LITHUANIAN UNIVERSITY OF HEALTH SCIENCES

FACULTY OF MEDICINE

DEPARTMENT OF PULMONOLOGY

Final master`s thesis

Lung Transplantation Guidelines of the Hospital of Lithuanian University of Health Sciences Kauno Klinikos and University Hospital of Zürich, Switzerland: A Review and Comparison

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1. SUMMARY

Author name: Lydia – Maria Canham

Research title: Lung Transplantation Guidelines of the Hospital of Lithuanian University of Health Sciences Kauno Klinikos (KK) and University Hospital of Zürich (USZ), Switzerland: A Review and Comparison

Aim: The aim of this literature review is to illustrate the differences in approach and conduction of lung transplantation guidelines postoperatively between the Hospital of Lithuanian University of Health Sciences Kauno Klinikos and University Hospital Zürich.

Objectives:

1. To compare lung transplantation guidelines in the post operative phase
2. To assess treatment guidelines for immunosuppression and infection
3. To illustrate the differences in postoperative management between Hospital of Lithuanian University of Health Sciences Kauno Klinikos and University Hospital Zürich

Methodology: This is a literature review about lung transplantation guidelines by searching electronically in The Medline (PubMed), ResearchGate, Google Scholar and Cochrane Library for studies and guidelines published during the last twenty-six years (1992–2018).

Results: Survival of lung transplant recipients is lower in recipients of most other solid organ transplants due to the immense quantity of possible complications in the first postoperative year. There are remarkable differences between USZ and KK in post transplantation management. Differences are found in ward rounds and observation schedules, fluid management, stabilisation phase medication and clinical practice. The medication for immunosuppression differs in both hospitals. Antifungal, antiviral and especially antibacterial treatment plans show more differences than similarities, both in respect to the choice of the drug as well as the initiation and duration of administration. Thorough postoperative observation is vital for the management of lung transplant recipients in order to detect and treat rejection and infection, especially during the early post transplantation period.

Conclusions: Chronic rejection (obliterative bronchiolitis) is the most significant cause of chronic allograft dysfunction and late mortality after lung transplantation. It is suggested that TAC may be superior to CsA in respect to bronchiolitis obliterans syndrome, lymphocytic bronchitis, treatment withdrawal, and arterial hypertension. The prophylactic antibiotic treatment in USZ starts intra operatively until week 3 or 4 post operatively, while in KK the administrations of the prophylactic antibiotics last from day 0-5 post operatively.

2. SANTRAUKA

Autoriaus vardas: Lydia - Maria Canham

Tyrimo pavadinimas: Lietuvos sveikatos mokslų universiteto ligoninės, Kauno klinikų ir Šveicarijos Ciuricho universitetinės ligoninės plaučių transplantacijos gairių: apžvalga ir palyginimas

Tikslas: Šios literatūros apžvalgos tikslas - iliustruoti plaučių transplantacijos gairių požiūrio ir vedimo skirtumus tarp Lietuvos sveikatos mokslų universiteto Kauno klinikų ir Ciuricho universitetinės ligoninės.

Tikslai:

1. Palyginti plaučių transplantacijos gaires pooperacinėje fazėje

2. Įvertinti imunosupresijos ir infekcijos gydymo gaires

3. Parodyti pooperacinio valdymo skirtumus tarp Lietuvos sveikatos mokslų universiteto Kauno klinikų ir Ciuricho universitetinės ligoninės

Metodologija: Tai literatūros apžvalga apie plaučių transplantacijos gaires, elektroniniu būdu ieškant „Medline“(„PubMed“), „ResearchGate“, „Google Scholar“ ir „Cochrane“ bibliotekų, per pastaruosius dvidešimt šešerius metus (1992–2018 m.) Paskelbtus tyrimus ir gaires.

Rezultatai: Dėl didelės įvairovės galimų komplikacijų pirmais metais po operacijos pacientų po plaučių transplantacijos išgyvenamumas yra mažesnis lyginant su kitų organų tranplantacijomis. Lyginant USZ ir KK potransplantacinio periodo valdymą pastebima daug skirtumų. Skirtumai randami lyginant palatas ir stebėjimo tvarkaraščius, taip pat tarp skiriamų skysčių ir stabilizacijos fazės medikamentų. Medikamentai skirti imunosupresijai abejose ligoninėse taip pat skiriasi, o priešgrybelinai, antivirusiniai ir ypač antibakteriniai vaistai bei jų paskiriamos dozes ir skyrimo trukmė turi daugiau skirtumų nei sutapimų. Kruopštus pooperacinis stebėjimas yra gyvybiškai svarbus plaučių transplantacijos recipientams, siekiant nustatyti ir gydyti atmetimą bei infekciją, ypač ankstyvuoju transplantacijos laikotarpiu.

