Most patients suffering from community acquired pneumonia do not appear at a radiology department since diagnosis is made on a clinical basis. In severe or unclear situations, a chest X-ray is done and analysis is frequently done by interns. Radiologists frequently see those patients that suffer from recurrent, nosocomial pneumonia, or an additional predisposing disease. The appropriate investigational technique, frequently targeted differential diagnosis, and the special needs of these patients need to be understood by radiologists. Early detection of a focus of infection is the major goal in immunocompromised patients. As pneumonia is the most common focus, chest imaging is to be done at the beginning. The sensitivity of chest X-rays, especially in the supine position, is known to be low. Therefore the very sensitive high-resolution CT (HRCT) became the gold standard in neutropenic hosts and is widely replaced by thin-section multi-detector-row-CT (MDCT). Underlying diseases such as pulmonary embolism or bronchial carcinoma might also be depicted. Furthermore, the costs of CT are low in comparison to antibiotics. The infiltrate needs to be localised, so that a physician can utilise this information as a guidance for invasive procedures for further microbiological work-up. The radiological characterisation of infiltrates gives a first and rapid hint to differentiate between different sorts of infectious (typical bacterial, atypical bacterial, fungal) and non-infectious aetiologies. Follow-up investigations need careful interpretation according to disease and concomitant treatment. Temporary exclusion of infectious involvement of the lung with high accuracy is, besides of pneumonia management, a hot topic for clinicians.
Community Acquired Pneumonia

27.1.1 Epidemiology

The community acquired pneumonia (CAP) is a frequently occurring disease. In Germany alone, approximately 800,000 people per year develop this disease. According to the Federal Statistical Office, nearly a third of them were hospitalized in 1998. The respective mortality rate is around 6%–8%.

27.1.2 Radiological Procedure

Chest X-ray is recommended only in those patients with at least one of the following criteria:
- Regional auscultatory finding
- Clinical assessment
- Co-morbidity
- Differential-diagnostic consideration
- Severe disease with vital dysfunction
- Admission to a hospital.

If chest X-ray does not show an infiltrate, the symptoms may be a result of an acute bronchitis or exacerbation of COPD or influenza infection. If an infiltrate is evident, a community acquired pneumonia (CAP) is very probable. The type of infiltrate has to be described morphologically as typical (lobar or bronchial) or atypical (interstitial) pneumonia. This provides the first hint to an underlying spectrum of micro-organism.

27.2 Forms of Pneumonia

27.2.1 Aspiration Pneumonia

This involves acute or chronic aspiration of gastric contents with a typical history, frequently after ENT or oesophageal disease with typically bronchogenic spread in the dependent lung regions. Lung abscesses may be a result of aspiration depending on virulence of the micro-organism and the immuno-competence. A CT is recommended to localize and measure the abscess as well as to demonstrate the relationship to adjacent organs for a possible surgical treatment.

27.2.2 Retention Pneumonia

The most frequent underlying disease for retention pneumonia is the endobronchial obstruction caused by a bronchial carcinoma. Further causes are metastases, cardiomegaly, pleural effusion, foreign-body aspiration, post lung surgery, pneumoconiosis, etc. These should be considered since imaging might be helpful in the differential diagnosis.

27.2.3 Non-Infectious Disease

Several diseases may clinically appear like pneumonia and go along with infiltration. However, antibiotic treatment failure takes place. Some differential diagnosis should be considered, especially since imaging might provide characteristic information to point indicate the following:
- Crypogenic organizing pneumonia (COP, formerly BOOP)
- Non-specific idiopathic pneumonia (NSIP)
- Exogene allergic alveolitis (EAA)
- Eosinophilic pneumonia
- Sarcoid, M. Wegener
- Histiocytosis X
- Systemic Lupus erythematoses
- Rheumatoide arthritis
- Bronchiolo-alveolar carcinoma
- Lymphangiosis carcinomatosa
- Pulmonary congestion

etc.

27.3 Pneumonia in Immuno-Compromized Patients

A variety of clinical situations go along with a certain kind of immuno-incompetence: acquired immuno-deficiency, immuno-suppression or temporal immuno-incompetence. Modern tumour therapy utilises a numerous of high-dose chemotherapy protocols. This induces an increasing number of long-term neutropenia (>10 days) with definitive immuno-deficiency (CHANOCK 1993; HÖFFKEN 1995). In long-term neutropenia, the risk for infections rises to more than 85% (HIDDEMANN et al. 1996). Furthermore, after initially successful empirical antibiotic treatment, an infectious relapse occurs.
in approximately 50% of the patients (Maschmeyer et al. 1994; Pizzo et al. 1982). Thus, physicians are confronted with an increasing number of immunocompromised hosts showing non-specific clinical signs of infection. An empirical antibiotic strategy will be started initially, which covers the most frequent types of infections. This approach is very successful nowadays (Maschmeyer et al. 1994a, b; Maschmeyer 2001), but non-targeted. Because the underlying micro-organism remains unknown, empirical antibiotic strategy has several disadvantages:

- A de-escalation of a broad-spectrum to narrow antibiotic usage, at least at the end of the infectious course, remains troublesome. This enhances costs for antibiotics as well as the rates of adverse effects, possibly over utilised drugs, and bacterial resistance.
- Beside infections, non-infectious inflammatory diseases such as relapse of haematological disease, graft vs host disease etc. might mimic infection. Therefore non-infectious differential diagnoses remain underestimated.
- After an empirically treated episode of infection, the next chemotherapeutic course usually includes an antibiotic prophylaxis. The so-called “secondary prophylaxis” is again non-specific.
- The local epidemiology remains unknown without appropriate diagnostic procedures.

