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Sepsis in the Immunocompromised Patient

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KEY MESSAGES

- Sepsis is one of the most common causes of morbidity and mortality of the immunocompromised patients.
- The inflammatory response blunted by immunosuppression attenuates manifestations of microbial invasion; in this patient population, sepsis is difficult to diagnose, and the clinical picture of sepsis is most variable.
- Infection in this population should be considered in the case of any deterioration of the patient's condition regardless of how inconspicuous and non-specific the symptoms are. The possibility of opportunistic and community-acquired infections as well as viral co-infection should be considered.
- A major role in the diagnosis and management of sepsis is played by the patient's net state of immunosuppression, epidemiological exposure, temporal relationships, and specific risk factors for the development of infection in various types of immunosuppressed patients.

Advances in the antiretroviral therapy and the treatment of malignancies, the use of newer immunosuppressive agents, antimicrobial prophylaxis, developments in the selection of organ and bone marrow transplant candidates on the waiting list, together with improved surgical techniques and novel options in intensive care have improved survival of immunocompromised patients in the last decades. This has logically led to an increase in the numbers of patients on follow-up, those treated in emergency departments and admitted to hospital and intensive care units (ICUs). One of the most common reasons for their hospitalization is infection [1-4]. While novel and more effective agents have reduced the risk of rejection, the incidence of opportunistic infection and malignant disease including viral infection has risen.

Sepsis remains the most common cause of morbidity and mortality of immunocompromised patients. This is despite the impressive advances in the prevention, diagnosis, and therapy of infection.

IMMUNOCOMPROMISED PATIENTS

The population of immunocompromised patients includes:

- patients permanently using immunosuppressive drugs following solid organ transplantation (SOT);
- patients undergoing hematopoietic stem cell transplantation (HSCT);
- patients with malignant diseases, hematologic malignancies;
- patients with autoimmune diseases, inflammatory bowel diseases;
- patients with acquired immunity deficiency syndrome.

A characteristic feature of immunocompromised patients is increased susceptibility to infection including **nosocomial** infection and infection by **opportunistic pathogens** (Figure 1 and Figure 2). **Community-acquired infection** may develop in out-of-the hospital settings while exposure that would be relatively benign for the normal host may result in significant infection in the immunocompromised patient.

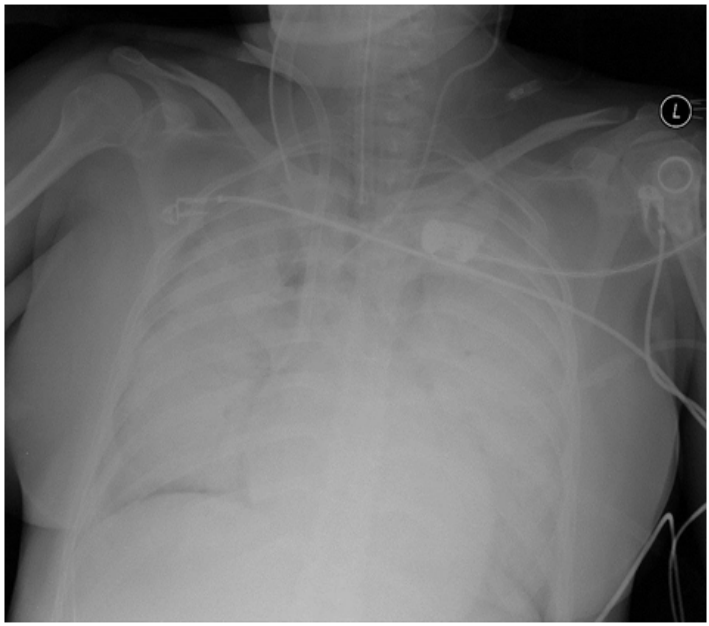

Figure 1: *Pneumocystis carinii pneumonia* in a female patient with pancreatic cancer.