Apibendrinimas:

Lėtinis atmetimas (obliteracinis bronchiolitas) yra svarbiausia lėtinės alotransplantato disfunkcijos ir vėlyvo mirtingumo po plaučių transplantacijos priežastis. Siūloma, kad broncholito obliteranų sindromo, limfocitinio bronchito, gydymo nutraukimo ir arterinės hipertenzijos atveju BLSK gali būti pranašesnis už CsA. Profilaktinis antibiotikų gydymas USZ pradeda veikti operatyviai iki 3 arba 4 savaitės po operacijos, o KK atveju profilaktinių antibiotikų skyrimas trunka nuo 0-5 dienos po operacijos.

3. ACKNOWLEDGEMENTS

I would like to thank Prof. Kestutis Malakauskas and PD Dr. Macé Schuurmans for their advice and help throughout this final master`s thesis.

4. CONFLICTS OF INTERESTS

The author reports no conflicts of interests during this master`s thesis.

5. ETHICS COMMITTEE FORM

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Kaunas, 3. December 2018

Master thesis: Literature review

Title: Lung Transplantation Guidelines of the Hospital of Lithuanian University of Health Sciences Kauno Klinikos and University Hospital of Zürich, Switzerland: A Review and Comparison

I, Prof. Dr. med. Kestutis Malakauskas, am the supervisor of student Lydia- Maria Canham, Group 35, 6th year Medicine, Lithuanian University of Health Sciences (LUHS). She is the author of the master thesis "Lung Transplantation Guidelines of the Hospital of Lithuanian University of Health Sciences Kauno Klinikos and University Hospital of Zürich, Switzerland: A Review and Comparison" under my supervision.

As it is a sole literature review, Ms. Lydia-Maria Canham uses only published articles or hospital management guidelines, which are publically accessible. She does not use any medical or personal patients` data or clinical cases of neither LUHS nor of University Hospital Zürich. Therefore I deem it unnecessary to acquire a bioethical approval from the Bioethics Department of LUHS, as no bioethical regulations are affected.

Kind regards,

Prof. Kestutis Malakauskas, MD, PhD

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6. ABBREVIATIONS

KK= Hospital of Lithuanian University of Health Sciences Kauno Klinikos

USZ= University Hospital Zürich,

LTRs = lung transplant recipients;

CRP = C-reactive protein;

CBC = complete blood count;

CsA = cyclosporine A;

TAC= tacrolimus

C0 = trough level of cyclosporine;

C2 = peak level of cyclosporine;

CMV = cytomegalovirus;

EBV = Epstein-Barr virus;

PCR = polymerase chain-reaction;

IVIG = intravenous immunoglobulin,

ICU=intensive care unit,

CNI=Calcineurin inhibitors,

TDM=therapeutic drug monitoring,

IV=intravenous,

PO= per os,

PSA= pseudomonas aeruginosa

FEV_1 = forced expiratory volume in the first second

BOS = obliterative bronchiolitis syndrome

FiO2= fraction of inspired oxygen

PEEP= positive end-expiratory pressure

PaO2= partial pressure of oxygen

COPD= chronic obstructive pulmonary disease

ECMO= extracorporeal membrane oxygenation

TB= Tuberculosis

7. INTRODUCTION

The first successful lung transplant was performed 30 years ago. Since then, lung transplantation has quickly become an established standard of treatment for end-stage lung disease in selected patients (1).