Thus, patients will profit from identification of the underlying disease, and are sent to a radiologist for identification of the focus of infection. This early identification of the infection site is a major task for clinicians taking care for neutropenic patients. Frequently fever is the only sign for infection and different aetiologies have to be considered in this setting (Table 27.1).

The major role of the radiologist focuses on the detection of the focus of infection or non-infectious disease. If an organ is affected, invasive diagnostic procedures can be undertaken for identification of the underlying micro-organism. The acquired information helps to localise the most suspicious region within this organ. For example, the selection of a certain segment helps in guiding broncho-alveolar lavage or biopsy (Schaefer et al. 2001). Furthermore, characterisation of the detected focus may give the clinician a clue for the underlying disease (Table 27.3) (Tanaka et al. 2002a; Schaefer et al. 2001). The detected focus might additionally serve as a practicable follow-up parameter to document the course of the infection and therapeutical success.

Besides detecting infectious sites, the utilised technique should also present a high negative predictive value to exclude the infectious involvement temporarily.

### 27.3.1 Risk and Epidemiology

Bacterial infections are responsible for approximately 90% of infections in the early phase of neutropenia (Einsele et al. 2001) (Table 27.1, Fig. 27.1). In an allogeneic transplantation setting, Gram-negative bacte-

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**Table 27.1.** Overview of frequent infectious and infectious-like diagnoses in neutropenia and thereafter

| Causes       | Description                                                                 |
|--------------|-----------------------------------------------------------------------------|
| Bacteria     | Bacterial infections occur especially during the early phase of neutropenia. Approximately three-quarters of bacterial infections are caused by Gram positive bacteria (Kolbe et al. 1997) |
| Fungi        | Invasive fungal infections (mycosis) occur especially during the late phase of neutropenia and especially during broad spectrum antibacterial therapy (Maschmeyer et al. 1994b; Uzun and Anaissie 1995). In Europe, the most frequent fungal organisms are Candida spp. and Aspergillus spp (Figs. 27.3, 27.6, 27.8 and 27.10). The latter invades the lung parenchyma as well as the blood vessels. The mortality rate of invasive aspergillosis is high (50%–70%) |
| Viruses      | These organisms lead to infection especially after allogeneous bone-marrow or stem-cell transplantation (Figs. 21.1 and 21.12) |
| Atypical bacteria | These organisms lead to infection especially after allogeneous bone-marrow or stem-cell transplantation (Fig. 21.11). They are frequently not covered sufficiently by the initial empirical antibiotic strategy |
| Non-infectious | Several aetiologies for fever or pulmonary infiltrates, particularly after allogeneous transplantation have to be considered (Fig. 21.13–21.17). Some of these infiltrates might appear very similar to those caused by infections |
ria are documented in 16%–31%, whereas in 65%–75% Gram-positive bacteria are found (Einsele et al. 2001). On the other hand, the Gram-negative bacteria lead to a significantly higher morbidity (Einsele et al. 2001).

Risk stratification and pharmacological improvements have enhanced the role of empirical antibiotic strategy (Table 27.2). Bacteria are covered sufficiently by antibiotic (antibacterial, i.e. neither antifungal nor antiviral) therapy (Maschmeyer et al. 1994). If this approach fails or an infection breaks through, an antibacterial second-line treatment has limited success. The low cure rate of 30% in the second line demonstrates the limited role of antibiotic switching. Antifungal supplementation at this time point, however, reaches cure rates of up to 78% (Fig. 27.1) (Maschmeyer et al. 1999). This underlines the point, that the early detection of non-bacterial pneumonia is the major task. From a clinical point of view, the detection of an ongoing bacterial infection appears less important than detecting non-bacterial pneumonia, e.g. fungal pneumonia. Therefore, making a further characterisation of a bacterial pneumonia becomes less desirable for the clinician.

Besides prophylaxis and efficient initial broad-spectrum treatment, interventional therapy regimens for second- and third lines are formulated (Einsele et al. 2001). In the treatment of pneumonia, prospective investigations demonstrate a major limitation of the empirical therapy due to fungal organisms (Maschmeyer et al. 1999). Due to the recommendation of the European Organization for Research and Treatment of 

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### Table 27.2. Risk factors for various infections in hosts suffering from different immunodeficiency

| Immuno-deficiency | Diagnosis | Microorganism |
|-------------------|-----------|---------------|
| Neutropenia       | Acute myeloid and lymphatic leukaemia | Extracellular Gram-positive and gram-negative bacteria, fungi |
| Hypogamma-globulinemia | Chronic lymphatic leukaemia, multiple myeloma | Encapsulated bacteria, Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis |
| Steroids, lymphocyte dysfunction | Hairy-cell leukaemia, acute lymphatic leukaemia, lymphoma, conditioning therapy including T-cell depletion, AIDS | Intracellular bacteria, Listeria, Mycobacteria, Salmonella, Cryptococcus neoformans, Pneumocystis jiroveci |