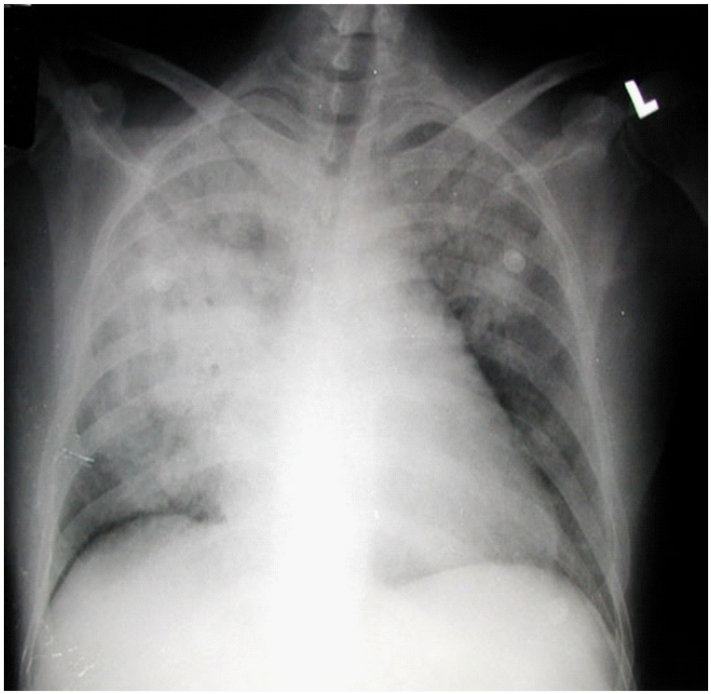

Figure 2: *Legionella pneumonia* in a renal transplant recipient.

NET STATE OF IMMUNOSUPPRESSION

The risk of infection in an immunocompromised patient is determined by net state of immunosuppression, the patients exposures to pathogens and the consequences of the performed invasive procedures [1,2]. The net state of immunosuppression includes:

- Primarily, the **intensity of immunosuppression** (type of the immunosuppressive agent, their dose, duration and time sequence of immunosuppressive agent administration);
- Previous therapy (chemotherapy, antimicrobials);
- Presence or absence of **neutropenia;**
- **Intact or impaired mucocutaneous surfaces** allowing the infectious agent to enter the body;
- **Tissue devitalization** or fluid collections;
- **Presence or absence of metabolic factors** (state of nutrition, uremia, hyperglycemia);
- Immunodeficiency (hypogammaglobulinemia, splenectomy or functional hyposplenism);
- Presence or absence of **infection by immunomodulating viruses** (cytomegalovirus, CMV; Epstein-Barr virus, EBV; hepatitis B and C virus, HBV, HCV; and human immunodeficiency virus, HIV).

Remember: *The immunocompromised patient often has several immunologic disorders at a time including neutropenia and lymphopenia, functional T cell impairment, reduced antibody response, and tissue injury. All critical determinants of immunocompetence may be impaired due to: antiproliferative activity induced by immunosuppressive agents, transient leukopenia, hyperglycemia as well as abnormal tissue perfusion of vascular etiology or related to a surgical procedure.*

IMMUNOSUPPRESSIVE THERAPY

Various variants of immunosuppressive therapy have been used with success in the treatment of malignant neoplastic processes, autoimmune disease, inflammatory bowel disease, and in SOT and HSCT.

Immunosuppressive therapy includes biologic antibodies, calcineurin inhibitors (CNI; tacrolimus, cyclosporine), antimetabolites or antiproliferative agents (azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil/sodium, mammalian target of rapamycin (mTOR) inhibitors such as sirolimus/everolimus), and glucocorticoids.

Immunosuppressive agents are often administered in combination, which allows increasing their effect and lowering their doses, and thus reducing their side effects [5,6].

