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Pulmonary Infections in Immunocompromised Hosts: Clinical

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INTRODUCTION

The immune system is specialized in preventing, containing and eradicating invasive microorganisms and internal threats (e.g. neoplasia). It is composed of an intricate network of proteins, cells and organs and failure at any level can result in increased susceptibility to infections. The immune system is commonly divided into the innate and the adaptive components¹.

The innate immune system is very well preserved and highly effective. Because it does not need to be “trained”, it is the first line of defense against most pathogens. Its components can be illustrated using the respiratory system and include barrier/mechanical components (e.g. laryngeal reflexes, the mucociliary escalator, mucosal tight junctions); molecular components which recognize highly preserved microbial products such as toll like receptors, the complement, antimicrobial peptides; the cells of the phagocytic system, including neutrophils and macrophages, basophils, NK-Cells, eosinophils and others which can in turn secrete cytokines that help promote the adaptive immune response^{1,2}.

The adaptive system is characterized by plasticity, specificity and memory. It has humoral and cellular components comprised of the B- and T-lymphocytes. It recognizes antigens via T cell receptors or antibodies produced by the B cells. When presented in the right environment along with co-stimulatory molecules they can trigger an adaptive immune response³. During their maturation lymphocytes that recognize self-antigens undergo apoptosis, and lymphocytes that recognize foreign antigens, including microorganisms, are preserved.

Failure at each level can result in infectious complications. These states of increased susceptibility to infections are known as immune deficiencies which can be primary, if present at birth, or secondary if they appear later in life, for example after chemotherapy⁴. : Given the complexity of the innate and adaptive immune response, a comprehensive review

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of all potential immune derangements is beyond the scope of this review. In what follows, we will focus on the opportunistic infections in the lung including their radiographic and clinical presentation, as well as differential diagnosis.

We will review specific aspects of the following groups of patients: solid and hematological malignancies including hematopoietic stem cell transplantation recipients (HSCT), solid organ transplants (SOT) and patients with HIV infection and autoimmune conditions requiring immunosuppressing medications.

Common features of pulmonary infections in secondarily immunocompromised patients

As a general rule one must consider the following aspects that will shape the clinical presentation and guide the clinician towards a diagnosis: the underlying disease (e.g. acute myelogenous leukemia or pre-transplant diagnosis of cystic fibrosis), previous therapies (e.g. the type and dose of chemotherapy will determine the duration of leukopenia), risk factors for certain infections like geographical location (e.g travel to areas where endemic fungal infections are prevalent) and seasonality (e.g during the winter months when influenza infections are increased). In organ transplantation, the cause of death of the donor as well as presence of infectious complications in organ recipients from the same donor are part of the evaluation process. All this information must be considered against the possibility of pulmonary toxicities of chemotherapeutic drugs, pulmonary complications as a consequence of the underlying disease and also mechanical complications (e.g. pulmonary vein stenosis, as in the case of lung transplantation)⁵⁻⁷.

Presentation and diagnostic tests

The typical signs and symptoms of infection will frequently be absent in immunosuppressed (IS) patients⁸. Dyspnea, hypoxemia, cough, wheezing, hemoptysis and fever can all be present at diagnosis but their role differentiating one type of infection versus another has not been thoroughly studied. Chest pain when present suggests pleural involvement by complicated pleural effusions or extra-pulmonary tissue invasion by the infectious pathogen such as invasive mold infections. When present they usually signal advanced disease and poor prognosis^{8,9}. Symptoms of upper respiratory tract infection can precede both viral and bacterial pneumonias. Many infections in this group of patients can be disseminated upon presentation and list non-specific complaints like weight loss, fever, fatigue.

Because the symptoms are non-specific and frequently absent, a sizeable number of patients will present with abnormalities in screening radiological studies or during surveillance bronchoscopies as in the case of lung transplant recipients. This surveillance is transplant-specific and occurs in the post-transplantation period. Conversely early imaging with computed tomography (CT) in symptomatic patients, even in the absence of chest radiograph abnormalities often proves helpful¹⁰ (see paper by Tanaka et al).

Although in order to decrease mortality¹¹ empirical treatment targeting the most likely infections should be started immediately, most clinicians agree that the toxicities associated with the treatment of common pulmonary pathogens (e.g. amphotericin, ganciclovir, trimethoprim-sulfamethoxazole) and the high mortality associated with misdiagnosis warrants pursuing a specific microbiological diagnosis. Although tissue samples are ideal,

these are invasive and at times cannot be performed due to the prohibitive coagulopathies that frequently accompany neutropenia. Treatment is then based on the clinical presentation and associated non-invasive testing.

Among non-invasive tests used in IS patients, the galactomannan antigen has gained a lot of merit as a biomarker of invasive aspergillosis. It can be measured in plasma and broncho-alveolar lavage (BAL) fluid via commercially available sandwich enzyme-linked immunosorbent assays. A result of an optical density index of > 0.5 ng/ml in plasma or BAL is considered a positive result. The average sensitivity of 82% (73% to 90%) can be increased to 93% if the test cutoff is raised at the cost of lowering specificity levels from 81% (72% to 90%) to 61%¹². Galactomannan performs better in patients with an absolute neutrophil count (ANC) < 100 cells/mm³. As the ANC increases above this level a negative test in plasma does not rule out infection¹³. False positives have been reported in patients receiving Piperacillin and Amoxicillin. BAL measurements outperform plasma in non-neutropenic patients¹⁴.

