

Received: 2012.05.27
Accepted: 2012.07.19

Radiological spectrum of pulmonary infections in patients post solid organ transplantation

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Summary

Pneumonia remains an important source of morbidity and mortality in transplant recipients. Since clinical findings are nonspecific and cultures may be time-consuming, imaging plays an important role in establishing the probable etiology of pneumonia. Plain films are used as an initial study. However, they have a limited capacity in differentiating the causative factors. HRCT is used as a problem-solving tool in patients with unclear plain film findings and/or no response to treatment. The main advantage of HRCT is a very detailed depiction of the lung parenchyma. Even though HRCT findings are not always specific, there are several signs that are more common in certain types of pneumonia. The aim of the article is to present radiological findings suggestive of a particular causative microorganism and show how they can narrow the differential diagnosis when coupled with clinical data.

Key words: pneumonia • transplantation • imaging

PDF file: <http://www.polradiol.com/fulltxt.php?ICID=883378>

Background

In Poland transplantation of organs is conducted since the end of the 1960-ties and within the last 10 years the number of transplanted organs amounted to approx. 1200 per annum [1]. In 2010 there were 1376 transplantations of organs including 1306 from the dead donors (970 kidneys, 212 livers, 79 hearts, 17 lungs, 20 pancreases, 3 forearms) and 70 organs of living donors (50 kidneys, and 20 liver fragments) [2]. Transplantation means prolongation and improvement of life comfort of the ill with the end-stage renal disease of internal organs. However, the number of patients prone to complications connected with immunosuppressive treatment increases every year. Lungs are one of the most frequent infection locations among patients receiving immunosuppressive treatment [3]. The highest morbidity can be observed among patients after lungs and heart transplantations. Lower morbidity rate relates to the patients after kidney and liver transplantations[3]. Pneumonia among patients with defective immunity constitutes a serious problem as it endangers their life and mortality rate amounts to 4–10% [4,5].

Plain chest X-ray is one of the first additional tests conducted among transplant recipients with infection

symptoms[6]. In case of anomaly noticed on the basis of X-ray, the treatment starts with empiric antibiotics therapy. The symptoms defined according to the X-rays allow the initial recognition of the character of infection changes and at the same time defining of probability regarding occurrence of the etiological factors. The important anomalies include:

- **congested and pulpy lungs** as a result of bronchopneumonia or pneumonia lobaris (bacterial infection),
- **lungs with reticular pattern** indicating infectious interstitial pneumonia (virus or pneumocystis),
- **pleural fluid** (it does not appear in pneumocystis however, frequent in gram-negative bacterial infections),
- **lung cavitation** (gram-negative bacteria, TB, aspergillosis) [6].

The test that finally verifies pneumonia etiology is the microbiological one of the materials collected from the patient. In 76% of cases thanks to this test it is possible to identify the pathogen [7]. The patients after transplantation – apart from sputum and blood tests – undergo bronchoscopy with BALF collection and optional bronchoscope lung's biopsy [7,8]. Unfortunately, the result is obtained after a few weeks [8]. Clinical data that can help in narrowing of the diagnosis are identification of immunosuppressive

Table 1. Influence of immunosuppressive drugs on patients' immunity and susceptibility to different microorganisms.

Immunosuppressive medicines	Type of defective immunity	Type of pathogens
Corticosteroids	Specific and non-specific immunity	Intra- and extracellular
Azathioprine Mycophenolate mophetil	Humoral and cellular	Intra- and extracellular
Calcineurine inhibitors (cyclosporine A, tacrolimus)	Cellular	Intracellular
mTOR inhibitors (sirolimus)	Cellular	Intracellular