That has been made possible by improving the techniques of the transplantation operation, the anaesthesia and following intensive care surveillance and new discoveries in immunosuppression therapy as well as infection prophylaxis and long term management. Globally, over 50,000 procedures have been performed (2). Annually, about 1200 lungs for adults and 85 lungs for children are transplanted. The first successful single transplantation with long term survival (patient survived for 7 years post operatively) was performed in Toronto 1983. The first bilateral transplantation was performed in 1985 in Toronto, as well (patient survived for 16 years) (3). In Switzerland, the first lung transplantation was done in 1992 (4). Lithuania was the first of the Baltic states to perform a successful heart-lung transplantation in 2009 (5). Lung transplantation leads to improvements in pulmonary function, as well as quality of life. Survival has progressively improved, but it is clearly inferior to survival rates observed after other solid organ transplantations (2). There are two main problems for lung transplantation nowadays: low availability of donor lungs and chronic rejection (bronchiolitis obliterans syndrome) in about 50% of cases observed during their entire survival time (3).The median survival rate presently stands at 5.8 years (2). The procedure is still relying heavily on cadaveric donors, unlike other organs i.e. the kidneys where living donation is possible (3). Whether or not a patient is eligible for lung transplantation, may be decided by consulting the ISHLT guidelines (11). The indication for lung transplantation is given if the patient suffers from a severe degree of a lung disease, after unsuccessful conservative treatment (6). In this stage the patient suffers from dyspnoea on minimal or no activity (NYHA Class III-IV). The life expectancy is less than 2 years and the quality of life is strongly reduced. Patients, who do not qualify for a lung transplantation, are those who either suffer from a concomitant systemic disease (which cannot be controlled sufficiently), or malignancy or sepsis, or generalised arteriosclerosis, kidney insufficiency (Clearance <50 ml/min), or liver insufficiency (Bilirubin >35 mmol/l, Factor V <50%). Furthermore, patients who do not have a healthy psychosocial environment and especially those who are addicted to alcohol, nicotine or drugs as well as patients of advanced age (> 65 years) do not qualify for lung transplantation, either (2). A healthy psychosocial environment is very important. A study established that higher levels of negative effects, especially depression and general distress, measured 6 months after lung transplantation are linked with greater mortality.

Patients with elevated levels of depression had a 15% greater 5-year mortality rate compared to patients who were associated with lower levels of depression (12).

The management postoperatively plays a vital role in successful lung transplantation. This phase consists of 3 parts:

1. Medication therapy, which consists of immunosuppressive drugs and prophylactic medication against bacterial, viral and fungal infections as well as medication to prevent adverse events of other drugs (osteoporosis etc) (3).

2. Regular bronchoscopies with bronchoalveolar lavage and transbronchial biopsies to detect infections and rejection reactions, while in preclinical phase (3).

3. Thorough education of the patient, so he/she knows how to react in case there are changes in lung function and how to interpret other bodily changes. He/she has to report changes to his/her transplant specialist as soon as possible (3).

As mentioned in above, adequate immunosuppression is a key issue. It prevents acute allograft rejection, while over-immunosuppression must be avoided as well because infection and malignancy may complicate the process. In general, a standard triple immunosuppressive regimen is used: Calcineurin inhibitors (CNIs), especially cyclosporine A (CsA) or Tacrolimus (TAC), are cornerstones of the immunosuppressive therapy (7). Bacterial infections cause around half of all infectious complications (8). Respiratory, non-herpes viral infections have become a serious problem (8). Thus, thorough postoperative observation is nonetheless vital for the management of lung transplant recipients in order to detect and treat rejection and infection (8). In spite of more than two decades of experience in the field of lung transplantation, the clinical practice varies significantly among transplant centres (9). Essentially, concrete guidelines for the management of the early postoperative period after lung transplantation do not exist (7).Variations in treatments is the main reason why this master thesis investigates the differences in clinical practice among transplant centres by studying the explicit example of Hospital of Lithuanian University of Health Sciences Kauno Klinikos (KK) and Zürich University Hospital (USZ). Published articles and/or treatment guidelines of the respective hospitals are used to write a literature review. This literature review will demonstrate the similarities and differences of treatment guidelines, post transplantation patient care and differences between the administrations of medications. Special attention will be paid to the daily ward rounds organisation and diagnostic tests as well as preventive strategies for infectious diseases. The aim is to highlight the importance of updating and unifying clinical practice and treatment guidelines in order to achieve excellent results in every transplant centre around the world.

8. AIM AND OBJECTIVES

AIM:

The aim of this literature review is to illustrate the differences in approach and conduction of lung transplantation treatment postoperatively between the Hospital of Lithuanian University of Health Sciences Kauno Klinikos and University Hospital Zürich.

OBJECTIVES:

1. To compare lung transplantation guidelines in the post operative phase
2. To assess guidelines for immunosuppression and infection
3. To illustrate the differences in postoperative management between Hospital of Lithuanian University of Health Sciences Kauno Klinikos and University Hospital Zürich

9. RESEARCH METHODOLOGY AND METHODS

Lung transplantation treatment guidelines of Lithuanian University of Health Sciences Kauno Klinikos were obtained from the Lithuanian online register of legislation “Teisės aktų registras”. The guidelines of the University Hospital of Zürich were obtained from articles about the management of lung transplant recipients at Zürich University Hospital published by Dr. M. Schuurmans, et all. For further information about the peculiarities and complications in the early post operative period, The Medline (PubMed) was searched with following keywords: “lung transplantation”, “treatment”, “complications” and “early post-operative period”. To use the most recent guidelines and research results, the focus was on articles published between January 2008 and December 2018. Relevant studies were found by cited references in guidelines and published articles. In order to find more pertinent studies, the data collection was conducted by searching electronically in The Medline (PubMed), ResearchGate, Google Scholar and Cochrane Library for studies published during the last twenty-six years (1992-2018) sing the keywords ‘‘treatment guidelines”, ‘‘lung transplantation’’, ‘‘University Hospital of Zürich”, “Lithuanian University of Health Sciences Kauno Klinikos”, “Baltic states lung transplantation”, “complications ”, “post-operative period” , “infection prevention”, “donation criteria”, and “immunosuppression”.