1–3 beta-D-Glucan is another cell wall component of most fungi and for this reason it does not provide a specific diagnosis. It is negative in infections secondary to *Cryptococcus* and the *Mucorales spp.* False positives are reported in patients receiving blood products, including albumin and immunoglobulins, and in patients on dialysis. When used in a syndrome driven approach the sensitivity and specificity are 64% and 84%¹⁵ when a plasma level 80pg/mL is used as the diagnostic threshold. The reproducibility of the test in BAL has been questioned by some authors¹⁶.

Other diagnostic test exists for mold and fungal infections and these include polymerase chain reaction and monoclonal antibodies. They can both be engineered to detect one or multiple mold species. Monoclonal antibodies are available as bedside rapid diagnostic tests¹⁷. Their role in different groups of patients (e.g. neutropenic vs. non-neutropenic) is not well established and they are not part of the European Organization for Research and Treatment of Cancer (EORTC) criteria for the diagnostic of invasive mold infections (IMI) in neutropenic patients¹⁸.

The biomarker procalcitonin is widely used in the diagnosis of community acquired pneumonia. In healthy non-infected individuals, it is only found in thyroid C cells where it is cleaved into calcitonin and participates in calcium homeostasis. Extra thyroidal production and release into plasma occurs in inflammatory states as a result of stimulation by endotoxin and Interleukins (IL) 1 and 6 among others. Interferon-gamma produced during viral infections inhibits its production. Therefore, an elevated plasma level suggests that a pneumonia is of bacterial rather than viral etiology. Its use in patients suspected of having hospital acquired pneumonia or ventilator associated pneumonia is however discouraged by the most recent IDSA guidelines¹⁹, limiting its usefulness in the early post-transplant period. In SOT recipients in a chronic stable state it was found to be useful at differentiating bacterial infections from transplant rejection²⁰. Procalcitonin has a delayed peak in bacterial and fungal infections in neutropenic fever usually after 2 days in bacterial and beyond 3 days in fungal infections, thus it is not useful at the onset of fever²¹.

Free circulating DNA is released into plasma of healthy and diseased individuals. Elevated levels of donor derived DNA in SOT and of recipient DNA in HSCT can help diagnose rejection and graft versus host disease (GVHD) without invasive diagnostic testing²². Since 2005 a commercial kit has been available for the diagnosis of rejection in heart transplant recipients²². Its major draw-back at the present time is its inability to differentiate transplant rejection from infection.

In the next pages, we will review the most common pulmonary infections in IS patients.

Neutropenia

Neutrophils are part of the innate immune system and are a subset of the white blood cells (WBC), accounting for 40% to 70% of total WBCs. Absolute neutrophil counts (ANC) below 1500 cells/ μ L are termed neutropenia and the susceptibility to infections raises continuously with the highest risk in patients with an ANC < 500 cells/ μ L (severe neutropenia). Nevertheless, most infectious complications develop at an ANC < 100 cells/ μ L. Although neutropenia can be seen as a result of multiple processes (e.g. ethnic, congenital, infectious, autoimmune) we will focus on neutropenia in recipients of HSCT, after chemotherapy for solid organ cancers and in SOT recipients.

Neutropenia in Hematologic Malignancies and Hematopoietic Stem Cell Transplant Recipients—Of all neutropenic patients, the group at the highest risk of infections is represented by patients with hematologic malignancies and the HSCT recipients. Currently over 19000 and 50000 HSCT procedures are performed annually in the United States and around the world (respectively) to treat from congenital disorders to cancer²³. Multiple myeloma, non-Hodgkin lymphomas and acute myelogenous leukemia are the most common indications accounting 70% of all HSCTs²³. During a HSCT procedure hematopoietic stem cells (HSC) are harvested from the patient (autologous) or from another person (allogeneic from a related or unrelated donor) either from peripheral blood, the bone marrow or the umbilical cord blood. Balancing the risk of GVHD – a condition where the donor immune system rejects the body of the recipient- and graft versus tumor activity – ability of the donor HSC to recognize tumor neo-antigens working as immunotherapy-, HSC are manipulated to include higher or lower proportions of T-cell precursors²⁴.

HSCs can differentiate into all mature blood cell lineages and are infused after a recipient has received a conditioning regimen that includes more or less potent chemotherapy +/- total body irradiation depending on the underlying disorder. The goals of conditioning regimens are to treat the underlying disease, produce a general state of immune suppression to aid graft implantation and provide physical space in the marrow for the donor HSC. The last decade has seen an evolution in conditioning regimens that has resulted in less toxicities and the ability to transplant older patients with more comorbidities²⁵. Finally, in the post HSCT period patients may require central lines, parenteral nutrition, frequent blood transfusions and more or less intense immune suppression and infection prophylaxis.

All these factors, recipient, underlying disease, conditioning regimen, source of transplant and manipulation and post-transplant therapies and complications, along with the local

epidemiology of the center providing care, generate a complex picture that shape the risk for infectious pulmonary complications in HSCT recipients²⁶ (Figure 1).

Risk of infection is highest once the ANC has dropped < 500 cells/ μ L and increases with the duration of neutropenia with > 7days defining high risk for infection²⁷. This high-risk state continues until hematological reconstitution which, depending on the type of transplant, can fluctuate from 30 days in allogenic unrelated HSCT to 5–7 days in reduced intensity autologous transplants^{28,29}. In patients with acute GVHD the period of neutropenia can be even longer. To make things worse this period of profound neutropenia coincides with mucositis technically abolishing the “front line” of the immune system.

The incidence of infectious pneumonias ranges between 15–25%^{30,31}. The pulmonary infectious processes that need to be differentiated during this period are bacterial, fungal and viral including CMV. Non-infectious etiologies such as engraftment syndrome, pulmonary edema and acute GVHD all need to be considered in the differential diagnosis.