medicines and the time which passed since organ transplantation. The basic immunosuppressive medicines are as follows: glucocorticosteroids, cyclosporine A and similar to some extent in mechanism of functioning are: tacrolimus, sirolimus, azathioprine and mofetil mycophenolate [9]. Each of the above mentioned medicines has different mechanism of functioning and as a result, their influence on non-specific immunity and humoral response (against microorganisms, especially bacteria) and viruses, fungi and some bacteria developing intracellularly is varying [9]. Table 1 presents types of immunity defected as a result of the most frequently applied medicines with the pathogen types which develop easily when they are used. The time that passed from transplantation to the first symptoms of pneumonia is relevant as it helps to identify the etiology of infection (Table 2). During the first month after the transplantation, the dominating infections are those of etiology similar to the ones in immunocompetent patients after surgeries in the chest and abdominal cavity area, which is aspiration pneumonia caused by the bacteria present in mouth cavity and bacterial infections [3]. Within 1-6 months virus infections prevail (mainly cytomegalovirus) and fungal (the most frequent etiology: *Aspergillus* and *Pneumocystis*, less frequently: *Cryptococcus*, *Candida*); that time also TB pneumonia may occur [3]. Pneumonia morbidity among patients with transplanted organs decreases after approx. one year from transplantation and etiology is close to those present among patients with normal immunity [3].

Patients with the suspicion of pneumonia and non-specific X-rays imaging of lung pulp and/or lack of response to the standard antibiotic treatment, undergo chest CT [6]. The medical tests protocol should include high definition images which allow detailed evaluation of changes morphology in lungs parenchyma. The CT imaging is not always characteristic however, it is possible to identify some typical symptoms which are recognized in case of specific pathogens. The aim of this article is to present the most typical radiological symptoms which in the relevant clinical context may help in recognition of the specific etiological factor.

Bacterial Infections

Gram-negative bacteria

In patients after liver and kidney transplantation gram-negative bacteria are responsible for 90% and 69% of

Table 2. Etiology of pneumonia depending on the time from transplantation to the onset of infection.

Time from transplantation	Infections etiology among the transplantation recipients
≤1 month	Aspiration pneumonia Gram-negative bacteria
1–6 months	Virus infections (CMV) <i>Aspergillus</i> , <i>Pneumocystis</i> Infections <i>Mycobacterium tuberculosis</i>
≥12 months	As in the overall population (In patients with the regular transplant function)

bacterial pneumonia respectively [5,10]. The group of gram-negative bacteria among others includes: *Pseudomonas*, *Klebsiella*, *Escherichia*, *Acinetobacter* and *Enterobacter*. Diversified radiological pneumonia imaging reflects this group's complexity: starting with well separated nodules to the complex multifocal congestions with air bronchogram. The most frequent in this group is *Pseudomonas aeruginosa* responsible for approx. 60% of infections [5]. The infection with *Pseudomonas* takes place mainly as a result of aspiration in the upper airways and rarely through the blood stream regarding bacteremia. That is why, infection changes have the character of bronchopneumonia [11]. Radiological imaging presents dominating on both sides complex nodules with lower lobes predilection [12]. The changes in the lung parenchyma are very often accompanied by pleural effusion or pleural thickening. With the development of the disease, the nodules conglomerate and form complex lung parenchyma with air bronchogram [12] (Figure 1). In *Pseudomonas* infection abscess in lung parenchyma often occur. They are visible in the chest X-rays and have the form of circle infectious infiltrations with the bright interval meaning destruction of lung tissue [12]. Central bright interval may transform into a cavity with thick walls and liquid inside. Another gram-negative bacteria very often causing pneumonia among transplant recipients is *Klebsiella pneumoniae*. It is responsible for lobe pneumonia similar in symptoms to pneumococcus infection however, in case of *Klebsiella*, the infected lobe has bigger size which results in higher visibility of the interlobe spaces [13] (Figure 2). Abscesses and effusions in the pleural cavity occur more often than in *pneumococcus pneumonia* [13].



Figure 1. Pneumonia with *Pseudomonas aeruginosa* etiology. The high definition CT shows complex consolidated infectious infiltrations in 6 segments of both lungs and in the upper right lobe. Additionally, there are spread nodules congestions with mid-lobule and bronchi distribution and bronchial congestion in the 3rd segment of the left lung.