Exclusion criteria compromised the following:

1. Studies of organ transplantation other than lungs and heart-lung transplantation.
2. Morbidities other than pulmonary fibrosis, cystic fibrosis, COPD, primary and secondary pulmonary hypertension or kidney failure not associated with lung transplantation.

Following the inclusion and exclusion criteria explained above, 31 articles were selected for the present review.

10. RESULTS AND THEIR DISCUSSION

There are two centres for lung transplantation in Switzerland: Centre Romandie and Zürich. In total there were 235 lung transplantations in Zürich. Per year and centre there were about 16 transplantations with a wide range (12-32) depending on the year (2). In Lithuania there is one transplant centre: Hospital of Lithuanian University of Health Sciences Kauno Klinikos in Kaunas. Transplantations are performed since 2007 and 14 patients received transplants until 2017 (10).

The median survival rate presently stands at 5.8 years worldwide (2). Survival of lung transplant recipients is lower to recipients of most other solid organ transplants, due to the immense quantity of possible complications in the first postoperative year (7)

10.1 LIVING AND DEAD DONOR AND DONATION CRITERIA

Lung transplantation is still relying heavily on cadaveric donors, unlike other organs i.e. the kidneys where living donation is possible. When there is a difference between the size of thorax volume in donor and recipient, the possibility of a partial living donation exists. The procedure can be done as flap transplantation or a non-anatomical resection like the lung volume reduction surgery. The donor should ideally be younger than 65 years and he should not show any lung diseases on history, clinical examination or radiological examination. Oxygenation of the donation lung should meet partial pressure of oxygen (PaO2) 200 mmHg breathing with 100% O2 (fraction of inspired oxygen (FiO2) =1)) and a positive expiration force of 5 cm H2O (positive end-expiratory pressure (PEEP) = 5cmH2O). Due to limited amounts of organs, these guidelines are about to be changed and so called "marginal" donors will be introduced (3). Donors are called marginal or extended, if any one of these criteria are met: age greater than 55 years, smoking for more than 20 pack-years, evidence of chest radiographic infiltrate, PaO2 less than 200 mm Hg, or purulent secretions on bronchoscopy. Caution is necessary when using marginal or extended donor lungs, because there seems to be an increased early mortality rate in that group of recipients (13).

Due to the aforementioned problem of organ shortage, living donation for lung transplants has been developed, but it is performed in just a few centres worldwide, mainly in Japan (15). Usually the lower lobe is resected together with the respective bronchus and vessels of two different donors and it is transplanted into a child or small adult in experienced centres. The short and intermediate results of this procedure are comparable to lung transplantation from cadaveric donor organs. Despite that, one has to keep in mind that this procedure involves 3 patients, who can potentially suffer complications and possibly die. So far, no death of a donor has been reported. Frequent complications include

pleural effusion, pneumothorax and postoperative pneumonia. Lungs do not regenerate themselves, so the procedure involves a higher risk than living liver donation (3).

10.1.1 IDIOPHATIC PULMONARY FIBROSIS

Patients who are diagnosed with idiopathic pulmonary fibrosis often have a fairly fast decline of pulmonary function. Frequently, their general condition declines as well very rapidly and they reach the transplant centre too late. Many times they die while waiting for a matching donor organ or they do not tolerate the immunosuppressive therapy. Accordingly, patients who are diagnosed with pulmonary fibrosis need to be referred to a transplantation centre as fast as possible.

With the advent of new anti-fibrotic medication the prognosis has improved for these patients and the chances of being referred, evaluated and transplanted in case of progression have improved. On the other hand the patients reaching end stage fibrotic lung disease tend to be older and have comorbid conditions that influence the overall outcome after lung transplantation (2).

10.1.2 CYSTIC FIBROSIS

Cystic fibrosis usually affects many organ systems. The lungs have been the organ most affected by the disease generally, thus it is the limiting factor. Frequently, patients who require lung transplantation are carriers of multiresistant bacteria such as Pseudomonas aeruginosa or less frequently Burkholderia cepacia. Thanks to progresses of the peri-and postoperative management and the young age of these patients, cystic fibrosis patients have one of the best prognoses after lung transplantation. Patients should be referred to the transplant centre before they lose a lot of weight irreversibly, which is known to influence post-transplant outcome (3). Considerable progress was made in the management of cystic fibrosis. During the last 10 years a new drug, consisting of small molecules targeting the CFTR protein, has been developed. That leads to a disease-modifying course over time and prevents progression of the underlying disease, thus postponing transplantation temporarily or definitely (14).