Bacterial infections after HSCT are breakthrough infections by pathogens that are not covered by the prophylactic antibiotic regimen³². In cohorts from the 1980's the predominant group of bacteria was gram negative rods (GNR), then with the introduction of antibiotic prophylaxis and increase in the use of central lines gram positive cocci (GPC) became predominant. In the latest transplant era, predominance has shifted once again towards GNRs, now antibiotic resistant²⁶. A highlight of recent multicenter surveys and cohort studies is that local incidence of different bacterial strains is highly variable. In the European Conference on Infections in Leukemia (ECIL) 4 survey, the ratio of GPC:GNR was 55%:45% with a range of 30%:70% to 85%:15% while rates of bacterial resistance were also highly variable between centers and geographical regions²⁶. This heterogeneity highlights the importance of developing local epidemiological knowledge.

Invasive mold infections are associated with a 1 year mortality as high as 75%^{33,34}. The port of entry for most molds is the respiratory tract after inhalation of spores. Of all fungal infections – including fungemia- in HSCT, *Aspergillus spp* was responsible for 49.5% of the episodes in the latest Prospective Antifungal Therapy Alliance (PATH alliance) update while *Candida spp* and other molds accounting for the reminder of the infections³⁴. The incidence of fungal pneumonias is also higher than that of bacterial pneumonias in some series. Given their incidence and mortality it is not surprising that the great majority of HSCT recipients except for those in whom the duration of neutropenia is expected to be < 14 days will be on preemptive or mold prophylactic regimens. A common preemptive strategy consists of measuring galactomannan levels twice weekly and to initiate treatment if the levels increase beyond a preset threshold or if molds are detected in any diagnostic specimen. Posaconazole is a broad spectrum triazole active against *Candida spp* as well as molds³⁵. It has a low rate of breakthrough infections and was superior to fluconazole and itraconazole in RCTs³⁶. It is currently available in delayed release formulations and as an intravenous solution which make it an ideal option for prophylaxis even in patients with severe mucositis. The other triazoles, voriconazole, itraconazole and isavuconazole are alternatives. For all of them to be effective minimal therapeutic blood levels need to be achieved and their measurement can also help guide diagnosis. The use of Amphotericin use as a prophylactic regimen is limited

by its toxicity, however some centers have used nebulized preparations as fungal prophylaxis. When mold infections occur while on prophylaxis they are more frequently caused by resistant molds – e.g. *zygomycetes*, *Scedosporidium* and *Aspergillus niger* if on voriconazole prophylaxis³⁷. Overall the use of prophylactic strategies has delayed the presentation of invasive fungal infections, with *Aspergillus spp* becoming the predominant pathogen over *Candida spp*.

Historically, human Cytomegalovirus (CMV) contributed to a significant proportion of deaths in HSCT recipients before the availability of effective antiviral treatment³⁸. The development of ganciclovir in 1989 and of quantitative PCR and antigenemia resulted in a rapid decline in CMV disease and its most deadly complication, pneumonia, with current incidences in RCTs of < 5%³⁹. Both, CMV disease and val- or ganciclovir can cause neutropenia and this represents a limiting factor for their use as prophylaxis prior to engraftment. Therefore, most centers opt for a preemptive strategy consisting of quantitative PCR or antigenemia monitoring with initiation of treatment once viremia surpasses a preset threshold³⁹. In patients presenting with rising CMV-PCR titers and diffuse interstitial infiltrates the diagnosis of CMV pneumonia should be strongly suspected. The incidence of CMV disease has decreased to such extent that in the latest RCT to test the efficacy of Letermovir, a new anti-CMV compound, the outcome was modified from CMV disease to the more prevalent diagnosis of clinically significant CMV viremia – viremia above the preemptive treatment threshold⁴⁰. As this new antiviral does not cause neutropenia its approval holds promise for its use prophylactically, particularly as the focus is now changing to preventing the long-term complications associated with CMV infection. Another clinically relevant characteristic of CMV infections is the frequent coinfection with bacterial and fungal pathogens thus an aggressive diagnostic workup is always warranted⁴¹.

Community acquired respiratory viruses including adenoviruses, influenza, parainfluenza and respiratory syncytial virus can also cause disease early after transplantation⁴², however their incidence before engraftment is low as most patients are still admitted to the hospital. Infections in HSCT recipients follow the same seasonal trends as in the community. HSCT recipients are more likely to suffer severe lower respiratory tract infections, late airflow obstruction and polymicrobial infections with molds and bacteria^{43–45}.

For all fungal and viral infections reduced intensity bone marrow transplants have a later onset of disease⁴⁶. The use of reduced intensity regimens preserves part of the immune system of the recipient while allowing engraftment. The preserved recipient immune cells provide temporary protection against molds, bacteria and viruses that wanes over time and after 100 days the incidence of infections tracks that of myeloablative HSCT⁴².

Finally the differential diagnosis of pulmonary infections in HSCT should always include the possibility of non-infectious complications, the most common being chemotherapy side effects, radiation⁷ and the engraftment syndrome (ES)⁴⁷. ES affects anywhere from 10 to 20% of HSCT recipients and coincides with improvements in the ANC. It is generally described in autologous SCT but can happen in allogeneic transplantation where the differentiation from acute GVHD is difficult. Patients develop skin rash, non-cardiogenic

pulmonary edema and fever and as opposed to the infectious complications it can respond to treatment with corticosteroids⁴⁸ making the differentiation with infection essential.

Neutropenia in Solid organ malignancies—Unlike hematologic malignancies, most episodes of neutropenia in solid cancers are usually the result of bone marrow infiltration, chemotherapy or multisite radiation therapy and are considered low risk for infectious complications. The neutropenia is usually short lived therefore the risk for infections caused by fungi like *Candida* and *Aspergillus spp* is considerably lower. Other factors to consider, which may increase risk, include the disruption of the mucocutaneous barrier and newer immunomodulating therapies (please see below). Comorbidities like COPD play a very relevant role in both increasing the predisposition to infection (including the risk for mold infections) and decreasing the likelihood of survival.