MTB (*Mycobacterium tuberculosis*)

MTBs are responsible for approx. 2% to 5% of pneumonia cases among patients with lungs and heart transplants and for approx. 20% of pneumonia cases among kidneys' recipients [5,14,15]. The patients undergoing long-term immunosuppression have increased risk of reactivation of diseases they had before. They are also prone to the initial infection. The radiological imaging of TB among patients after transplantation is not characteristic. The spectrum of changes is very wide and includes separate nodules in lung parenchyma, complex nodules, complex lobe parenchyma changes, fibrocavitary changes in the upper parts of lungs, enlargement of lymph glands in mediastinum and effusion in pleural cavity [16] (Figure 3A, B). The only change that statistically more often occurs in lungs' TB than in other bacterial infections is tree-in bud symptom [17] (Figure 3C). It is visible in high definition CT and results from the infectious effusion of bronchial walls. It occurs in active TB and patient's contagiousness. In patients treated with small doses of immunosuppressive medicines, the radiological imaging may be similar to the initial TB of patients with normal immunity so the congestions may appear in the upper and back part of the upper lobe or the upper part of the bottom lobe with the possibility of cavity development [18]. The deeper immunosuppression, the more frequent lobe's parenchyma congestions (caseous pneumonia), miliary changes taking form of small nodules (TB spread through the blood) and enlargement of the lymph glands of mediastinum and spaces in lungs including central necrosis and increased contrast [18] (Figure 3D). Evaluation of the activity regarding TB changes is a frequent clinical question. The changes indicating activity of the disease are parenchyma congestions, tree-in bud symptom, miliary changes and cavities [16]. Linear congestions, calcified nodules and bronchiectasia are inactive modifications [16]

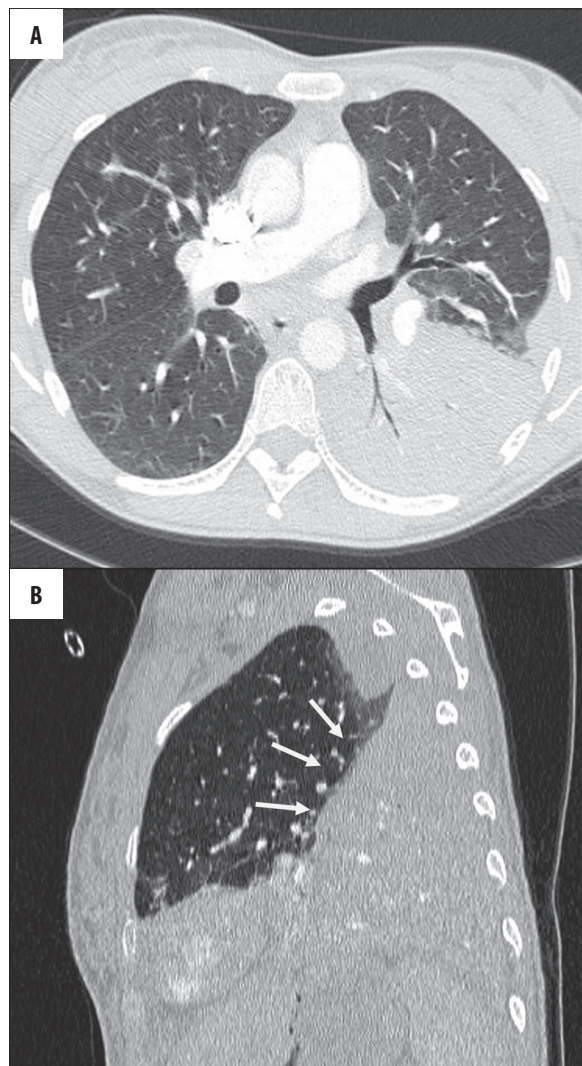


Figure 2. Pneumonia with *Klebsiella pneumoniae* etiology. The high definition CT shows unified parenchyma congestions with air bronchogram located in the bottom lobe of the left lung (A). The sectional view includes (left side) the visible space between lobes (B).

(Table 3). However, the evaluation of the disease's activity should be based on the conducted tests and stated lack of dynamics regarding radiological imaging within 6 months minimum [16].