10.1.3 COPD

Globally, COPD is known to be the most common indication for lung transplantation. Patients on the waiting list have a good prognosis and generally survive until transplantation. It is important to

know when a volume reduction surgery is needed or possible. Patients, who are older than 65 and who have a forced expiratory volume 1 (FEV1) of more than 20% and a heterogenic emphysema with severe lung dilation, generally meet the requirements for a lung volume reduction procedure (3).

Younger patients with severely decreased lung function and homogeny emphysema should preferably receive a lung transplant. In COPD, uni- or bilateral lung transplantation is adequate. In case of a unilateral transplantation, the operation time is decreased, but the remaining lung can cause complications postoperatively. The functional results and long term survival rate after bilateral transplantations are better, that is why USZ prefers this method (3), as well as KK (13).

10.1.4 PRIMARY AND SECONDARY PULMONARY HYPERTENSION

Primary and secondary pulmonary hypertension (i.e. after recurrent embolism to the lungs) is an indication for lung transplantation, theoretically. But due to IV/ inhalation prostacyclin (vasodilator) therapy and other potent drugs (endothelin receptor antagonists), lung transplantation is required less frequently, nowadays. Only patients who do not respond to drug therapy are in need of a lung transplant (3).

Apart from the aforementioned diseases, lung transplantation can be used as a treatment of other rare end stage diseases such as lymphangioleiomyomatosis, histiocytosis X and sarcoidosis. These diseases have in common that after the successful lung transplant other organ systems can continue to be affected and the new transplant can sometimes be affected again (3).

10.2 POSTOPERATIVE MANAGEMENT

10.2.1 CHRONIC REJECTION REACTION

Chronic rejection (obliterative bronchiolitis) by itself is the most significant cause of chronic allograft dysfunction and late mortality after lung transplantation (16). Obliterative bronchiolitis syndrome (BOS) develops in 48% and 76% of patients by year 5 and 10, respectively, after lung transplantation, according to ISHLT reports (17). BOS is a scarring process that affects mainly the small non-cartilaginous airways of the lung transplant (18). Clinically, BOS manifests as an obstruction of the airway and dyspnoea will develop.

These symptoms are typically progressive and may lead to death of the patient. Nevertheless, the course of the disease is extremely variable, and discernible phenotypes may possibly exist (17). The diagnosis of BOS is defined by a sustained (≥ 3 weeks) decrease in the forced expiratory volume in the first second of expiration (FEV_1). Other causes of pulmonary dysfunction i.e. anastomotic stricture/complications, infection, acute rejection, or recurrent/progressive native disease must be excluded previously (19). The histological characteristic sign of BOS is obliterative bronchiolistis. It is an inflammatory and fibrotic process of the membranous and respiratory bronchioles characterized by subepithelial fibrosis causing partial or complete luminal occlusion (20). When BOS is diagnosed, it can be too late for treatments to reverse the airway pathology for most of the patients (17). Treatment options for BOS commonly remain unsatisfactory. Uncontrolled studies show treatment responses with miscellaneous strategies. Often, they present positive responses as "stabilization" or decrease in the pace of decline of FEV_1; improvement was documented, seldomly (21). Re-transplantation is a treatment option for BOS. It has been performed for LTRs with BOS, but it resulted in inferior survival rates than those of the initial transplants. On the other hand, survival after re-transplantation for BOS is superior than survival after re-transplant for early (within 30 days of transplantation) transplant failure (22).

10.2.2 INITIAL IMMUNOSUPPRESSION AND ANTIMICROBIAL THERAPY

A key issue of the successful lung transplantation is the establishment of adequate immunosuppression in order to prevent acute allograft rejection, while over-immunosuppression must be avoided as well. In general, a standard triple immunosuppressive regimen is used. Initial dosing has been discussed at the time of listing the patient for lung transplantation. Calcineurin inhibitors (CNIs), especially cyclosporine A (CsA) and tacrolimus (TAC), are cornerstones of the immunosuppressive therapy (7). Both TAC and CsA are administered as immunosuppressive agents. It is not clear which of these medications is better in reducing rejection and death without causing adverse effects. A study suggests that TAC may be superior to CsA in respect to bronchiolitis obliterans syndrome, lymphocytic bronchitis, treatment withdrawal, and arterial hypertension. However TAC may be inferior concerning development of diabetes. There was no difference noted regarding mortality and acute rejection among patients treated with TAC and CsA (23).