The location of the tumor can also promote infection. Lung malignancies either primary or metastatic can be associated with postobstructive pneumonias (20–30% of lung cancers) resulting in, polymicrobial infections. These can evolve into lung abscesses and empyemas. Evolution over time and acuity of symptoms usually define the diagnosis.

Radiologic findings can identify airway obstruction but the definitive diagnosis is made via bronchoscopy and sometimes transbronchial biopsies. There is a limited role for cultures except for ruling out resistant microbes like methicillin resistant *Staphylococcus aureus*, extended spectrum betalacmase enterobacteriaceae and *P. aeruginosa* as most of these infections will require prolonged broad antibiotics.

The dose and duration of corticosteroids also influences the risk of infection especially in central nervous system malignancies without *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis. PJP occurs in <2% of the solid tumor patients (non-Human Immune Deficiency Virus) when the prednisone dose or its equivalent is higher than 15mg per day for more than 4 weeks. Given the low incidence in these patients, the positive predictive value of staining methods usually used to diagnose PJP on induced sputum is low and the chosen path usually involves high resolution CT imaging with 1,3 β D glucan with broncho-alveolar lavage plus PCR based assays or PCP stains. High dose prednisone use can also lead to pulmonary infections caused by *Nocardia*, *Aspergillus spp* and endemic fungi.

Patients with head and neck cancers undergo surgeries and radiation therapies that leave them with an impaired swallowing mechanism rendering them susceptible to aspiration pneumonias/pneumonitis. In general, procalcitonin may be an useful tool in delineating infectious etiology especially in pneumonias (see above). It can also help shorten duration of antibiotics when it falls below the laboratory's threshold or by more than 80%. Radiation pneumonitis/radiation induced lung injury and drug induced lung injury will also be included in the differential diagnosis of infectious etiologies. Symptoms like dry cough, low grade fever, shortness of breath and pleuritic chest pain mimic those of typical pneumonia. CT imaging remains the test of choice and ruling out infectious etiologies. Sometimes, serum biomarkers like SL-6 (expressed on bronchial cells and type II pneumocytes) and surfactant protein –D may be employed in detecting patients at high risk for radiation complications.

In general since less long term neutropenia is encountered in solid organ cancers, the most likely infectious complications remain those caused by the presence of malignancy (i.e. postobstructive and aspiration pneumonia) along with common bacterial and viral infections (*Streptococcus pneumoniae*, Legionella, influenza) and infections caused by prolonged use of corticosteroids (PJP, Nocardia etc)

Neutropenia in Solid Organ Transplants

Similar to HSCT recipients, the early postoperative period after SOT is a phase of particular susceptibility to pulmonary complications including pulmonary infections⁴⁹. Although neutropenia may occur, it is not a classical feature after SOT. While patients after SOT are not frankly neutropenic, treatments can result in dysfunctional neutrophils and predispose them to opportunistic infections seen in neutropenic patients.

The lung is the primary site of infectious complications in heart and/or lung organ transplant recipients. In liver, kidney and small bowel recipients the abdomen is most commonly affected by infection, followed by the lungs. By the time of transplantation both the donor and recipient have been exposed to the hospital environment and bacterial pneumonia is usually secondary to resistant GNRs and MRSA. The incidence has declined with the use of infection prophylaxis and it now affects < 5% of kidney, < 10% of liver and cardiac and <20% of lung transplants recipients^{50–52}. Despite the use of trimethoprim- sulfamethoxazole prophylaxis, there is still a risk of breakthrough infections with *Nocardia spp*. Most will still respond to therapeutic doses. In large volume centers *Nocardia spp* libraries with antibiotic susceptibilities can be generated and drug resistance presumed based on sub-species identification usually done with 16s RNA sequencing⁵³.

Invasive mold infections (IMI) are more common in lung transplant and small bowel recipients³⁴. *Aspergillus spp* remains the most common etiology. However, with the use of prophylactic antifungals the proportion of non-*Aspergillus* molds is increasing similar to breakthrough bacterial infections³⁷. Neutropenia is not a feature in SOT recipients that develop IMIs, similarly the classical radiological findings described in neutropenia are often missing⁸. Mold species exhibit different antifungal sensitivities and a specific diagnosis should be obtained whenever possible to help guide treatment. Liver transplant recipients appear to have a disproportionate rate of infections with *Mucorales spp* thought to be secondary to the iron overload of the cirrhotic liver.

In addition to pneumonia lung transplant recipients are also susceptible to airway anastomotic infections⁵⁴. Local ischemia and mechanical disruption of the mucosa with impaired clearance of secretions have been implicated. Epidemiologic reports of anastomotic infections are scarce, both bacterial and fungal pathogens being reported. In patients infected with *Aspergillus spp*, anywhere between 16% and 58% of the cases are confined to the airway^{8,9}. Many other molds, including, the *Mucorales spp*, *Scedosporium* and endemic fungi like *Coccidioides spp* have been reported in mono-microbial and poly-microbial infections. Anastomotic dehiscence, obstruction and metastatic distal infection should be evaluated with imaging and bronchoscopy⁸.

The immunosuppressive regimen plays a determining role in the risk of infections and in the differential diagnosis. In SOT the IS is generally divided into 3 periods, induction, maintenance and in some patients, rescue therapies for acute and chronic rejection^{55,56}. Induction and rescue regimens have higher intensity and include higher doses of standard maintenance drugs plus specialized induction agents and are associated subsequently associated with higher rates of infectious complications. Currently interleukin-2 receptor antagonists (IL2R) are the most popular class of induction agents while anti CD52 antibody (Alemtuzumab) and polyclonal anti-thymoglobulin (ATG) are used less frequently⁵⁷.