Virus infections

Cytomegalovirus (CMV)

Cytomegalovirus pneumonia is a frequent complication during the first 6 months after transplantation. Cytomegalovirus is responsible for approx. 56% of lung infections among patients with transplanted lungs and 47% of pneumonia in patients after liver transplantations [10,14]. Pneumonia caused by CMV can occur in approx. 2% of kidneys' recipients [5]. High definition chest CT shows small spread nodule places located in the central part of lobule and the shading areas of 'dim glass' which in case of some patients may develop in the direction of parenchyma

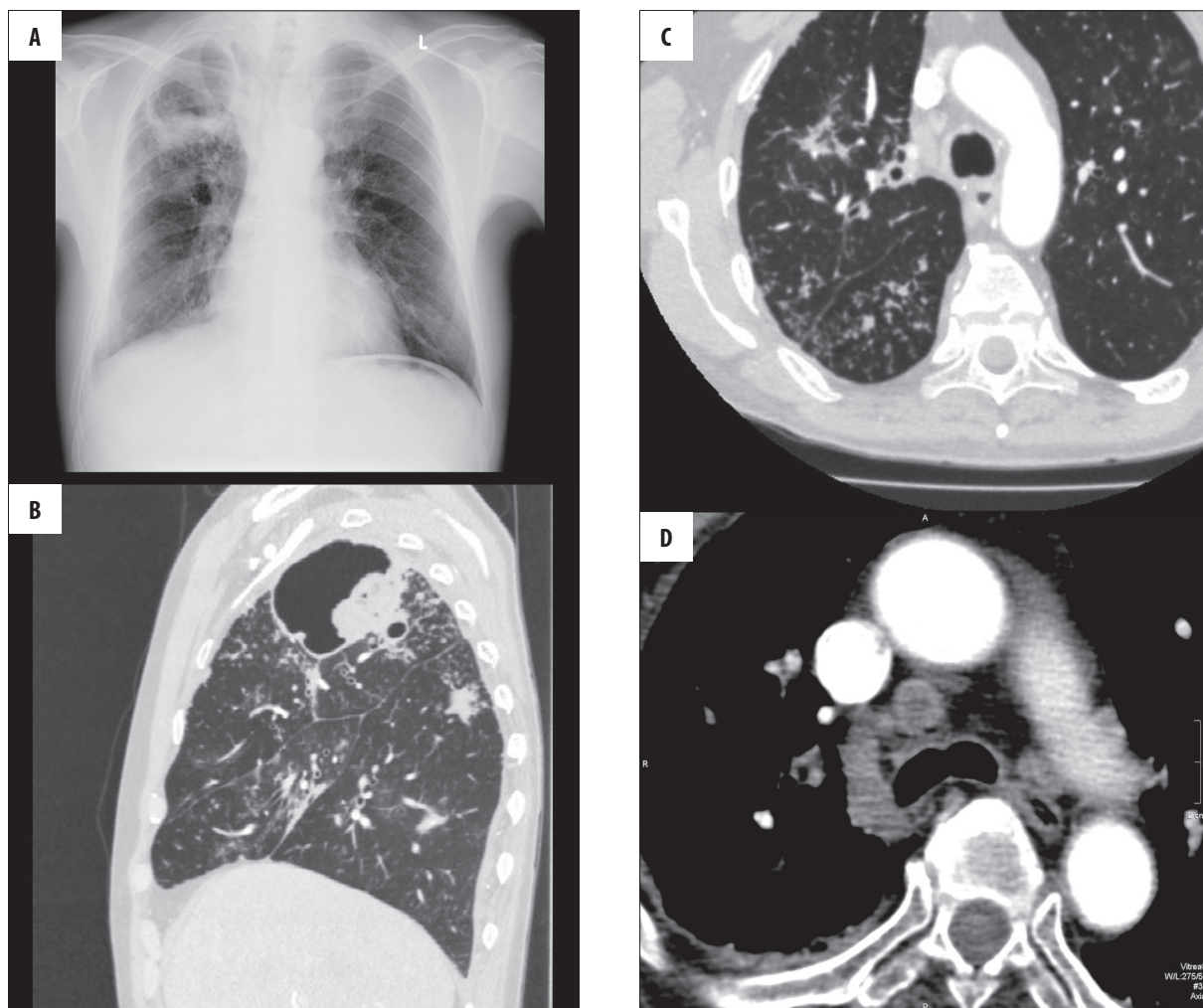


Figure 3. TB pneumonia. The chest imaging P-A shows a cavity with thick walls in the upper part of the right lung with the parenchyma congestions and bronchial thickening in the central and bottom part of the right lung (A). The high definition CT of this patient shows cavity with thick walls including aspergilloma in the upper part of the right lung, there is also thickening of pleura on its level and alveolar congestions in the surrounding parenchyma (B). There are also spread tree-in bud changes in the parenchyma of the right lung (C). CT of another patient shows bottom trachea lymph gland with the central necrosis and contrast in the circuit (D).