DIAGNOSIS OF SEPSIS IN THE IMMUNOCOMPROMISED PATIENT

Remember:

- *Immunosuppression attenuates manifestations of inflammation.*
- *The clinical picture of sepsis in the immunocompromised patient is most variable, hence standard definitions of sepsis may not be applicable.*
- *Laboratory findings may be modified (leukopenia associated with antimetabolite therapy).*
- *The differential diagnosis should rule out non-infectious causes of fever and organ dysfunction.*

The diagnosis of sepsis in the immunocompromised patient is difficult, mainly due to host factors blunting or minimizing objective and subjective symptoms of inflammation. As a result, infection should be considered in this population in every change of their condition.

The clinical picture of sepsis is most variable, with the symptoms often being non-specific; frequently, there are no typical presentations of a systemic inflammatory response seen in the immunocompetent individuals. The only symptom of sepsis can be fever in an otherwise asymptomatic patient. Occasionally, there may be present one or several symptoms such as general weakness, impairment of consciousness, tachypnea, dyspnea, fever, or the typical picture of septic shock. Organ dysfunction may be due to sepsis, nonetheless, causes of non-infectious etiology should be excluded (Table 1).

Table1: Examples of non-infectious etiology of organ dysfunction in the immunocompromised patient.

Recurrence of neoplastic processes
Allograft rejection
Graft versus host disease (graft-versus-host-disease)
Relapse of autoimmune diseases
Organ toxicity immunosuppressant therapies
Impaired organ own tumor process
Amyloidosis
Vasculitis
Damage due to therapeutic interventions (oxygen, radiotherapy)

In granulocytopenia (i.e., < 1000 granulocytic white blod cells), the ability of inflammatory infiltrate formation is limited; skin infection is often associated with phlegmona instead of abscess formation; with lung infection, pulmonal infiltrate on the lung scan may not be visible; urinary tract infection is not accompanied by pyuria.

Given the reduced febrile response and attenuated response to infection in the white blood cell count, standard definitions of sepsis may not be applicable [7,8]. Leukocytosis and CRP elevation may not be present. Procalcitonin (PCT) is a specific and more sensitive marker of bacterial

infection [9,10]; however, its levels may also be raised due to other causes. Determination of selected pro- and anti-inflammatory cytokines, sepsis mediators, and use of gene expression methods for improved diagnosis of sepsis in the immunocompromised are currently subject to research. Crucial for the successful therapy is early pathogen identification, which can be accomplished using a combination of various techniques (Table 2).

Table 2: Identifying the infectious agent.

Microbiological examination
Serological investigation (identification of antibody or Ag)
Molecular biology
Imaging (X-rays, US, CT, MRI)
Histology
Specific laboratory markers of infection

Some types of infectious processes are most likely to occur in a specific phase of immunosuppressive therapy, at a specific period of time after SOT and/or HSCT, with specific infectious complications typical for each organ transplant.

Remember:

Crucial factors in the diagnosis of infection:

- *Analysis of epidemiological and temporal relationships;*
- *Consideration of a broad spectrum of potential pathogens;*
- *A thorough patient´s history and physical finding;*
- *Use of invasive diagnostic workup;*
- *Early pathogen identification (a combination of molecular biology techniques, immunological and microbiological investigations).*

Differential Diagnosis of Infection and Organ Transplant Rejection

Given the similarity of clinical presentations, while it is often difficult to distinguish between allogeneic graft infection and rejection, this is crucial for guidance of future therapy.

Rejection is an immunological response between the recipient's defense mechanisms and donor antigens, which may eventually result in graft destruction and pose a threat to the allograft recipient.

Typical features of rejection include rapidly deteriorating graft function, fever, fatigue, weakness, often there also leukocytosis and unexplainable elevation of CRP levels.

An episode of rejection is confirmed or excluded by immunological assessment and biopsy of the transplant followed by histology.