IL2R inhibitors are chimeric murine-human antibodies and compared to regimens without specialized induction agents (e.g. high dose steroids only) are not associated with increased risk of bacterial, fungal or viral infections⁵⁸. The risk of CMV increases only in patients receiving IL2R inhibitors in combination with a second induction agent.

ATG is obtained from horses or rabbits immunized with thymocytes or T cell lines. These xeno proteins of ATG can be associated with fever, serum sickness and pulmonary edema⁵⁹. ATG increases the risk of CMV disease but this risk can be overcome by the use of appropriate CMV-prophylaxis⁶⁰. This agent also increases the risk of Epstein Barr Virus related post-transplant lympho-proliferative disease (PTLD)⁶¹. Early PTLD will most frequently affect the transplanted organ, and accordingly, pulmonary PTLD is more frequently seen in lung transplant recipients. ATG has been associated with falsely positive Histoplasma antigen tests.

Alemtuzumab results in pan T cell depletion. It is associated with lower rates of early bacterial infections when compared to other induction regimens⁶². Infections with *Mycobacterial spp* disease and *Nocardia spp* have been reported mostly after the use of Alemtuzumab for the treatment of acute rejection and not during induction.

Belatacept belongs to a new class of induction agents targeting the co-stimulatory pathway of CTLA4 and CD28 that is necessary along with antigen recognition by T cell receptors for activation of the immune response. It has been used mostly in renal transplantation in an attempt to avoid the need for long term maintenance with calcineurin inhibitors which are associated with chronic renal failure. When comparing the two regimens – Belatacept without calcineurin inhibitor vs. classic IS with a calcineurin inhibitor containing regimen- Belatacept has higher rates of acute rejection but overall it may increase renal graft survival⁶³. Experience is still accumulating and reports of infections are few but late onset PJP, *Aspergillus fumigatus*, histoplasma and *Cryptococcus* have been reported and are consistent with a defect in cell mediated immunity. Its mechanism of action is opposite to that of checkpoint inhibitors and PTLD has also already been reported. The increased rates of rejection will probably prevent its use in thoracic transplant recipients.

Long term IS most frequently consists of combinations of 3 drug classes, cell cycle inhibitors (mycophenolate, azathioprine), calcineurin inhibitors (tacrolimus and cyclosporine) and prednisone. Mammalian target of rapamycin inhibitors (mTOR), (sirolimus and everolimus) can also be used in chronic IS but are more frequently introduced once chronic rejection occurs. Mycophenolate mofetil increases the risk of bacterial, fungal

and viral infections in general including CMV but decreases the risk of PJP. Tacrolimus is reported to have antifungal properties and is synergistic in vitro when used along with azoles against resistant *Candida spp.* Overall these findings are mostly of anecdotal importance and the risk of a particular infection will depend on the “net level of IS” and the above-mentioned factors. In terms of pulmonary drug toxicities mTOR inhibitors are the most problematic class generally causing diffuse GGO with lymphocytic alveolitis and anastomosis dehiscence when initiated early after lung transplantation⁶⁴.

The infectious prophylactic regimens and their associated breakthrough infections are illustrated in table 1.

Human Immune Deficiency Virus Infection

In the recent decades, important strides have been made in the HIV treatment arena with HAART (highly active antiretroviral therapy) being now widespread. The pulmonary system remains still the most affected organ in patients with HIV with pulmonary infections and complications contributing significantly to the mortality and morbidity of patients with HIV⁶⁵. However, the use of HAART has changed the epidemiology, clinical presentation and even radiographic patterns of HIV associated pulmonary conditions. Therefore, the differential diagnosis and clinical approach have changed but chest thoracic imaging remains at the cornerstone of managing pulmonary conditions in patients with HIV/AIDS.

With the widespread use of HAART, opportunistic infections have decreased in incidence with new focus on non-infectious complications like COPD, lung cancer, pulmonary hypertension⁶⁶. While HAART has also lowered the incidence rates for Kaposi sarcoma of the lung and non-Hodgkin lymphoma, the rates for other malignancies have not experienced the same beneficial trend. Patients living with HIV have an increased risk for developing lung cancer⁶⁷ with the peak occurring during the first five years after diagnosis. Kaposi sarcoma, caused by HHV8 in MSM (men who have sex with men) is still encountered in burned out AIDS and has some typical features on thoracic imaging. Of note 20% of the patients may present with pulmonary findings only, lacking skin lesions⁶⁸.

With the initiation of HAART, a severe symptomatic immune reconstitution inflammatory syndrome (IRIS) can ensue. This often unmasks previous infections but can also solely cause sarcoid lung lesions on pulmonary imaging. The clinical presentation mimics infection and the approach should be to rule out an opportunistic infection that would require immediate treatment while HAART is continued. Very rarely steroids are needed in patients with severe inflammatory symptomatology.

As previously mentioned, opportunistic pulmonary infections are less common in patients living with HIV while on HAART. For instance, even with CD4 counts between 100–200, patients whose viral load is suppressed by HAART may not require PJP prophylaxis⁷⁰. Opportunistic infections still occur in severely immunocompromised hosts without access to HAART or who are travelling from abroad. Of note, many infections may coexist in a patient suffering from AIDS (e.g. in 15% of the cases *Pneumocystis jirovecii* coexists with tuberculosis) so careful definitive diagnosis may be warranted. *Pneumocystis jirovecii* remains the most common opportunistic infection but with much lower rates in the era of

HAART. Over 10 years between 1997 and 2007, the incidence has decreased to just over a tenth of its initial rate, falling from 29.9 per 1000 person years to 3.9 per 1000 person years⁶⁹. For unclear reasons, more cases are now being described in sub-Saharan Africa, an area where it was rarely described⁷¹.