Table 3. HRCT features suggesting active vs. inactive tuberculosis.

Active TB	Inactive TB
Congested and pulpy lungs	Congestion lines
Tree-in bud symptom	Calcified lung nodules
TB miliaris changes	Bronchiectasis
Cavities	

congestions [19] (Figure 4). Rather rarely the alveolar congestions constitute initial changes. Thickening of the bronchial walls or a tree-in bud symptom occur rather rarely [19].

Flu virus (Influenzavirus)

Flu virus is a frequent cause of the upper air passages infections among immunocompetent persons. In patients undergoing immunosuppressive treatment it also may cause pneumonia. However, it is not the only

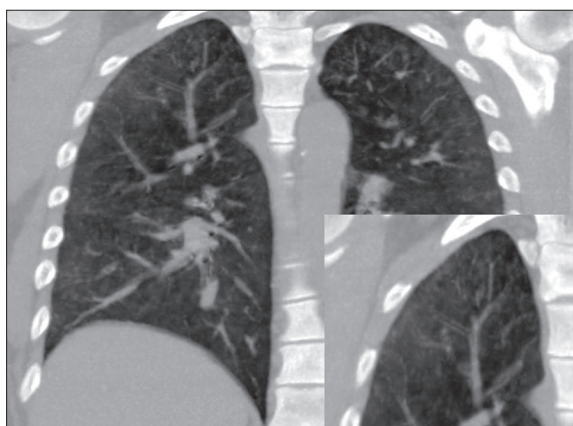


Figure 4. Pneumonia with CMV etiology. The high definition CT shows numerous but not well visible mid-lobule nodules.

pathogen responsible for the lungs infection as very often the etiology is rather mixed. Microorganisms which are most frequently isolated from the patients after lungs

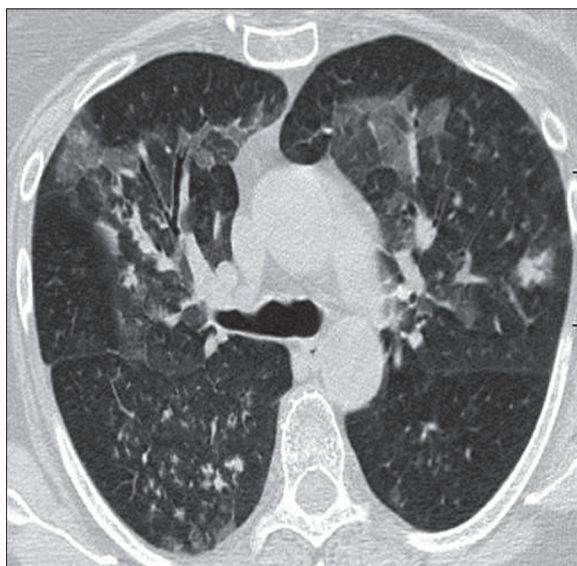


Figure 5. Pneumonia with the mixed etiology: flu and *Pseudomonas aeruginosa*. The high definition CT shows spread areas of the 'dim glass', alveolar congestions and individual nodules forming an image of the tree-in bud.