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**Fig. 27.1.** Infectious and infectious-like syndromes as well as major risk factors at various times after bone marrow transplantation. Day 0 = day of transplantation. HZV = Herpes simplex virus, CMV = cytomegalovirus, Adeno = Adenovirus, VZV = Varicella zoster virus, GvHD = graft vs host disease (adapted to Heussel et al. 2000a)
Cancer (EORTC)/Invasive Fungal Infections Cooperative Group and Bacterial and Mycosis Study Group (BAMSG), every new infiltrate is a minor criterion for fungal pneumonia and typical signs are a major criterion of fungal pneumonia (AscioGlu et al. 2002). This classification cannot be transferred to other immunodeficiencies such as AIDS (Edinburgh et al. 2000).

27.4 Early Detection

The necessity for an early detection of the focus of infection bases upon high mortality of infections in immunocompromised hosts and high costs of prolonged hospitalisation. Newer antifungals as Voriconazole or Caspofungin alone result in daily therapy costs of 400–1000€. Combination with antibiotics result in even higher costs. This is a relevant amount of money in comparison to the costs of a non-enhanced CT scan of around 230€ (in Germany, in-patients, including report and comparison to previous scans). Thus, making expensive methods more cost-effective in early detection is important. Usually the search for the focus of infection consists of:

1. A physical examination and laboratory findings. Besides epidemiological knowledge, the results should be taken into account to identify the organ system which is most likely affected.
2. After identification of the most suspected organ system(s), select the appropriate imaging technique for investigation. A high sensitivity and useful negative predictive value are needed.

Exact frequencies of organ infections are difficult to determine and differ between clinical (i.e. patients alive) and pathological evaluation (i.e. patient deceased). Clinically, lungs are affected in 30% and paranasal sinuses in 3% of neutropenic patients, and 30% in an allogeneous transplantation setting (concomitant to pneumonia). Gastrointestinal tract, liver, spleen, central nervous system especially after allogeneous transplantation, and kidneys are rarely affected (Maschmeyer et al. 1994b). Due to the tremendously higher frequency of pneumonia in comparison to all other organ systems, this review focuses on early detection of pneumonia. A detailed discussion of the other organ systems and techniques is far beyond the scope of this review. The reader is referred to other publications in the literature (Heussel et al. 1998; Heussel et al. 2000b).

27.4.1 Chest X-Ray

Chest X-ray (CXR) is widely performed when pneumonia is suspected or should be excluded (Azoulay et al. 2002; Navigante et al. 2002). CXR has several advantages such as: quick, widely available (even on the ward), inexpensive, low radiation dose. Some refer-

![Fig. 27.2a–c. Neutropenic febrile patient receiving broad spectrum antibiotic therapy. CXR was normal at day 3 of fever (a,b). HRCT performed the same day demonstrates bilateral infiltrates, which were hidden behind the heart in posterior-anterior and the spine in lateral projection (c)](image)
position achieved a sensitivity for the early detection of pneumonia of only 46% (Weber et al. 1999). Although CXR provides relevant clinical information concerning central venous catheters (CVC), pleural effusion, and pulmonary congestion (Weber et al. 1999), it fails in the early detection or even exclusion of pneumonia, which is a major task in immuno-deficient patients. CXR in supine position alone is not recommended for the early detection of pneumonia in immuno-compromised hosts (Maschmeyer 2001).

On the other hand, if an infiltrate is apparent at CXR, the options for pneumonia characterisation are very limited. Thus, if pneumonia is in question in these hosts, CT should be preferred at any time point if somehow available (McLoud and Naidich 1992).

**Fig. 27.3a–d.** The small ill-defined nodule in the right upper lobe (c) of the 34 year-old neutropenic AML patient was even retrospectively not visible at chest X-ray done at the same day (a,b). Amphotericin B treatment was started due to suspicion of fungal pneumonia; however, the nodule size increased during haematological reconstitution 2 weeks later (d). In preparation of bone marrow transplantation, the lesion was resected to prevent from septical spread. Aspergillus pneumonia was verified.
**27.4.2 HRCT**

The effective radiation dose of CXR is approximately 0.2 mSv but can be 10 times higher depending on the equipment used (Cardillo et al. 1997). In low-dose multi-detector-row CT of the chest, an effective radiation dose of 1.1 mSv is reported, whereas the gap in single-slice HRCT can reduce the dose to approximately 10% of this value (Schöpf et al. 2001). Any low-dose technique goes along with a loss of low-contrast information. However, this information is essential for the determination of pneumonia (ground-glass opacification). Radiation dose is not a real limitation in the investigation of neutropenic patients because they frequently receive radiation for conditioning therapy for transplantation (total body irradiation, TBI) in more than 1000 times higher dosages than for diagnostic purposes. Furthermore, chemotherapy has similar cytotoxic effects on the patient. Thus, standard dose high-resolution or thin-section CT (HRCT) has been introduced as the standard technique in neutropenic patients.