Clinically, patients present with fever, cough and shortness of breath. The onset is gradual, over weeks which is different from transplant patients. Thoracic imaging (see paper by Tanaka et al) plays an important role in making the diagnosis since many patients will be empirically treated based on the clinical presentation and radiographic findings. Usually LDH and 1,3 Beta D glucan are elevated and the confirmatory diagnosis requires visualization of the cystic or trophic forms in bronchial secretions: expectorated or induced sputum, oral washes, endotracheal sputum or broncho alveolar lavage. In the past, multiple staining methods (e.g. Grocott-Gomori methenamine silver [GMS], Giemsa, Wright, Diff-Quick, calcofluor white, etc) have been used with usually with sensitivities ranging between 50–80% and high specificities > 99%⁷². These histologic staining techniques are being replaced by immunofluorescence antibody staining along with PCR testing. Even though the specificity is lower compared to calcofluor, immunofluorescence staining has significantly better sensitivity including on sputum samples⁷³. PCR testing can be performed but does not differentiate between colonization and active infection. Its use on expectorated or induced sputum may provide a more cost-effective approach in countries with a high prevalence⁷⁴.

When a host at risk (late stages of AIDS, not on HAART) presents with the typical gradual onset symptoms and a compatible thoracic imaging, a presumptive diagnosis of *Pneumocystis pneumonia* is made. Treatment is usually initiated at this stage while waiting for the confirmatory diagnosis.

Across the globe, the second most common opportunistic pulmonary infection in patients with HIV remains tuberculosis⁷⁵. In the USA, tuberculosis presents as a new infection rather than reactivation, in patients with additional risk factors like homelessness, incarceration and intravenous drug use. Use of HAART has modified not only the clinical presentation of tuberculosis but it also decreased its incidence. These new strategies initiate HAART early on, before the decline of immune function. When HAART was initiated at CD4 >500cells/ μ L, the incidence of tuberculosis had an adjusted hazard ratio of 0.27 (95% CI 0.12 – 0.62) compared to initiation at CD4 counts <500cells/ μ L⁷⁶. Ongoing HIV viral replication represents an important risk factor for tuberculosis irrespective of the CD4 count, emphasizing again the role for sustained HAART⁷⁷. In patients with high CD4 counts above 350 cells/ μ L, the presentation of tuberculosis mimics the usual subacute symptoms of non-immunocompromised hosts: cough sometimes with hemoptysis, fevers, chills, night sweats, weight loss. The presence of subacute systemic symptoms (e.g. night sweats, weight loss) differentiates tuberculosis from most other infections more commonly characterized by localized symptoms like cough, pleuritic chest pain, dyspnea. The lower the CD4 count, the higher the chances of disseminated tuberculosis with a more fulminant course.

As with other pulmonary infections, radiographic imaging represents the first step in the diagnostic work-up and CXR tends to correlate with the CD4 count. When the CD4 count is higher than 200 cells/ μ L, a typical post-primary infection appearance is common. At lower

CD4 counts, CXR findings vary from normal to military pattern. Use of HAART has changed previously described patterns⁷⁸ and as such post-primary radiographic findings have increased in incidence, now making up close to 50% of the tuberculosis cases.

When tuberculosis is suspected based on epidemiologic clues and clinical presentation, patient should be placed on airborne isolation while active disease is being ruled out. Skin testing and IFN gamma release assays do not differentiate between latent and active tuberculosis and moreover, false negative results do occur in the setting of immunocompromise⁷⁹. Therefore, the diagnosis relies on demonstrating *Mycobacterium tuberculosis* in sputum samples. The initial step is to obtain 3 induced sputum which is the safer approach in terms of infection control and is also more cost effective compared to bronchoscopy even in patients who do not produce sputum spontaneously or are smear negative⁸⁰. In recent years, nucleic acid amplification tests have been used for a rapid diagnosis of tuberculosis. To date, 2 tests (E-MTD, Gen-Probe, San Diego, California and Amplicor, Roche Diagnostics) are approved for use in the USA. While both tests have a sensitivity >95% when used on smear positive samples, E-MTD has better sensitivity of 70–90% vs 60–70% on smear negative specimens⁸¹.

While IRIS can unmask tuberculosis, it can also unmask infections caused by non-tuberculous mycobacteria. In late stages of HIV infection, MAC usually manifests as disseminated disease affecting the bone marrow, liver, spleen and lymph nodes without pulmonary involvement. Pulmonary focal involvement is occasionally seen with *M. kansasii* and *M. xenopi*.

IRIS - unmasked pulmonary infections occur soon after initiation of HAART, but infection with community acquired organisms can occur throughout the course of HIV infection. Even though the incidence of pneumococcal pneumonia has decreased due to access to HAART, its relative contribution increased when compared to other pulmonary infections⁸². Similar to its success in diminishing the incidence of tuberculosis, initiation of HAART upon entry into care at CD4 counts higher than 500cell/μL lowers patient risk of bacterial infections more than 50% compared to patients started on HAART at CD4 <350 cells/μL⁸³. Pneumonia was the most common diagnosis. Nevertheless, pneumococcal pneumonia and acute bronchitis remain common diagnoses even in HIV patients with high CD4 counts especially in smokers, malnourished patients with unsuppressed viral loads. Pneumococcal vaccines are now universally recommended in patients with HIV although disease specific data are not very prevalent⁸⁴. The robustness of the immune response depends on the CD4 count as well as initiation of stable HAART. A better and longer lasting immune response is obtained by using a prime-boost effect of PCV7 followed by PPSV23⁸⁴.