transplantations together with the flu virus are CMV and *Pseudomonas aeruginosa* [20] (Figure 5). Due to the overlapping of changes caused by different infectious factors in the radiological imaging, it is difficult to define characteristic features of flu pneumonia. In most of the cases with the microbiologically confirmed pneumonia flu etiology, the chest X-rays present spread bilateral parenchyma congestions and small not well separated nodules [21]. High definition chest CTs of these patients present shadings taking form of 'dim glass' with the nodules of 2-9 mm located in the central part of lobule, minor areas of alveolar congestions and a tree-in bud symptom [21] (Figure 5).

Fungal infections

Aspergillus

Aspergillus is isolated in approx. 13% of patients with pulmonary infections after lungs transplantations, 12% after heart transplantations, 9% after kidney transplantations and 3% after liver transplantations [5,10,14,15]. *Aspergillus* in the pulmonary area is responsible for a few diseases which develop depending on the immunological conditions of the patients. In patients with the normal immunity, it can cause saprophytic aspergillosis – aspergilloma or allergic broncho-pulmonary aspergillosis (ABPA) [22]. The patients with minor defects of immunity suffer from necrotic aspergillosis (half-invasive) [22]. Invasive aspergillosis – the form overtaking vessels, bronchi and the lungs parenchyma concerns patients with the serious immunity decrease. The invasive form of aspergillosis with infected bronchi and lungs parenchyma visible in CT includes dominating spread mid-lobule nodules which together with the line shading constitute a tree-in bud image [22]. They are accompanied by the bronchial parenchyma congestions and thickening of bronchial walls. The angi-invasive form concerns only patients with a serious defects of immunity i.e. patients undergoing treatments with the

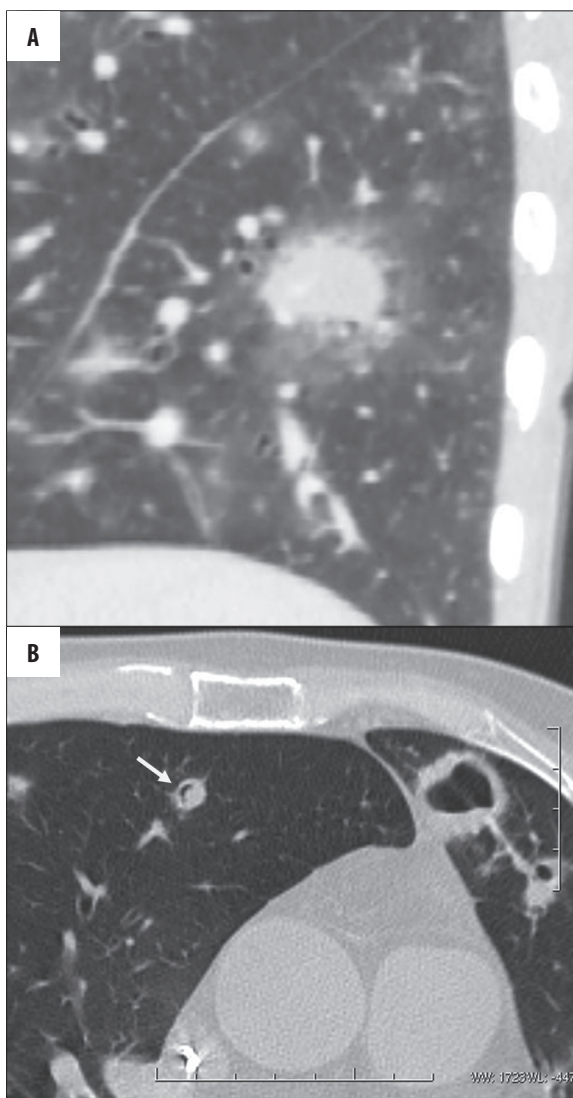


Figure 6. Angio-invasive form of aspergillosis. The high definition CT shows in the bottom left lung parenchyma congestions surrounded by the edging of the 'dim glass' – halo sign (A). The high definition CT of another patient during the period of the clinical improvement showed nodules surrounded by the air edging (B).