After previous studies describing a limited use of CXR in these patients (Barloon et al. 1991), a prospective study investigated the benefit of HRCT in comparison to CXR in the early detection of pneumonia: 188 febrile neutropenic patients who did not defer after 48 h on empirical antibiotic therapy (Heussel et al. 1999) were included. If CXR was normal at this time, HRCT was done. In approximately 60% of the patients with normal CXR, HRCT demonstrated infiltrates (Fig. 27.4). During the following days, in approximately 50% of the cases (total 30%) the pneumonia seen at HRCT was verified either by microbiology or an infiltrate became visible on CXR. Another 40% had a normal chest X-ray and a normal HRCT when entering the study. In these patients, pneumonia occurred in only 10% during follow-up (Heussel et al. 1999).

Methodological limitations are: (1) a mixed immune-status due to inclusion of patients after conventional chemotherapy or transplantation setting, and (2) the verification of underlying micro-organism, which is either uncertain, or when taking only certain identifications into account, a selection bias resulting (Heussel et al. 1999). Also, the efforts in this trial (broncho–alveolar lavage, interdisciplinary clinical conference required) have limited effect. For the interpretation of microbiological results, super-infection, non-relevant isolates and contamination always have to be considered.

Besides the detection of pneumonia, the exclusion of pneumonia is a relevant information for the referring physician. Therefore the time point of pneumonia verification (by CXR or microbiology) has been evaluated in (Heussel et al. 1999) to assess the negative predictive value of HRCT. In patients with normal HRCT pneumonia verification happened rarely, slowly, and con-

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**Follow-up after HRCT**

**Neutropenia + CXR normal + empir. ABx**

![Fig. 27.4. Number of HRCT demonstrating an infiltrate (shaded) or no infiltrate (white) with normal CXR the same day in neutropenia and empirical antibiotic therapy (ABx). The verification of pneumonia was done either by detection of an infiltrate on CXR or evidence of a relevant micro-organism during follow-up after HRCT. Very few verifications occur after normal HRCT (white), whereas many verifications are done after HRCT demonstrating infiltrate (shaded).**
continuously during the whole follow-up, but never during the first 5 days (Fig. 27.5). In patients with infiltrates at HRCT, pneumonia was verified during the next 5–10 days in most cases (Fig. 27.5) (Heussel et al. 1999).

Thus, HRCT yielded very promising results to be used as a screening technique with good sensitivity (87%) and negative predictive value (88%). The gap to 100% was mainly caused by later occurring pneumonia leading to a false negative result, and minor infiltrates which were only detected at HRCT but, due to early detection and early treatment, did not progress to become visible on CXR. The additional and early use of HRCT achieved a time gain of approximately 5 days during which HRCT was able to exclude pneumonia (Weber et al. 1999). This fact is essential in the management of immuno-deficient hosts (Maschmeyer 2001).

27.4.3 CT Technique

Besides HRCT, which is established as the technique of choice for detailed investigation of the lung parenchyma, multi-detector-row thin-section CT is available for lung imaging. Limitation of thick slices in CT is especially relevant in detection of inflammatory lung disease, especially ground-glass opacification (Remy-Jardin et al. 1993). Therefore, thin-section CT should be performed as a standard (Kauczor et al. 1995). However, the non-contiguous scanning using HRCT involves limitations in nodule detection and quantification. This topic is most relevant in follow-up scans and is solved by usage of contiguous thin-section multi-detector-row CT (MDCT) (Grenier et al. 2002; Flohr et al. 2002; Eibel et al. 2003).

Contrast enhancement is generally unnecessary for detecting and characterising pneumonia (Mcloud and Naidich 1992, Schaefer et al. 2001). Only in special situations, like pulmonary embolism or bleeding, e.g. due to vessel arosion by aspergillosis or mucormycosis, is CT-angiography beneficial (Heussel et al. 1997). In an allogeneous setting, bronchiolitis obliterans has to be considered (Conces 1999; Grenier et al. 2002). Air-trapping is a relevant finding in this respect. Therefore, an additional expiratory CT scan is helpful (Conces 1999; Grenier et al. 2002).

27.4.4 MRI

MRI has been evaluated for the investigation of pulmonary disease since it has a known benefit in lesion characterisation (Leutner et al. 2000; Leutner and Schild 2001). However, there are no studies that demonstrate the benefit of MRI in the early detection of pneumonia, where a high sensitivity is required (Fig. 27.6). In advanced stages, CT and MRI are comparable in the visualisation of infiltrates (Leutner and Schild 2001). But CT is highly available, easier, and faster to perform.
as well as less susceptible to breathing artifacts. MRI is superior to CT in the detection of abscesses due to a clearer detection of central necrosis in T2w images and rim enhancement after contrast application in T1w images (Leutner et al. 2000). However, this fact has limited clinical impact and duration of MRI and required compliance are substantially higher compared to CT.

27.4.5 Standard Recommendation

In contrast to systemic infections, identification of the underlying organism in pneumonia is more difficult and complex. Trials to enforce this identification did not improve the therapeutical outcome significantly (Maschmeyer et al. 1999). Therefore, an empirical therapy in febrile immuno-deficient patients based on imaging results also is widely used.

