen-extraction methods have been developed. The reported sensitivities of these assays vary substantially, from 41% to 75% [47, 48]. Low titres of antibodies against *Legionella* spp. have been found in healthy volunteers, blood donors, outpatients, and hospitalised patients [49, 50]. These low titres seem to indicate previous exposure to *Legionella* spp. The urinary antigen test produced positive results 1–3 days after the clinical onset and remained positive for almost 1 year in a small proportion of patients [51, 52]. Importantly, the urinary antigen test showed greater than 99% specificity [53]. Sensitivity for *L. pneumophila* infections ranged from 56% to 99% [54]. Low sensitivity of urinary antigen assays for serogroups other than *L. pneumophila* serogroup 1 has been reported, the range being 14–69% [55, 56]. In the future, an easy-to-perform PCR test with high sensitivity and greater than 99% specificity will probably become available on a wider scale [57].

Streptococcus pneumoniae

The diagnosis of pneumococcal infection requires recovery of the microorganism from an uncontaminated specimen (e.g., blood or pleural fluid). Blood culture results are positive in only about one-fourth of cases, and prior antibiotic therapy significantly reduces the proportion of positive blood culture results. Bacteraemia may be absent in 70–80% of cases of *S. pneumoniae* pneumonia. Sputum cultures provide only a probable diagnosis, since *S. pneumoniae* carriage in the nasopharynx is common. PCR assays for *S. pneumoniae* have shown inadequate sensitivity when used on blood or urine and inadequate specificity for infection when used on respiratory samples. Several publications have described antigen detection assays. Good sensitivity and specificity have been reported with commercial kits for urinary C polysaccharide detection in adults. For example, the Binax NOW *S. pneumoniae* urinary antigen test was 82% sensitive and 97% specific when positive blood cultures were used as the reference standard. The test is simple to perform, detects the C polysaccharide cell wall antigen common to all *S. pneumoniae* strains, and provides results within 15 min. Urinary antigen was still detected in 83% of patients who were retested on treatment day 3 and persisted for at least 7 days in many patients [58]. Additional studies produced similar results (Table 15.5) [59–61]. A nested PCR assay targeting the pneumolysin gene was used to detect *S. pneumoniae* DNA in multiple sample types from 474 adults with community-acquired pneumonia and 183 control patients without pneumonia. The assay added little to information from existing diagnostic tests for *S. pneumoniae* and was unable to distinguish colonisation from infection when used on respiratory samples [59, 61]. Studies of *S. pneumoniae* antigen tests involving latex agglutination or counter-current immunoelectrophoresis showed detection rates ranging from 0% to 88%, and specificity was often poorly defined.

Table 15.5 Binax NOW *Streptococcus pneumoniae* urinary antigen test: sensitivity and specificity

Reference	Type of infection	Number of patients	Sensitivity (%)	Specificity (%)
Smith, J Clin Microbiol 2003 [58]	Pneumococcal bacteremia	107	82	97
Murdoch, J Clin Microbiol 2001 [61]	Community-acquired pneumonia	420	80	100
Dominguez, Chest 2001 [60]	Bacteremic and nonbacteremic pneumonia	51	82	97

Mycoplasma pneumoniae

The diagnosis of hard-to-culture pathogens such as *Mycoplasma pneumoniae* classically relies on testing paired sera to demonstrate a rise in the antibody titre. This method is of uncertain value in immunocompromised patients, most notably those with impaired cell-mediated immunity. Culturing is relatively insensitive and time-consuming, requiring up to 3 weeks for pathogen detection [62]. A number of PCR assays for *M. pneumoniae* have been evaluated in various respiratory specimens and patient populations, with promising results. PCR is more sensitive and considerably faster than culturing. In general, PCR results correlate well with serological results [63]. Both upper and lower respiratory tract samples are suitable for PCR testing. Upper respiratory tract samples (throat swabs and nasopharyngeal samples) may be the preferred sample types, as they are easy to obtain and ensure high sensitivity [59]. PCR on throat swabs may be the best existing diagnostic test for *M. pneumoniae*. However, standardised protocols will have to be developed before this test is recommended for widespread use [64].