high amount of immunosuppressive medicines. The most characteristic change of this form of aspergillosis is halo sign present at the first stage of the disease even in 96% of patients [23] (Figure 6A). This symptom visible in CT reflects blocking of small vessels by fungus and microcollapses in the lungs parenchyma. This symptom also includes nodules and masses surrounded by the 'dim glass' shadings. The nodules present places of collapsing and shadings reflect alveolar bleeding. Although the symptom is also described in other diseases (among others in Wegener's Granulomatosis, shifts of multivessel tumours, lung form of Kaposi tumour or infection of other etiology) in patients with infections resistant to the standard antibiotic therapy, it is considered to constitute the initial stage of angio-invasive aspergillosis [23]. When the patient's immunity improves (decrease of immunosuppressive medicines doses) and implementation of antifungal treatment, the separation

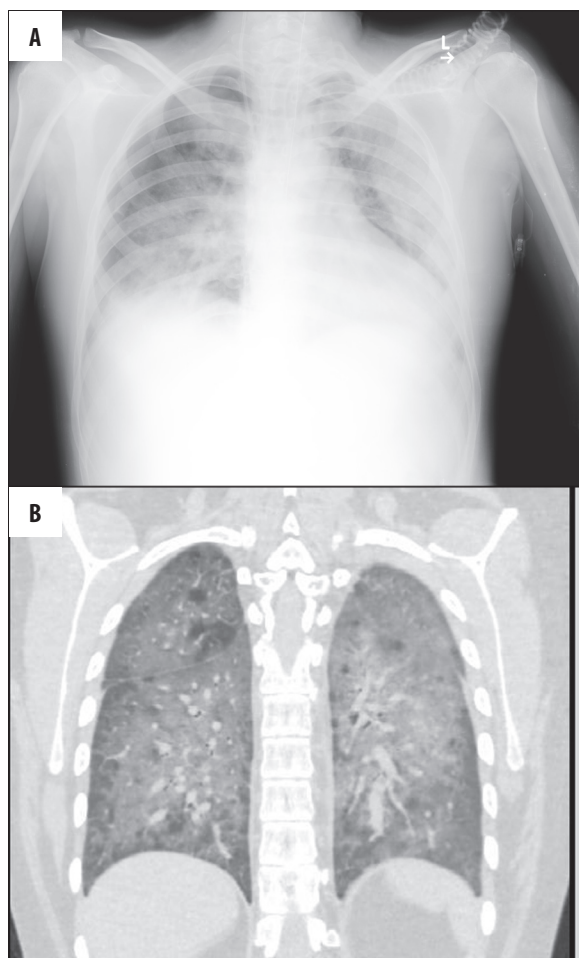


Figure 7. *Pneumocystis pneumonia* (PCP). The chest imaging A-P of the intubated patient presents bilateral linear changes in central parenchyma (A). The high definition CT of this patient shows massive spread ground-glass attenuation located in both lungs and minor cystic changes – pneumatocele – mainly in the upper lobes of both lungs (B).

of necrotic part of the lung from the surrounding parenchyma takes place and in the radiological imaging it is shown as air edging (Figure 6B) [24].

***Pneumocystis jiroveci* (archaic: *carinii*)**

Pneumocystis pneumonia occurs in 13% of patients after lungs transplantation, 6% after liver transplantation and 4% after kidney transplantation [5,10,14]. The chest imaging typically shows in this case bilateral internal linear changes in parenchyma which within a few days undergo development to alveolar congestions [25], (Figure 7A). In 10–39% of patients the chest imaging may be correct and in another 5% the radiological imaging may be different and may include: isolated area of parenchyma congestions (mainly in upper lobes), spread nodules and cystic changes [25]. X-rays of 6% of patients show edema. In the high definition chest CT one can notice dominating bilateral internal shadings so-called ‘dim glass’ (present in 90% of patients [25]. 33% of patients have visible cystic changes in lung parenchyma, predilections to the upper lung lobes (Figure 7B). Cystic changes with thin or thick walls have tendency