The use of thin-section MDCT is recommended for early detection of pneumonia (Maschmeyer et al. 1999). The crucial fact is that CT allows for an optimisation for the indication and localisation of invasive diagnostic procedure, e.g. broncho-alveolar lavage (BAL). On the other hand, the exclusion of pneumonia can be obtained with a higher confidence compared to the exclusive use of CXR. The sequential cascade as shown in Fig. 27.7 can be modified if the CT capacity allows for the skipping of CXR.

On the other hand, our own experience demonstrates the known limited success rate of invasive procedures. From 183 BAL specimens derived from 1/2002 until 11/2002, 71 had a positive bacterial/fungal result (39%). Only 9 of the 71 isolates were considered to be relevant for the suspected infection (8%), which results in an efficiency rate of 5% for the whole BAL and microbiological approach.

27.5 Follow-up

The observation of growing infiltrates during haematological reconstitution has been quantified and documented recently (Caillot et al. 2001). Caillot et al. (2001) performed CT at a standard interval in 25 neutropenic patients with proven pulmonary Aspergillosis once a week. They documented the time point of different patterns and evaluated the size of the infiltrate. They frequently found the halo-sign (Fig. 27.8) in their first CT and report a low sensitivity of this well described pattern (68%). During follow-up this pattern disappeared. In contrast, the more specific air-crescent sign

![Fig. 27.6a–d. Fungal pneumonia in HRCT (a), T2w (b), non-enhanced T1w GE MRI (c) and after Gd application performed the same day (d). Lesion contrast is similar in CT and contrast enhanced MRI (Ullmann AU, personal communications)](image)

![Fig. 27.7. Recommendations of the Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Haematology and Oncology (DGHO) (Maschmeyer et al. 1999)](image)
Fig. 27.9. Neutropenic febrile patient who underwent autologous stem-cell transplantation due to non-Hodgkin lymphoma. At day 2 after transplantation, neutropenia and fever occurred. Therefore, antifungal treatment (Amphotericin B) was started. Ill-defined pulmonary nodules were diagnosed at day 7. Haematological reconstitution took place at day 13, simultaneously the nodule size reached its maximum during this course. Under continuously antifungal treatment and nearly normal leukocytes, the halo disappeared slowly, the lesions shrunk and a central cavitation occurred. Finally, the lesions almost disappeared.

Characterization

The radiologists’ dream is to be capable to identify the underlying micro-organism in pneumonia of immunocompromised hosts with a sufficient specificity. In clinical routine, however, one has to wait for the results of microbiological and pathological analysis of samples. This requires several days to be obtained and it will only be feasible in some cases (Davies 1994). Furthermore, the isolated organism is not necessarily the underlying problem: Surface colonisation provides difficulties in the correct interpretation of microbiological results and super-infection with an additional organism takes place in approximately 20% (Maschmeyer et al. 1999; Serra et al. 1985).

In some cases, imaging can give more or less useful clues—instead of verifications—for the underlying disease. The quality of these clues depends on the interdisciplinary co-operation between clinician and radiologist and the radiologists experience with these diseases. This requires an informational exchange concerning relevant patient data like standard neutropenia, allogeneous or autologous transplantation setting. Furthermore, the positivity for viral disease in graft and host is an essential information for correct interpretation of HRCT. Also the applied chemotherapeutical substances or the conditioning regimen need to be discussed (Table 27.3).
There are several differential diagnoses of FUO in immunocompromised hosts, which might appear clinically similar and where HRCT gives valuable hints for the differential diagnosis (Tanaka et al. 2002a, b; Schaefer et al. 2001; Reitnuer et al. 2003). The most useful clues are listed in Table 27.3.

27.6.1
Bacterial Pneumonia

Since bacterial infections are responsible for approximately 90% of infections during the early phase of neutropenia (Einsele et al. 2001) (Tables 27.1 and 27.2, Fig. 27.1), their empirical treatment has been optimised during the last decades.

The radiological appearance of bacterial pneumonia includes consolidation, especially bronchopneumonia, and positive pneumo-bronchogram (Fig. 27.2) (Concues 1998; Reitnuer et al. 2003). In contrast to immunocompetent patients, ground-glass opacification is found more often and remains non-specific.

27.6.2
Fungal Pneumonia

Continuous febrile neutropenia is associated with invasive fungal infection (Przzo et al. 1982). In Europe, Aspergillus species are the main underlying organism. Mucormycosis seems to increase, but besides the “bird’s nest” sign, it is clinically and radiologically similar to aspergillosis. Ante mortem, Candida species are a rare pathogen entailing pneumonia (Fig. 27.10) (Maschmeyer 2001). Most isolates represent contamination due to surface colonisation. To describe typi-