Many lung transplant centres make use of induction therapy starting in the peri-transplant period to grant improved immunosuppression during this critical period. Induction therapy focuses on the inhibition of T-cells (24).

Frequently occurring medical emergencies are linked to the lifelong immunosuppressive therapy and the manifold associated drugs ensuing in long term polymedication with many adverse effects and drug interactions. The complications that are seen, frequently arise, because of infection, graft rejection and other drug related effects i.e. bone marrow suppression, skin and/or bone lesions(25).

Complications associated with infections in particular are one of the most significant causes of morbidity and mortality in patients who received a lung transplant (26). Recognizing the pathology can be difficult, and signs and symptoms may be deceptive. Lifelong immunosuppression is obligatory to avert acute and chronic rejection. Thus, the immune system is impaired, which increases the patients` susceptibility to infectious agents. Transplant recipients can congregate infections from a large range of microorganisms. Transmission of infectious agents could originate from donors and it is important to notice that transplant recipients can suffer from severe infections from microorganisms that are comparatively harmless for a immunocompetent host (27). It is important to mention that LTRs are more vulnerable to infections in comparison not only to immunocompetent hosts but also to solid organ transplant recipients. In LTRs respiratory tract infections (RTIs) are feared especially, because they have a negative impact on the long-term functional outcome (28). Bacterial infections cause around half of all infectious complications (8). One of the most hazardous infections is tuberculosis (TB), due to its more frequent occurrence (20–74 times) in lung transplant patients compared to the general population (5). Cytomegalovirus (CMV) infections have become less frequent, due to prophylactic treatments. Invasive fungal infections remain a threat, but they have decreased as well, because there is better control of the risk factors and because of the use of pre-emptive antifungal therapy. Respiratory, non-herpes viral infections have become a serious problem. Some of the viral infections may be treated with Ribavirin. Thus, thorough postoperative observation is vital for the management of lung transplant recipients in order to detect and treat rejection and infections (8).

10.3 COMPARISON OF KK AND USZ: POST TRANSPLANTATION TREATMENT PLAN

10.3.1.1 WARD ROUNDS AND OBSERVATION SCHEDULES

After transplantation, the patients are transferred to the intensive care unit (ICU) directly from the operating theatre in USZ (7), as well as in KK (29).

In general, patients are still intubated and some may need postoperative extracorporeal membrane oxygenation (ECMO) support. Weaning from both ventilator and ECMO is primarily in the responsibility of the ICU physicians, but they consult with the thoracic surgeon and transplant pulmonologist, too.

The consultation of the transplant physician and transplant surgeon with the other doctors, who are involved in the care of the transplant patient, consists during the whole treatment. For example, the ICU physician goes on ICU ward rounds twice daily together with the transplant team. It is very important in order to assist with monitoring the patient's clinical status and to receive a cross-functional picture on the patient's progress and status, including vital signs, early immunosuppression, monitoring of wounds and wound drains, nursing information and physical therapy. At least one daily ward round should be attended by a senior thoracic surgeon, a transplant physician and the ICU physician in charge, who work as a team. In USZ, there is a transplant infectious diseases specialist who can be consulted on demand. Infections are one of the most frequent complications in this period. (7). In KK centre, the LTRs are transferred to the intensive care unit of thoracic and cardiac surgery. They are consulted by a cardio surgeon, a specialized physician for the cardiologic and thoracic ICU and a pulmonologist. They do rounds once a day, unlike in USZ, where two patient visitations are done per day. In KK there is a clinical microbiologist for infectious diseases as well, who is also consulted on demand (29).

10.3.1.2 CHECKS ON DAILY WARD ROUNDS

During daily ward rounds in USZ, the transplant team takes into account all aspects related to the patients' polymedication, which helps to continuously adjust the medication and optimize therapeutic measures. Before the vital signs and clinical parameters are accessed, the doctors of USZ discuss laboratory and imaging results. The ICU physician and nurse inform the transplant team about the most recent developments, and the further treatment plan is discussed (7). In KK, the vital and clinical parameters, polymedication and laboratory as well as imaging results are evaluated and corrective measures are applied, if it is required. The aforementioned cardio surgeon, pulmonologist and ICU physician however do not necessarily work in a team every day during the ward round. They may consult the patient individually during the day. Whether a meeting of these specialists is required or not depends on the patient`s clinical status: If he is unstable and requires special care the specialists will work as a team every day in order to stabilize the LTR. The ICU physician updates the specialists of the patient`s status on every ward round individually (29).