A useful tool for the differential diagnosis between rejection and infection is determination of serum PCT levels, however:

- Elevated PCT levels will not rule out rejection if concurrent with infection.
- PCT levels increase in the early post-transplant period due to surgical trauma without the presence of infection. Nevertheless, they normalize rapidly in patients with an uncomplicated course.
- PCT has not been shown to have adequate sensitivity in invasive fungal infection and in abscess.
- PCT synthesis is also stimulated by administration of antithymocyte globulin as part of induction immunosuppression [11].

RISK OF INFECTION

The most important risk factor for infection-related complications in **cancer patients** is a decrease in peripheral blood granulocyte count below 0.5×10^9/l; the risk increases with neutropenia duration.

Patients with **HIV infection** are classified by the clinical picture and $CD4^+$ lymphocyte count into three categories, which also reflects the presence of infectious complications.

In **transplant recipients**, the risk of post-transplant infection varies by the level of immunosuppression. It is also influenced by post-transplant profylaxis. Introduction of post-transplant prophylaxis with trimetoprim-sulfometoxazole reduced the incidence of pneumocytic pneumonia and infection caused by some types of pathogens (*Toxoplasma gondii*, *Cyclospora cayetanensis*, *Listeria species*, *Nocardia species*, common urinary and respiratory pathogens), introduction of prophylaxis with antivirals reduced the incidence of cytomegalovirus and herpes simplex virus infection. However, infection caused by resistant pathogens has become more frequent. More sophisticated microbiological diagnostic techniques have made it possible to define new clinical syndromes (e.g., polyomaviral nephropathy) as well as some rare types of donor-transmitted infection (e.g., caused by lymphocyte choriomeningitis virus).

Estimating the Risk of Infection in Post-Transplant Patients

To estimate the risk of infection associated with SOT, it is recommended to use the CREDIT system based on exposure to microorganisms acquired in several ways [1,12]:

- **Community-acquired pathogens;**
- **Reactivation** of previous infection transmitted by the donor or recipient ;
- Specific **epidemiologic exposures,** including hobbies, work, recreational activities, contact with pets, zoonotic infections, sexual activity;
- **Donor-derived infections;**

- **Iatrogenic** or nosocomial infection;
- Specific pathogens related to **travel** including tropical disease.

Temporal Relationships of Infection

Infections occur in a generally predictable pattern after SOT and HSCT. The pattern reflects the relationship between epidemiological factors and the immunosuppressive strategy [2,12,13].

Infections occurring outside the usual season or of unusual severity are suggestive of excess immunosuppression or signal increased epidemiological risk.

Post-HSCT Timeline

The type of transplant related to the risk of infection and graft versus host disease (GVHD) in post HSCT.

The post-HSCT period can be divided into 3 phases: 0–30 days (neutropenic-pre-engraftment phase), 30–100 days (early post-engraftment phase) and over 100 days (late post-engraftment phase) or, possibly, into early and late periods [14,15].

1. Early (0–30 days and/or 0–100 days post-transplant)

Immediately after transplantation, irrespective of implementation of myeloablative regimen, there is a period of pancytopenia and thus patients are most prone to febrile neutropenia. Myeloablative regimens are associated with significant transmigration of pathogens, increasing the rates of bacteremia and infection. During the pre-engraftment phase, the bacterial infections are the most prevalent pathogens. Bacterial infections occurring during the neutropenic phase are similar to those observed in other neutropenic patients, i.e. streptococci and Gram-negative bacteria. Fungal infection is also frequent. The most common fungal pathogen during pre-engraftment period is candida albicans. This period is also associated with viral infection (Herpes simplex virus).

2. Late (100 days post-transplant and beyond)

In this phase the presence of chronic graft versus host disease are at a higher risk of infectious complications. Infections typical of this period include viral (CMV, herpes simplex virus, respiratory viruses), and community-acquired infections. During this period, the most common fungal infection is invasive Aspergillosis secondary to increased risk of GVHD and prolonged use of corticosteroids. Pnemocystis jiroveci may occur, but usually is prevented by the use of trimethoprim/sulfamethoxazole.