Table 27.3. Clinical and radiological appearance for various infectious and non-infectious lung diseases in neutropenic hosts and after bone-marrow or stem cell transplantation. GGO = ground-glass opacification

| Diagnosis         | Clinical setting                      | Radiological appearance                                      |
|-------------------|---------------------------------------|--------------------------------------------------------------|
| Infection bacterial | Early phase neutropenia               | Consolidation, bronchopneumonia pneumobronchogram, GGO       |
| Fungal            | Long-term neutropenia (>10 days)      | Ill-defined nodules of each size cavitations (late phase)    |
| Pneumocystis      | Allogeneous transplantation           | GGO left out subpleural space intralobular septa (late phase) |
| Mycoplasma pneumoniae | Outpatient                            | Angiotrophic micronodules, tree-in-bud                      |
| Mycobacterium tuberculosis | Each                                  | Small ill-defined nodules/cavitations, tree-in-bud, homogeneous consolidation |
| Viral             | Transplantation history in graft or host | GGO—mosaic pattern                                          |
| Graft vs host     | Allogeneous transplantation           | GGO—mosaic pattern intralobular septa tree-in-bud air-trapping |
| Radiation toxicity | Total body irradiation                | GGO—paramediastinal distribution intralobular septa         |
| Drug toxicity     | Bleomycine, Methotrexate, Cytarabine, Carmustine etc. | GGO—mosaic pattern intralobular septa |
| Pulmonary congestion | Extensive hydration, renal impairment, hypoproteinosis | GGO thickening interlobular septa |
| Leukemic infiltration | Chronic leukemic infiltration         | Thickening bronchovascular bundles, thickening interlobular septa, GGO |
| Pulmonary hemorrhage | Thrombocytopenia, intervention       | GGO—sedimentation phenomenon                                |
cal findings of fungal pneumonia caused by different pathogens, a dedicated review is necessary (Heussel et al. 2000a). This manuscript focuses on the most relevant information for haematological patients. The appearance of pulmonary infiltrates with fungus typical patterns in the:

• Early phase:
  - Ill-defined nodules (Figs. 27.6, 27.8, and 27.10; Reittner et al. 2003) in combination with the
  - Halo sign (Figs. 27.8 and 27.10; Reittner et al. 2003), which is non-specific

• Late phase:
  - Air-crescent-sign (Kim MJ et al. 2001)
  - Cavitations (Fig. 27.10)

For use in the context of clinical and epidemiological research in neutropenic patients, the EORTC and BAMSO have defined standards for the interpretation of radiological findings in invasive fungal infections (Ascioglu et al. 2002): The new occurrence of these “typical” CT patterns (halo sign, air-crescent sign, or cavity within area of consolidation) are classified as a major clinical criterion for fungal pneumonia. Furthermore, if a new infiltrate is observed even without a typical fungal pattern, it is classified as a minor clinical criterion for fungal pneumonia (Ascioglu et al. 2002).

Air-crescent-sign and cavitation occur simultaneously with haematological reconstitution during the late phase of infection (Fig. 27.10) (Kim MJ et al. 2001). Therefore air-crescent and cavitation signs are known

Fig. 27.10. Bilateral ill-defined nodules made the suspected diagnosis of a fungal infection which was treated accordingly. Candida spp. were identified from blood-culture and suspected to be involved with this pneumonia. The small lesions developed into cavitations at haematological reconstitution and decreased. Due to increasing liver enzymes and because of known hepatosplenic candidiasis after candidemia, contrast enhanced CT scan was done. Biopsy from the detected lesions revealed Candida spp. once again

1 Candida pneumonia is a rare condition. Microbiological identification of Candida species in lavages or swabs usually have to be considered as colonization, not as infection.
to have a positive prognosis. However, the specificities of these findings are limited and relevant differential diagnoses have to be considered (Fig. 27.9) (Kim K et al. 2002). The histopathological work-up verified fungal pneumonia only in 56% (Kim K et al. 2002). Relevant differential diagnosis for the halo sign such as bronchiolitis obliterans organising pneumonia, pulmonary haemorrhage, and other infections (CMV, TBC, abscesses (Fig. 27.9), Candida (Fig. 27.10) etc.) have to be considered (Kim K et al. 2002).

There are other useful patterns in the identification of fungal pneumonia: distribution along the bronchovascular bundle resulting in the feeding vessel sign with an angiotropic location.

### 27.6.3 Pneumocystis Jiroveci Pneumonia (PCP)

*Pneumocystis jiroveci* pneumonia (former: *P. carinii*, the abbreviation PCP continues for *Pneumocystis pneumonia*) (Stringer et al. 2002) is not a typical finding in haematological patients except in the late phase after allogeneous transplantation together with chronic GvHD (Einsele et al. 2001). Under the standard Trimethoprim/Sulfamethoxazol prophylaxis, 8% of the patients develop PCP, without prophylaxis even 29% (Einsele et al. 2001). Mortality is 4%–15% in these cases (Einsele et al. 2001).

CT provides a valuable characterisation for this micro-organism (Tanaka et al. 2002a; McLoud and Naidich 1992; Schaefer et al. 2001; Reittner et al. 2003) and is a reliable method for differentiating PCP from other infectious processes (Hidalgo et al. 2003; Reittner et al. 2003). A combination of ground-glass opacities and intralobular septa sparring out the subpleural space (i.e. perihilar distribution) are very typical for PCP (Fig. 27.11) (McGuinness and GruDen 1999; Reittner et al. 2003; Hidalgo et al. 2003; Reittner et al. 2003).