Chlamydia pneumoniae

Cell cultures for *C. pneumoniae* detection are technically demanding and time-consuming, and their yield is generally low. Therefore, the diagnosis of *C. pneumoniae* infection relies largely on serological testing, whose value in immunocompromised patients is uncertain. Furthermore, both acute- and convalescent-phase sera must be tested, which can only provide a retrospective diagnosis. These major limitations have prompted many studies of PCR for diagnosing *C. pneumoniae* infection. Unfortunately, the results have been conflicting. Overall, PCR was at least as sensitive as culturing, but its specificity was difficult to assess given the absence of an appropriate reference standard [59]. *C. pneumoniae* DNA can be detected in both upper and lower respiratory tract samples, but it is unclear which sampling site is better. Highly sensitive PCR techniques may increase the ability to detect *C. pneumoniae* carriage, the clinical relevance of which is unclear.

15.4.1.2 Diagnosis of Viral Respiratory Infections Using Nasopharyngeal Aspirates

In the past, viral cultures were the reference standard for the laboratory diagnosis of respiratory viral infections. However, 2–10 days were usually needed to obtain the results. To overcome this major limitation, faster diagnostic techniques, such as viral antigen detection, were introduced. These faster techniques are generally considered less sensitive and less specific than cell cultures. Moreover, viral antigen detection is not feasible for all respiratory viruses. PCR has proven extremely specific and sensitive for detecting respiratory viruses: it is now the reference standard for diagnosing respiratory viral infections and the only method available for detecting some viruses [39]. PCR was not only more sensitive than viral culture or antigen or antibody tests for detecting respiratory viruses in patients with haematological malignancies, but also decreased the time to diagnosis [65, 66]. Parainfluenza viruses 1–3, respiratory syncytial virus, rhinovirus, influenza viruses A and B, enteroviruses, and coronaviruses were reliably detected by PCR [67–69]. Nose-throat swabs yielded the same results with PCR as did BAL samples [39]. In a recent study of patients with haematological malignancies and respiratory viral infections, PCR on nasopharyngeal aspirates usually provided the diagnosis [70]. In the near future, widespread use of multiplex PCRs in patients with haematological malignancies will raise additional concerns about the relevance of virus retrieval from nasopharyngeal aspirates in patients with lung infiltrates [69].

Cytomegalovirus frequently causes severe disease after stem cell transplantation. The cytomegalovirus antigen assay is a rapid quantitative tool for monitoring cytomegalovirus infection. However, this method is tedious, as it requires counting the cells in the samples. In addition, the results may be influenced by factors such as storage and fixation methods. PCR assays have been used to diagnose cytomegalovirus infection. Real-time PCR provides a qualitative assessment of viral load. However, although the antigenaemia cutoff has been determined, the viral load cutoff is unknown [39, 71].

BMT recipients and patients with haematological malignancies who have severe impairments of cell-mediated immunity are at risk for HSV pneumonia. Although HSV type 1 accounts for most cases, other

herpes viruses such as cytomegalovirus, varicella zoster virus, Epstein-Barr virus, HHV-6, and HHV-8 are also common causes of pneumonia in this population. Advances in diagnostic techniques and the use of preventive or pre-emptive treatments have altered the epidemiology of some of the herpes virus infections. However, herpes viruses continue to cause significant morbidity and mortality in stem cell recipients [72]. A multiplex PCR assay designed to amplify herpes virus DNA in a diverse range of clinical specimens yielded higher detection rates for the viruses represented in the assay than did virus isolation and immunofluorescence-based antigen detection [73]. The turnaround time was far less than for the other techniques. Overall, the multiplex PCR detected substantially more herpes viruses, in some cases in specimens or at body sites where these viruses were found only rarely or never using conventional methods. Multiplex PCR has not yet been evaluated as a tool for diagnosing herpes virus pneumonia in patients with cancer. However, multiplex PCR may help to assess the pathogenic role for herpes viruses found in respiratory samples. An oligonucleotide microarray for herpes virus detection in clinical samples has been developed and needs to be evaluated in clinical practice.