10.3.1.3 FLUID MANAGEMENT AND ROUTINE CHECK UPS

Lung transplant patients show a tendency to be fluid overloaded in the first postoperative days. It predisposes the patient to pulmonary oedema, so it is an important factor to be managed.

It can be seen by increased weight in most cases (10%–15% increase in body weight) and oedema

usually in the lower limbs, but it is not necessarily limited to the lower limbs only. Lack of lymphatic drainage in the transplanted lung requires careful fluid management as well, since there is the possibility of pulmonary oedema in LTRs. In USZ the aim is to carefully reduce fluid balance, with the use of diuretics (weight reduction should not be >1 kg/day). Measures such as bandaging or compression stockings are applied. Resolution of leg oedema usually takes weeks. It can speed up, when the patient`s mobility increases. Routine checks include, electrolytes, liver and kidney function, signs of infection/inflammation like C-reactive protein (CRP), procalcitonin and CsA levels (C0 and C2). These are measured, daily, initially (7).

In KK the fluid management is entirely in the hands of the ICU physician and it is not accessed by the other specialists. Since in KK Tacrolimus (tac) is used instead of Cyclosporin A (CsA), the Tac levels are measured every day 1 hour before next dose administration. Usually the drug level measurements as well as the next dose are done in the morning. Laboratory tests for electrolytes, liver and kidney function, markers of infection/inflammation, like C-reactive protein (CRP), procalcitonin are obtained and evaluated daily. These values are determined in order to detect signs of infection or diagnose other complications as early as possible(29).

Later, in the stabilisation phase it will be measured 3–4 times per week. In addition, CMV and EBV viral load via PCR, as well as serum level of itraconazole are measured weekly in the first month after the transplantation. Additionally, immunoglobulin levels are obtained once postoperatively before administration of IVIG (7) In Kaunas University hospital, the aforementioned measurements are conducted in the stabilisation phase once a week. CMV and EBV viral loads are checked via PCR pre and postoperatively, as well as immunoglobulin levels once preoperatively , in order to assess the patients' immunological status. CMV and EBV levels are checked weekly in the stabilization phase thereafter. In the ambulatory phase of a stable patient, Tacrolimus levels are checked at every visit (29).

10.3.1.4 STABILISATION ON THE WARD

In the USZ once the LTRs are extubated, and depending on the course and current status of the early postoperative phase, patients are transferred to the regular transplant ward. This can happen as early as day 2 post operatively. During the following days it is important to fine-tune the immunosuppression, introduce additional prophylactic medication, as well as to remove all the chest tubes, and increase physiotherapy and mobilisation of the patient. (7)

In KK the LTRs are not transferred from the ICU ward before week 1. If they are stable they will be

transferred to the regular cardiac surgery ward. After that they are brought to the pulmonology department. From there the patient is discharged from the hospital to rehabilitation if they are in a good clinical condition. The average lung transplant patients stays in KK for about 3-4 weeks. The wound drains are checked and removed by the cardiac surgeon in the ICU. When the patients arrive on the pulmonology ward the drains have been removed already(29).

Under the required profound immunosuppression therapy, wound healing is delayed. For USZ centre that means removal of suture material is postponed until week 3 postoperatively to allow for sufficient healing to occur(7). In KK the sutures can be removed 7 days postoperatively earliest, but depending on the situation they may be removed later. However, physicians do not wait for 3 weeks postoperatively to remove sutures as a rule(29).

In USZ there are patients, who previously required ECMO. In these individuals local wound healing complications at the sites of cannulation, such as inguinal, anterior chest wall or jugular region, occur frequently. Infections manifest as skin erythema and lymphatic fistula as protracted secretion of lymph. Sometimes conservative treatment is insufficient and surgical revisions have to be undertaken. There is no such observation in Kaunas hospital, since the use of ECMO occurs very rarely in KK transplant patients; only in very critical cases this method has been used. Those patients who needed ECMO did not show local wound healing complications (29).

Due to immobility and increased risks of thromboembolic events, LTRs receive prophylactic IV heparin (generally 10000 IU/24h) from day 0 to the day of discharge unless oral anti coagulation is needed for diseases such as preoperatively diagnosed pulmonary hypertension or arrhythmia. Removal of the chest drainage is required when the daily drainage amount is <200 ml with concomitant weight loss. LTRs are prone to reflux and aspiration, therefore positioning in reverse Trendelenburg position is of importance, as it aids to prevent these events. Correct drainage and fixation of the tubes has to be checked by the transplant team daily on ward rounds.