Other etiologies for bacterial pneumonias are *H influenzae* and *Legionella pneumophila* (40 times more common than in the general population). When an aggressive diagnostic pursuit is employed, atypicals are isolated in 10% of the cases⁸⁵ along with *Staphylococcus aureus* and other rare bacteria like *Nocardia spp* and *Rhodococcus spp*. Nosocomial pathogens like MRSA, *Pseudomonas spp* dominate the microbiology of hospital acquired pneumonia especially in patients with neutropenia caused by advanced AIDS.

The clinical symptoms are very acute with cough (sometimes productive of sputum), fevers, chills pleuritic chest pain differentiating bacterial pneumonias from the more subacute presentation of PJ and TB. Diagnostic workup relies on microbiological identification via sputum cultures, urinary antigens or cultures of the pleural fluid. Regardless of the HIV status, pneumococcal urinary antigen offers a reliable diagnostic tool. In 60% of the cases of pneumococcal pneumonia, blood cultures also return positive for *Streptococcus pneumoniae*. HIV patients have a higher risk for invasive pneumococcal disease due to higher rates of colonization, lower protection from the vaccines and also humoral deficiency despite polyclonal hypergammaglobulinemia. On the other hand, virologically suppressed patients with CD4 counts >350 cells/ μ L have similar outcomes to non-HIV patients⁸⁶.

Common pulmonary infections in the general population like acute bronchitis, viral respiratory infections remain common in the HIV population as well. Influenza may have a more severe clinical presentation. CMV contributes to significant morbidity in HIV patients but its role in pneumonitis remains unclear⁸⁷. Undoubtedly, immunocompromised hosts, including HIV patients reactivate CMV in bronchoalveolar secretions. It is common for CMV to have a similar clinical presentation as PJ and to be isolated along with it but unless a cytopathic effect is demonstrated, treatment is not necessary. CMV pneumonitis occurs very rarely in patients with CD4 counts <50 cells/ μ L and old studies have shown no additional benefit when CMV is treated along with PJ.

Depending on the geographical area, reactivation of endemic mycoses (*Histoplasma capsulatum*, *Cryptococcus spp* and *Coccidioides immitis*) contribute significantly to pulmonary infections in HIV patients. At high CD4 counts, symptoms may be localized to the lung with chest pain, shortness of breath, cough while more immunocompromised patients may present with disseminated disease and septic picture. While *Histoplasma* affects the RES system, *Cryptococcus neoformans* is a frequent cause for meningitis and skin lesions. In localized pulmonary disease or in patients with high CD4 counts, the antigens (*Histoplasma capsulatum* and *Cryptococcus neoformans*) may remain negative. *Histoplasma* serologies may be useful in disseminated disease. *Coccidioides immitis* follows a pattern similar to *Histoplasma* with findings confined to the lung with high CD4 counts and dissemination to the CNS, liver skin at low CD4 counts. Sputum or tissue cultures make the diagnosis for fungal etiologies along with serologies and antigens.

Uncommon fungal etiologies responsible for pulmonary complications in HIV include *Penicillium marneffe*, *Aspergillus spp*. Parasitic infections caused by *Toxoplasma gondii*, *Strongyloides stercoralis*, *Cryptosporidium*, and *Microsporidium* may also be encountered.

Infections seen with immune suppressive treatment of non-neoplastic disease

Connective tissue disorders compose another group of disorders characterized by immune-dysregulation at multiple levels. Immune defects include damage to anatomic barriers caused by pulmonary pathology associated with the underlying disease and by medication adverse reactions and infectious complications. We will only briefly focus on Tumor Necrosis Factor alfa (TNF alpha) inhibitors in the next paragraphs.

Biologics like anti TNF alpha drugs have been approved for a significant number of autoimmune diseases with infections being a common adverse event. Due to the pathophysiology of the TNF alpha pathway in the granuloma formation, these medications carry a high risk of granulomatous infections (mycobacterial infections and fungal). This risk is higher with monoclonal antibodies (e.g. infliximab) than with other TNF alpha inhibitors. While tuberculosis (TB) is usually secondary to reactivation, fungal infections (histoplasmosis, coccidioidomycosis, blastomycosis) are usually acutely acquired new infections. Therefore, screening for TB is mandatory but it remains unclear if serologic screening for fungal diseases adds to the risk profile. The risk of infection is increased by multidrug therapy usually, with corticosteroids and methotrexate and by the baseline disease and its complications (e.g. rheumatoid arthritis (RA) may intrinsically increase the risk for TB).

Mainly a reactivation disease, TB symptoms usually develop earlier than with newly acquired infection (e.g. 3 months for infliximab). Clinical presentation is often similar to TB in immunocompetent hosts but more than 50% of patients may present with disseminated disease. A meta-analysis that included rheumatologic diseases and also inflammatory bowel disease found the highest incidence for RA patients treated with infliximab.

Clinical workup is similar to patients not treated with biologics: chest imaging, followed by isolation of *Mycobacterium tuberculosis* including susceptibility panel.

Legionellosis is caused by *Legionella pneumophila*, an intracellular gram-negative coccobacillus. Its symptomatology is similar to community acquired pneumonia and patients can even present with acute hypoxemic respiratory failure requiring mechanical intubation. Legionella infections occur most commonly at 1–80 months after initiating treatment with biologics. Usually the diagnosis is made with rapid diagnostics (urinary antigen or PCR) and chest imaging may help differentiate it from other causes of pneumonia. After 80 reported cases, FDA added increased risk of legionellosis to the drug labels of all the TNF alpha blockers.