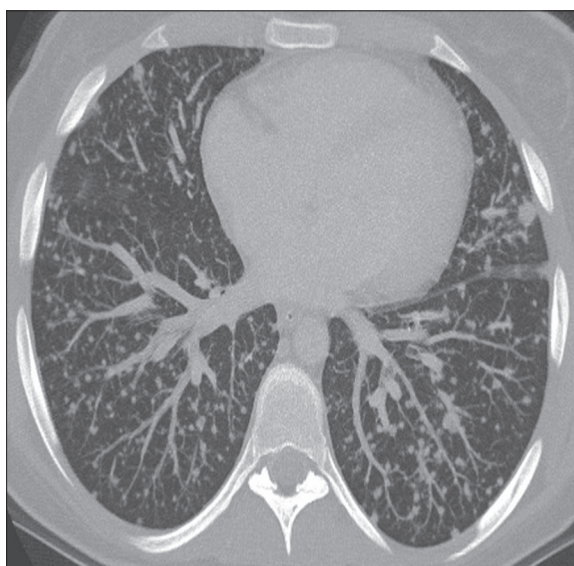


Figure 8. Pulmonary candidiasis pneumonia. The high definition CT shows numerous minor, well-separated nodules in both lower lung lobes.

Table 4. Radiologic manifestation of bacterial and viral pneumonia in HRCT.

Etiology	Changes in HRCT
<i>Pseudomonas aeruginosa</i>	Nodules in the lower lung lobes, abscesses
<i>Klebsiella pneumoniae</i>	Lobes congestions with air bronchogram, increased size of the infected lobe, visible inter-lobe spaces
<i>Mycobacterium tuberculosis</i>	Tree-in bud symptom Changed imaging: from fibro-cavitary changes in the upper parts of the lung to lobes congestions and miliary changes
CMV	Nodules and ‘dim glass’ areas
Flu virus	Nodules, ‘dim glass’ areas, tree-in bud symptom

to consolidating and if their location is underpleural, they constitute a risk of edema [25]. Edema fluid and enlargement of the mediastinum lymph glands occur very rarely in case of pneumocystic pneumonia and should suggest other disease recognitions

Candida albicans

Candida albicans is another blastomyces responsible for pneumonia in patients undergoing immunosuppression. It is most frequently isolated in patients after lungs transplantation, as it colonizes necrotic areas of lungs parenchyma [26]. The changes visible in the chest imaging are non-specific and include segmental or lobe parenchyma congestions [26]. The high definition chest CT shows in

Table 5. Radiologic manifestations of fungal pneumonia in HRCT.

Etiology	Changes in HRCT
Aspergillosis with changes in bronchi and lung parenchyma	Tree-in bud symptom, parenchyma and bronchit congestion, thickening of bronchial walls
Angio-invasive aspergillosis	Halo sign, air edging
<i>Pneumocystis jiroveci</i>	'Dim glass' areas, cystic changes
<i>Candida albicans</i>	Nodules in the lower lung lobes, parenchyma congestions, areas of the 'dim glass'

most of the cases bilateral, well separated nodules mainly in the lower lung lobes [26] [Figure 8]. They may also be

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accompanied by other changes: mainly parenchyma congestions and shadings, less frequent are tree-in bud symptom and thickening of bronchial walls [26]. Rarely in the cases of lungs *cadidiasis* halo sign or nodules occur.

Conclusions

The Tables 4 and 5 present changes visible in high definition chest CT of the patients with pneumonia after transplantations. Unfortunately, only in some cases the radiological imaging is so characteristic that it suggests etiology of the lungs infection – it mainly concerns changes in *Pneumocystis jiroveci* infections and angio-invasive aspergillosis. The changes observed in pneumonia cases with different etiology are less characteristic however, together with clinical data regarding medical treatment and the time of infection occurrence they may constitute basis for implementation of more specific treatment while waiting for the inoculation results.