15.4.1.3 Non-invasive Diagnostic Strategy for Diagnosing Pneumocystis Pneumonia (PCP)

The standard method for diagnosing PCP pneumonia is microscopic identification of the organism using stains (methenamine silver, Giemsa, or toluidine blue O) or antibodies in BAL or induced sputum samples [74]. Several studies confirmed that PCR was more sensitive than microscopy for detecting *P. jiroveci* [75]. PCR is useful to rule out *P. jiroveci* infection in HIV-negative immunocompromised patients, who often have lower parasite counts than AIDS patients [43]. Nested PCR methods tend to have low specificity with high false-positive rates, whereas real-time PCR seems more specific [39, 76–78]. Samples similar to those used for microscopy can serve for PCR [75]. BAL specimens have the best yield; induced sputum samples, which are commonly used for HIV-infected patients, may be diagnostic but have not been evaluated in patients with other causes of immunodeficiency. [77]. Oral washes may be used as alternative non-invasive samples, despite lower sensitivity of PCR compared to lower respiratory tract samples [42, 79]. In a recent study [80], 448 patients were screened for *P. jiroveci* pneumonia with PCR and Gromori-Grocott staining. BAL was performed in 351 patients and induced sputum was diagnostic in 39 patients. PCR sensitivity was 87% and specificity was 92%, Negative predictive value on BAL samples was 98.7%. Given this excellent negative predictive value, we recommend PCR as the leading method for excluding PCP in cancer patients with pulmonary infiltrates. Negative PCR results on BAL fluid or induced sputum indicate that PCP treatment can be safely discontinued [81].

15.4.1.4 Diagnosis of Fungal Infection

The diagnosis of invasive aspergillosis in haematological patients is often challenging. Until recently, only specimens from normally sterile sites were considered necessary for the definitive diagnosis of invasive fungal infections. Specimens from sites that may be colonised (e.g., sputum, BAL fluid, or sinus aspirate) were rarely diagnostic. BAL fluid cultures positive for *Aspergillus* spp. may indicate colonisation instead of invasive infection. Cultures may require days or weeks. The reference standard is histologically proven hyphal invasion in tissue specimens obtained by invasive procedures, but these may be deemed unsafe in patients with cytopenia [44, 82]. The first prospective, pathology-verified evaluation of a sandwich ELISA using a monoclonal antibody to galactomannan (GM) showed that serial monitoring was 92.6% sensitive and 95.4% specific [83]. The positive predictive value was 93%, and the negative predictive value was 95% [83]. In more than half the cases, antigenaemia was detected before invasive aspergillosis was suspected clinically [84, 85]. Based on this study and others, the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group convened a consensus panel to develop standard definitions for invasive fungal infections, introducing *Aspergillus* antigenaemia testing as an important diagnostic tool. The panel recommended that *Aspergillus* antigenaemia testing be used to support a probable diagnosis [44]. The value of this diagnostic strategy has been clinically validated [86, 87]

and shown to be clinically relevant. Moreover, the diagnostic yield of *Aspergillus* antigenaemia may be higher in neutropenic patients [88]. Finally, PCR has been used to detect *Aspergillus* spp., but false-positive results were noted, and no standardised commercial method is available [89–91].

15.4.1.5 Microbial DNA Identification by Blood PCR

Numerous multivariate analyses have shown that inadequate antibiotic therapy in patients with severe sepsis is a strong and independent risk factor for death [92]. In clinical practice, diagnostic uncertainty regarding the causative microorganism leads to the use of broad-spectrum combinations of antibiotics. The high selection pressure created by these combinations may lead to the emergence of multi-drug resistant bacteria. Moreover, in patients with haematological malignancies, who are often neutropenic, the diagnostic yield of blood samples is low (25% in one study [93] and probably even less in patients on concomitant antibiotic therapy), and more than half the clinically diagnosed infections are treated empirically. These data may reflect the presumed low bacterial/fungal load necessary for clinical infection. Therefore, rapid diagnostic tests are needed [94]. In recent years, several diagnostic tools based on culture-independent molecular biology-based techniques, such as real-time polymerase chain reaction, were developed [95]. However, their usefulness in clinical practice needs to be demonstrated. Numerous studies are ongoing. In severe sepsis [96], the match between PCR and blood culture results seems disappointing, with only 70% of positive PCRs in patients with positive blood cultures. However, positive PCR results showed statistically significant associations with higher organ dysfunction scores, as well as a trend toward an association with higher mortality. In immunocompromised patients, the results of preliminary studies of PCR seem more promising, although the true accuracy of these methods needs to be determined [97, 98]. PCR seems more sensitive than blood cultures, with a 100% match between positive blood cultures and positive PCR, as well as a high negative predictive value (98.6%) of negative PCR. However, these results require confirmation in larger studies, and their clinical usefulness needs to be tested in terms of antibiotic use and treatment reduction.