#### 27.6.4 Tuberculosis

Tuberculosis (TBC) has always to be considered as a rare but relevant differential diagnosis. In an immuno-compromised host, TBC appears different compared to immunocompetent hosts (e.g. gangliopulmonary (primary) forms) (Van Dyck et al. 2003). More widespread lymphogenic and hematogenous dissemination can occur and, therefore, the clinical course might be fulminant (Goo and Im 2002; Van Dyck et al. 2003). On the other hand, TBC might mimic or come along with other infections like pulmonary aspergillosis or systemic candidiasis (Goo and Im 2002).

In immuno-compromised hosts a peribronchial distribution (resulting in a “tree-in-bud” sign) of small, sometimes cavitated ill-defined nodules can be obtained due to miliar distribution (Goo and Im 2002; Van Dyck et al. 2003). Gangliopulmonary (primary) forms, however, present with homogenous consolidation and necrotic mediastinal/hilar lymphadenopathy (Van Dyck et al. 2003).

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**Fig. 27.11a–c.** Bilateral pneumonia caused by *Pneumocystis jiroveci* (PCP) at different stages of immunosuppression. The subpleural space is typically left out. Diffuse ground glass opacification appears typically in the early phase of infection (a), while consolidations appear at a fulminant course (b). The predominance of intralobular linear patterns takes place during a later and treated stage of PCP (c).
27.6.5 Viral Pneumonia

Atypical pneumonia in neutropenic patients and especially after haematological reconstitution is frequently caused by virus infection. Viral pneumonia is associated with a mortality of approximately 50% in neutropenic hosts. The most frequent suspected microbe is cytomegalovirus (CMV); furthermore herpes, influenza, parainfluenza, adenovirus, respiratory syncytial (RSV) viruses have to be considered. There are no radiological patterns available to differentiate various forms of viral pneumonia. However, even the information that there is viral pneumonia is very valuable to the clinicians. Appropriate drug regimens are available for many of these viruses. The typical appearance of viral pneumonia in the early stage is ground-glass opacification (Reittner et al. 2003) and mosaic pattern with affected and non-affected secondary lobules lying adjacent to one another (Fig. 27.12).

27.6.6 Non-Infectious Disease

Certain non-infectious diseases have to be considered in hematological patients: graft vs disease (GVHD), radiation or drug toxicity, COP, pulmonary congestion, bleeding, or early tumour recurrence. Fever, dyspnoea or lab findings (C-reactive protein, transaminases) might be caused by some of these diseases and obscure the differentiation from infection. For instance, in GVHD the therapeutic approach to non-infectious caused infiltrates is in contrast to infection: further suppression of the immune system. This differential diagnosis is very helpful for clinicians. CT is able to assist in the detection and characterisation of these diseases (Tanaka et al. 2002a, b; McLoud and Naidich 1992; Schaefer et al. 2001).

27.6.6.1 Graft vs Host Disease

Pulmonary manifestation of chronic GVHD occurs in approximately 10% of patients usually 9 months after allogeneic transplantation (Fig. 27.13) (Leblond et al. 1994). Bronchiolitis obliterans is the pulmonary manifestation of this rejection (Conces 1999). Unfortunately, the radiological appearance is similar to viral pneumonia, and to make things more complicated, clinical appearance and time point for both diseases are often similar (Fig. 27.1).

Ground-glass opacification and mosaic pattern, as in patient A, is caused by cytomegalovirus (CMV), patient B by respiratory syncytial virus (RSV). Note the mosaic pattern which results from affected and non-affected secondary lobules lying adjacent to one another.

Fig. 27.12. Bilateral ground-glass opacification and mosaic pattern in both patients. However, pneumonia in patient A is caused by cytomegalo virus (CMV), patient B by respiratory syncytial virus (RSV).
well as signs of bronchiolitis obliterans such as air-trapping (Conces 1999; Grenier et al. 2002) and bronchus wall thickening occur during the early stage of pulmonary GvHD (Fig. 27.13), whereas intralobular septa and tree-in-bud follow in later stages (Leblond et al. 1994; Tanaka et al. 2002a; Oikonomou and Hansell 2002). An incidence of 5%–25% even after total body irradiation (TBI) is reported, which is applied for conditioning therapy prior to bone-marrow or stem cell transplantation (Monson et al. 1998). One problem in detecting radiation toxicity is the time delay after radiation, which is approximately 3 weeks, but can also occur several months later (Monson et al. 1998; Oikonomou and Hansell 2002).

At CT, it is characterised by ground-glass opacities with transition to consolidations (Fig. 27.14) (Monson et al. 1998; Oikonomou and Hansell 2002). The key finding is the limitation of these patterns to the parenchyma within the radiation field. And even in TBI, lung parenchyma is blocked out, thus, para-mediastinal and apical lung parenchyma suffers mainly from radiation toxicity.

### 27.6.6.2 Radiation Toxicity

An incidence of 5%–25% even after total body irradiation (TBI) is reported, which is applied for conditioning therapy prior to bone-marrow or stem cell transplantation (Monson et al. 1998). One problem in detecting radiation toxicity is the time delay after radiation, which is approximately 3 weeks, but can also occur several months later (Monson et al. 1998; Oikonomou and Hansell 2002).