Post-SOT timeline

The post-SOT period can be divided into 3 time intervals, with most infections reported within the first two intervals (6 months post-transplant) (Figure 3).

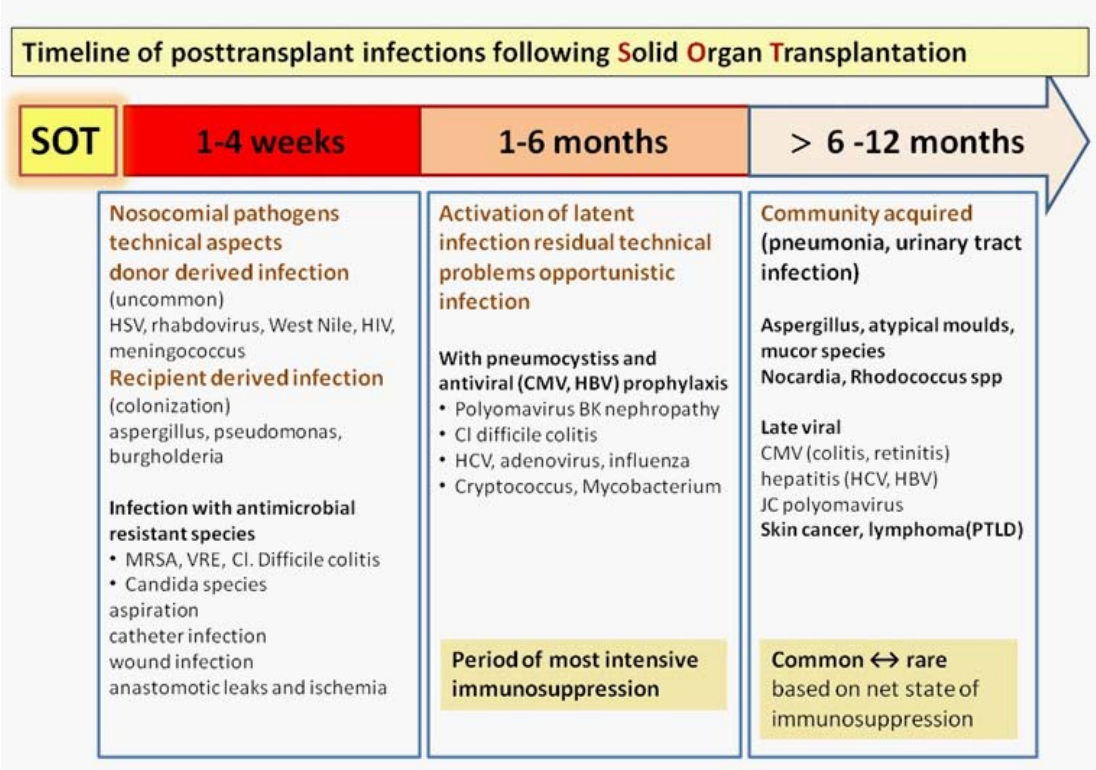

Figure 3: Changing timeline of infection after solid organ transplantation (SOT).

(Adapted from Fishman JA. Infection in Solid-Organ Transplant Recipients. N Engl J Med. 2007; 25: 2601-2614 and Gabrielli A, Critical Care. 4th edition, Philadelphia: Lippincott Williams & Wilkins. 2009).

MRSA: methicillin-resistant *Staphylococcus aureus*, VRE: vancomycin-resistant *Enterococcus faecalis*, HSV: herpes simplex virus, CMV: cytomegalovirus, LCMV: lymphatic choriomeningitis virus, HIV: human immunodeficiency virus, HBV: hepatitis B, HCV: hepatitis C, VZV: varicella-zoster virus, EBV: Epstein-Barr virus, SARS: severe acute respiratory syndrome, PML: progressive multifocal leukoencephalopathy, PTLD: post-transplant lymphoproliferative disease.