15.4.1.6 Biomarkers

ARF in cancer patients can be related to many conditions, including infections (opportunistic or bacterial) and non-infectious events (infiltration by malignant cells, drug-related pulmonary toxicity, or cardiogenic pulmonary oedema) [11]. Identification of the exact cause of ARF is associated with a marked improvement in survival. Rapid evaluation of the contribution of left ventricular failure to ARF enables prompt adequate treatment, obviating the need for invasive diagnostic procedures. Echocardiography is the reference standard for diagnosing left ventricular dysfunction but requires the availability of an experienced sonographer. B-type natriuretic peptide (BNP) is a predominantly ventricular cardiac hormone whose levels increase in the event of cardiac overdistension [99]. BNP measurement has been found highly sensitive and specific for the diagnosis of heart failure [100]. However, in the initial cohort, no cancer patients were included.

The accuracy of BNP in cancer patients with ARF was evaluated in a recent study [101] of 100 patients. This study showed that BNP was useful only for ruling out a role for cardiac dysfunction in ARF, when NT-pro BNP was under 500 pg/mL (100% specificity and 100% negative predictive value). However, due to the direct cardiac toxicity of anti-cancer chemotherapy and high rate of renal failure among cancer patients, BNP elevation was not accurate for diagnosing cardiac dysfunction.

The morbidity of anti-infectious treatment can be high. Systemic inflammatory response syndrome (SIRS) can be related to various causes (i.e., toxicity of chemotherapy), and a highly specific marker for sepsis would therefore be valuable. In non-neutropenic patients, procalcitonin (PCT), produced by the reticulo-endothelial cells, is a specific and sensitive marker for bacterial infections [102]. For example, PCT can differentiate between bacterial and viral meningitis. Data from neutropenic patients are scarce except in the paediatric population, where small studies [103, 104] suggested that PCT might be a good marker for bacterial sepsis with more than 95% negative predictive value and more than 85% sensitivity. In adults, no convincing data are available. Some studies in neutropenic patients [105] indicated that PCT was unhelpful (although we have personal data that seems somewhat more promising). Therefore, we cannot

recommend PCT as a diagnostic tool in patients with haematological malignancies or other forms of cancer.

15.5 Conclusion and Avenues for Future Research

The diagnostic and therapeutic impact of FO-BAL has been evaluated in several studies, and other diagnostic investigations have been evaluated individually. However, the routine use of all available investigations except FO-BAL has not been assessed, nor have the diagnostic strategy and outcomes been compared in cancer patients managed with versus without FO-BAL. The number of patients in whom non-invasive investigations obviates the need for FO-BAL may also deserve to be determined.

In the future, the development of new tools will contribute to improve the diagnosis of bacterial pneumonia (16S RNA) and viral pneumonia (oligonucleotide microarray). These new tools can be expected to improve the diagnostic yield of BAL analysis, and non-bronchoscopic lavage may cause less respiratory deterioration than FO-BAL [106]. Markers for heart failure (brain natriuretic peptide) or bacterial infection (procalcitonin) need to be evaluated in cancer patients.

We predict that advances in diagnostic tools will decrease the role for FO-BAL, just as in the past FO-BAL decreased the role for lung biopsy [107]. When the diagnosis remains uncertain despite extensive investigations including FO-BAL, the feasibility, safety, and diagnostic yield of lung biopsy should be evaluated, since identifying the cause of pulmonary infiltrates is known to reduce mortality [11, 16].

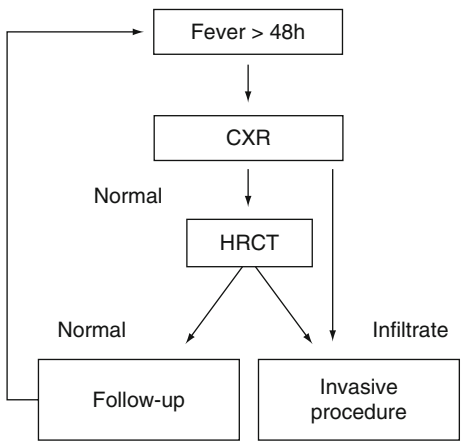

Fig. 15.3 Recommendations from the Infectious Diseases Working Party of the German Society of Haematology and Oncology (Adapted from [45])

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