The most prevalent endemic fungal infection is histoplasmosis but coccidioidomycosis and blastomycosis can also occur especially in patients treated with infliximab. Histoplasmosis is endemic across the Midwestern and Central American states but also in central and South America, Africa and Asia. Presenting symptoms are nonspecific: fever, malaise, cough, weight loss which may delay the diagnosis and treatment. Patients may present with disseminated infection in septic shock. Chest imaging may be very valuable in raising the suspicion for histoplasmosis. In the largest retrospective study that included 98 patients with histoplasmosis the urinary antigen level correlated with severity and dissemination of disease⁸⁷. TNF alpha blockers were restarted after 12 months of antifungal therapy with 2/3 recurrences occurring in this group.

Conclusion

The relationship between immunosuppression and pulmonary infections is complex, involving both the innate and adaptive immune systems. This relationship is also nuanced as

demonstrated by the differences in infectious complications in patients with neutropenia related to HSCT and neutropenia related to therapy for solid organ tumors. These complexities are now navigated both with thoracic imaging and with a variety of novel diagnostic agents, including galactomannan antigen, procalcitonin, and many less widely available laboratory tests.

Recent advances in therapy for the underlying disease and for infection prophylaxis also need to be factored into the management of respiratory infections. These changes may diminish the clinical importance of some pathogens, but increase that of others. The advent of ganciclovir and valganciclovir for CMV prophylaxis and of PCR for CMV viremia surveillance has dramatically decreased the incidence of this infection in transplant recipients. The availability of HAART has depressed the relative prevalence of PJP, but increased that of pneumococcal pneumonia among patients with HIV infection. These kinds of changes in our understanding of immune suppression and in our clinical response to it are likely to continue to progress in the future.

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Fig 1.

Timeline and prophylaxis of pulmonary infections in hematopoietic stem cell transplant recipients

HSV infections very low incidence in the pre-engraftment period given acyclovir prophylaxis

- * “late-onset” infections once prophylaxis stopped
- ** Usually antipseudomonal antibiotics, antimold prophylaxis added in prolonged neutropenia. Breakthrough infections with pathogens not covered by the selected regimen
- *** Center dependent and immunosuppression - dependent

Abbreviations: GPC = Gram positive cocci, GNB = Gram negative bacilli, HSV = herpes simplex virus, CMV = cytomegalovirus, PJP = Pneumocystis jirovecii, TMP – SMX = trimethoprim – sulfamethoxazole, GVHD = graft vs host disease, VZV = varicella zoster virus

Fig 2.

Timeline and prophylaxis of pulmonary infections in solid organ transplant recipients

- * “late - onset” infections now once prophylaxis has been stopped
- ** According to the transplanted organ (see text)
- *** Prophylaxis is center and organ dependent

Abbreviations: GPC = Gram positive cocci, GNB = Gram negative bacilli, HSV = herpes simplex virus, CMV = cytomegalovirus, PJP = *Pneumocystis jirovecii*, TMP – SMX = trimethoprim – sulfamethoxazole

Table 1

Frequently used infection prophylaxis regimens organized by type of solid organ transplant (SOT) and infectious organism. Gaps only include pathogens causing pneumonia.

Solid Organ Transplanted	Post-operative bacterial infection prophylaxis*	Gaps	Post-operative Fungal Prophylaxis*	Gaps	Post-operative anti-viral prophylaxis*	Gaps
Lung	Vancomycin + Antipseudomonal Penicillin	MDRO GNRs, mycobacterias	Clotrimazole lozenges + Systemic triazole +/- nebulized Amphotericin B	Mucorales, Scedosporium, Triazole resistant Aspergillus spp. Airway anastomosis and pneumonia.	Gancyclovir, valgancyclovir +/- CMV Immunoglobulin If CMV-/CMV- then acyclovir	Resistant CMV De novo CMV infection
Heart	Vancomycin, Cefazolin before surgery	GNRs, Staphylococcal spp., mycobacterias	Nystatin or Clotrimazol lozenges	Molds, resistant Candida spp.	Gancyclovir, valgancyclovir +/- CMV Immunoglobulin If CMV-/CMV- then acyclovir	Resistant CMV De novo CMV infection
Small bowel	Antipseudomonal Penicillin + SDD +/- Vancomycin	MDRO GNRs, mycobacterias	SDD + Fluconazole or Equinocandin	Molds particularly Aspergillus spp and Mucorales	Gancyclovir, valgancyclovir +/- CMV Immunoglobulin If CMV-/CMV- then acyclovir	Resistant CMV De novo CMV infection
Liver	No consensus. Antipseudomonal Penicillin.	MDRO GNRs, Staphylococcal spp., mycobacterias	Fluconazole or Equinocandin	Molds Particularly Mucorales**** and Aspergillus.	Gancyclovir, valgancyclovir +/- CMV Immunoglobulin If CMV-/CMV- then acyclovir	Resistant CMV De novo CMV infection
Renal	Single dose cefazolin before surgery	GNRs, Staphylococcal spp.	Fluconazole or clotrimazole lozenges	Rarely molds	Gancyclovir, valgancyclovir +/- CMV Immunoglobulin If CMV-/CMV- then acyclovir	Resistant CMV De novo CMV infection

* For all SOT, the prophylactic regimen is modified based on recipient or donor history of infection (e.g. Cystic fibrosis patients may be colonized with MDROs). Regional and center variations in rates of infections with resistant pathogens determine programmatic changes in prophylaxis regimens.

SDD: selective digestive decontamination; MDRO: multidrug resistant organism; GNRs: Gram negative rods; CMV: cytomegalovirus; CMV-/CMV-: donor and recipient uninfected by CMV.