At CT, it is characterised by ground-glass opacities with transition to consolidations (Fig. 27.14) (Monson et al. 1998; Oikonomou and Hansell 2002). The key finding is the limitation of these patterns to the parenchyma within the radiation field. And even in TBI, lung parenchyma is blocked out, thus, para-mediastinal and apical lung parenchyma suffers mainly from radiation toxicity.

### 27.6.6.3 Drug Toxicity

Especially high-dose chemotherapy protocols are used for conditioning therapy which results in pulmonary drug toxicity. Some of the frequently used agents are Bleomycin, Methotrexate (MTX), Cytarabine (Ara-C), Carmustine (BCNU), and many more (Fig. 27.15) (Erasmus et al. 2002). Radiologists have to suspect treatment with these drugs and should ask for it. (www.pneumotox.com)

The term drug induced pneumonitis includes mainly diffuse alveolar damage, non-specific interstitial
pneumonia (NSIP) and cryptogenic organizing pneumonia (COP, former: bronchiolitis obliterans organizing pneumonia, BOOP) (Erasmus et al. 2002). The CT appearance consists of ground-glass opacities with transition to consolidations, intralobular septa, air-trapping, and possibly the non-specific “crazy-paving” pattern (Oikonomou and Hansell 2002; Erasmus et al. 2002). This is quite similar to radiation toxicity but without being limited to the radiation field.

27.6.6.4 Pulmonary Congestion

Dyspnea and infiltration are frequent in patients suffering from pulmonary congestion. Due to CVC, extensive hydration for renal protection during chemotherapy, frequent temporary renal impairment, hypo-proteinosis, or pulmonary congestion appear even in younger patients. It is one of the most frequent disorders in intensively treated patients.

At CXR, pulmonary congestion might be combined with infiltration. CT demonstrates a thickening of the lymphatic vessels, which corresponds to the well-known Kerley lines (Fig. 27.16).

27.6.6.5 Leukemic Infiltration

Leukemic pulmonary infiltration is a less common clinical finding. Especially the peri-lymphatic pulmonary interstitium is involved (Heyneman et al. 2000). This can be visualised at CT as thickening of the bronchovascular bundles and interlobular septa. Besides this, non-lobular and non-segmental ground-glass opacifications can be seen (Tanaka et al. 2002b). This pattern arrangement might mimic pulmonary congestion (Fig. 27.16).

27.6.6.6 Pulmonary Hemorrhage

In pancytopenia, pulmonary bleeding occurs spontaneously, after interventions (e.g. BAL), or during haematological reconstitution after fungal pneumonia (Heussel et al. 1997).

Pulmonary bleeding might be a focal or diffuse pattern, and the phenomenon of sedimentation within the secondary lobules can sometimes be depicted (Fig. 27.17).
Radiological guided interventions in neutropenic patients suffer mainly from the coincidental thrombocytopenia. Interventions are limited to patients with at least 50,000 platelets/µL ideally with a running substitution during the biopsy.

**27.7.1 Biopsy**

There is great interest in organ specimens for microbiological or pathological investigations. In most cases of fungal pneumonia, BAL fails to detect the fungi. Therefore, this frequent differential diagnosis is a special task for percutaneous intervention. There is no literature available, analysing risk and benefit in this population. Actually, neutropenic patients undergo biopsy rarely. On the other hand, the limited risk of radiological interventions in lungs or liver are known to radiologists:

Risk for pneumothorax requiring therapy is less than 3% (Froelich and Wagner 2001), for bleeding in liver lesions less than 2%. The probability to hit pulmonary nodules under CT guidance is approximately 95% (Froelich and Wagner 2001). Using CT fluoroscopy, investigation time and sensitivity are improved especially in small lesions. Non-culture detection tests on the other hand are becoming widely available (Galactomannan antigen test, Platelia®, Aspergillus-PCR) and reduce the necessity to perform invasive diagnostics procedures.

**27.7.2 Local Drug Instillation**

As mentioned earlier, the response of fungal pneumonia to antifungal drugs is limited. Only when reconstitution of the leukocytes emerges can a substantial response be achieved. Dose escalation has been tested, but costs and adverse effects increase without significant improvement. Several groups have evaluated repeated local instillation of an Amphotericin B preparation into the fungal pneumonia under CT guidance. They had an improved outcome: eight lesions completely resolved, four greatly improved, and one was without change (Veltréi et al. 2000). Since a wide range of new antifungal drugs has become available, a local therapy appears not to be attractive any more.

**27.8 Conclusion**

Imaging in pneumonia has to be indicated depending on the clinical status of the patient starting with no-imaging in simple respiratory infection, going over CXR in CAP and ending in early CT in immunocompromised patients.

Several chest complications occur in patients suffering from neutropenia after bone-marrow or stem-cell transplantation. Due to the clinical risk, CXR in the supine position is not recommended for early detection of pneumonia in these hosts. If pneumonia is suspected, HRCT or thin-section MDCT is suggested to identify the focus of fever or even to exclude pneumonia for some days.

In addition, characterisation of the infiltrate is a relevant topic in thoracic imaging. Therefore, close interdisciplinary co-operation as well as careful image interpretation may deliver rapidly a clear number of valid differential diagnoses.
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