1. Early post-transplant period (0–4 weeks)

During the first month after transplantation, the infections are usually (above 95%) of bacterial and candidal etiology and **associated with the surgical procedure and management of the patient** (surgical wounds, dehiscence of biliary and intestinal anastomoses, vascular access, mechanical ventilation, urinary catheter). These infections are comparable to post-surgical complications of the immunocompetent patient.

Despite routine detection of infection in organ donors the donor-derived infections cannot be completely ruled out, although transmission occurs rarely. During acute infection, as

seroconversion may not occur and test sensitivity is below 100%, some acute infections may remain undetected [16].

Donor infection, in general, is not a contraindication to donor harvesting: antimicrobial prophylaxis is adapted to current microbiological findings.

Organ recipients are carefully screened for the presence of infection. While on the waiting list, colonization occurs with nosocomial microbes resistant to antimicrobial agents; hence, infection may occur. Recipient infection is currently not a contraindication to transplantation; adequately managed pre-transplant infections do not pose a major risk of increased post-SOT morbidity and mortality rates [17].

2. Intermediate post-transplant period (1-6 months)

The infections occurring between months 2 and 6 are mainly caused by immunomodulatory viruses and those caused by opportunistic pathogens. This period is associated with the most intensive immunosuppression.

Viral pathogens and allograft rejection are responsible for the majority of febrile episodes in this period. Viral infections may cause the disease directly (tissue invasion) or they may manifest themselves by indirect effects, that is, an immunological response predisposing to:

- development or deteriorated course of other opportunistic infections;
- post-transplant EBV-related lymphoproliferative disorder (PTLD);
- increased risk of acute or chronic injury to the graft or its rejection.

3. Late post-transplant period (6 months above beyond)

In this period the risk of infection decreases. Immunosuppressive therapy is usually tapered in recipients who have good allograft function. Transplant recipients have a increased risk of community-acquired pathogens.

In that period, patients can be divided into 3 groups:

- Most recipients (over 2 thirds) show adequate allograft function and receive minimal immunosuppressive therapy. Their major risk consists of community-acquired respiratory viruses.
- An approximately 10–15% of recipients show chronic viral infection, which may cause allograft injury (HCV, HBV, CMV, EBV).
- About 5–10% of patients have relatively poor graft function, have rejection episodes and receive intensive immunosuppression. These patients represent a subgroup at highest risk of opportunistic infection.

SPECIFIC INFECTIOUS COMPLICATIONS RELATED TO ORGAN TRANSPLANTATION

Solid organ transplantation is associated with typical specific infectious complications due to the underlying disease, surgical transplant procedure, and nature of the graft [18], (Table 3).

Table 3: Specific type of infections in allograft recipients.

Allograft	The most common type of infection, risk factors
Kidney	Urinary infection, BK polyoma virus, pneumonia **Risk factors:** ureteral stenosis, urinary leak, stents, lymphocele
Liver	Intra-abdominal infections, cholangitis, intrahepatic abscesses Recurrence of the underlying disease Thirty to 70% of liver recipient patients experience at least one Episode of infection in the year following surgery Highest incidence of Candida infection **Risk factors:** biliary complications, poor graft perfusion, biliary stents, intra - abdominal hematoma
Heart	Pneumonia, wound infection, mediastinitis **Risk factors:** surgery, intra-balloon pumps, total artificial hearts and ventricular-assist devices Toxoplasma gondii myocarditis in seronegative recipients of seropositive donors
Lung	Highest risk for pneumonia, highest risk for aspergillosis Longest risk period for CMV and Pneumocystis jiroveci Burkholderia cepacia and Pseudomonas aeruginosa are more frequent in patients with cystic fibrosis Infections at the tracheal or bronchial anastomosis **Risk factors:** pre-transplant colonization, the long-term use of steroids, ventilator associated lung injury, denervation of allograft, which leads to an impaired mucociliary clearance and diminished cough reflex; absence of lymphatic drainage, dehiscence of anastomosis
Pancreas	Technical complications (thrombosis, bleeding, fistula) Pancreatitis in the allograft, intra-abdominal and wound infections **Risk factors:** pre-transplant diabetes and many of its complications (i.e. peripheral vascular disease, chronic renal insufficiency) strong immunosuppression, surgery
Small bowel	High incidence of infectious complications, the highest incidence of fungal infections, high incidence of post-transplant lymphoproliferative disease **Risk factors:** translocation-induced sepsis syndrome with concurrent rejection/ischemia

MANAGEMENT OF SEPSIS

The principles of sepsis management in the immunocompromised patient are in line with the current guidelines despite the fact that immunocompromised patients have not been included into clinical trials in sepsis management [19].

In cases of fever persisting despite adequate therapy with broad-spectrum antibiotics, empirical antifungal therapy should be considered.

Viral co-infection should be recognized and treated concurrently with antimicrobial and antifungal therapy.

Should the infection be due to surgery, correction of the anatomical abnormality leading to infection is reasonable.

Immune deficiency such as neutropenia or hypogammaglobulinemia should be corrected by administration of colony-stimulating factors or intravenous immunoglobulin.

Temporary Withdrawal of Immunosuppression in Life-Threatening Sepsis

In cases of life-threatening infection, reduction or, possibly, withdrawal of immunosuppressive therapy should be considered. Although reduction and/or withdrawal of immunosuppression is generally accepted in cases of severe sepsis, data on its impact on the fate of the patient and allograft are scarce. This approach is not based on results of trials but on clinical experience of transplant center physicians. It has not been clearly shown that short-term withdrawal for a necessary period of time in the setting of severe sepsis would lead to a significantly higher incidence of allograft rejection rates and higher mortality post SOT [20]. This option should be considered on an individual basis depending of the type of SOT and patient status while also closely monitoring the level of immunosuppression and graft function.

While abrupt discontinuation of corticoids is not recommended, withdrawal of immunosuppression does not rule out corticoid administration in the setting of septic shock and suspected adrenocortical insufficiency.

Progressive resumption of immunosuppression should be based on routine daily assessment of the patient´s status.

Remember

- *Therapy of severe sepsis in transplant recipient includes temporary reduction of immunosuppression while closely monitoring allograft function.*
- *Reduction of immunosuppression requires strictly individualized assessment of the patient´s current status with respect to the type of allograft and severity of sepsis.*
- *Monitoring of the level of immunosuppression and ongoing monitoring of graft function are crucial.*
- *Resumption of immunosuppression should be considered daily based on the patient´s current status.*
- *It is recommended to consult both reduction and resumption of immunosuppression with transplant center physicians.*

INTERACTION OF IMMUNOSUPPRESSIVE AGENTS AND ANTIMICROBIALS IN THE MANAGEMENT OF INFECTION

Calcineurin inhibitors and mTOR are metabolized by the cytochrome P-450 (CYP 450) and via P-glycoprotein. Administration of inductors or inhibitors of these systems results in either inadequate immunosuppression or increased immunosuppressive agent toxicity (Table 4). Administration of grapefruit juice (CYP 450 inhibition) or St John´s worth (CYP 450 induction) should also be avoided [21].

A knowledge of the common interfering compounds is essential, during the therapy using these agents, the patients must be monitored closely (drug levels, the effectiveness of immunosuppression).

Table 4: Important interactions for calcineurin inhibitors (CNI).

CYP 450 inhibitors = drugs that increase levels of CNI	CYP 450 inductors = drugs that decrease levels of CNI
Diltiazem, verapamil Amiodarone Ketokonazole Fluconazole, voriconazole Caspofungin Metronidazole Erythromycin Clarithromycin, azithromycin Gentamicin, cotrimoxazole	Rifampin Izoniazid Phenytoin Karbamazepin Phenobarbital Octreotide Ticlodipin

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