In KK low molecular weight heparin is administered during the early post-operative phase in ICU. Later when the LTRs are in the pulmonology ward, they do not receive any anticoagulants unless there are clinical conditions that require prescribed anticoagulation therapy. The responsibility of checking the drainage and fixation of tubes lies with the cardiac surgeon, who checks the transplant recipients on the daily rounds. The therapy for prevention of reflux and aspiration in KK is similar to the one in USZ described above: Reverse Trendelenburg position as well as the administration of omeprazole is used as a reliable method to prevent these complications (29).

10.3.1.5 CHEST IMAGING

Chest X ray: At USZ centre, initially a chest x-ray is performed every day during the first week. Important aspects that have to be checked on the chest x-ray are the following: Are there signs of chest tube obstruction, haemothorax, atelectasis or infection?

Chest x-rays (CXRs) are useful to detect early and late complications. In unclear situations, chest computed tomography (CT) without contrast agent can be performed in addition. A potentially fatal early postoperative complication with features on chest x ray is primary graft dysfunction. It may be present as diffuse pulmonary oedema and/or by mimicking an acute respiratory distress syndrome. Primary graft dysfunction is defined as a triad of worsening gas exchange, decreased lung compliance, and alveolar and interstitial infiltrates typically most extensive in the perihilar region. These changes occur typically during the first 72 hours.

In KK chest x-rays are performed daily during the first week post operatively to check for the same signs as mentioned above. During the stabilisation phase chest x-rays are performed once per week. Primary graft dysfunction is rarely encountered in KK, therefore there are no routine check –ups(29).

10.3.1.6 LABORATORY VALUES

Following values have to be checked during the treatment of LTRs in USZ:

CRP, creatinine, electrolytes, glucose, complete blood count, C0/C2 levels, microbiology results from recipient and from donor. Pre-albumin, albumin, protein, weight of patient, immunoglobulin levels, calcium and vitamin D levels, CMV and EBV via PCR(7).

The laboratory values that are important for treating LTRs in KK are nearly identical except for vitamin D levels which are not assessed and the fact that the levels of immunosuppressant tacrolimus (in USZ Cyclosporine A) are measured 1 hour before administration of the next dose once per day. No C0 and C2 level evaluations are conducted(29) since this is only established for Cycolsporine A.

10.3.2 IMMUNOSUPPRESSION, INFECTION PREVENTION AND TREATMENT

10.3.2.1 INITIAL IMMUNOSUPPRESSION

A central issue of successful lung transplantation is adequate immunosuppression in order to prevent allograft rejection, while over-immunosuppression has to be avoided too. In most centres, a

standard triple immunosuppressive regimen is used. Calcineurin inhibitors(CNIs), particularly cyclosporine A (CsA) and tacrolimus (TAC), are very important agents for immunosuppressive therapy. There are good points for both medications, but a majority of lung transplant centres use TAC as first line CNI, nowadays(7). The table below shows differences in immunosuppressive therapy in USZ and KK. The medications that are used vary from one institution to the other as well as the start and/or duration of the individual medication, even if the same one is used.

Table 1: Immunosuppression: Differences in drug use in USZ and KK(30)(29)

Medication	**USZ**	**KK**
Basiliximab (induction therapy)	yes	no (ATG antimocytic globulin is used instead)
Duration:	Day 0 and 4 (a total of 2 doses)	-
ATG antimocytic globulin (induction therapy)	no	yes
Duration:	-	Day 0-10 or 14
Tacrolimus:	not first choice, second line	yes
Duration	Maintenance if CsA inadequate	Maintenance therapy
Mycophenolate Mofetil	yes	yes
Duration	early post-op phase every 12 h lifelong	Day 1- lifelong
Methylprednisolone	Yes 500mg after each lung intraoperatively	yes
Duration	intraoperative, early post-op phase every day	induction therapy intraoperative
Prednison	yes	yes
Duration:	Day 1-lifelong	intraoperative, Day 1-2 post-op, every 12 hours
Cyclosporin A	yes	no
Duration	Start: 2 hours pre-op, lifelong	
Prednisolone	Second choice, if prednison inadequate	yes
Duration	when switched -lifelong	Day 3-lifelong
Azathioprine	No (was used in early phase of transplant programme)	no (alternative)

Table 1: CsA is USZ`s drug of choice because of their experience for many years with the particularities of the compound, and they reserve TAC for rare situations as a second-line CNI. Immunosuppressive medication is started shortly before the transplantation surgery with the first dose of oral CsA approximately 2 hours before anaesthesia is initiated.

Steroids and mycophenolate (MMF) are instigated postoperatively. Both are continued postoperatively

every 12 hours. At USZ , induction therapy is employed consisting of basiliximab on both day 0 and day 4 post-operatively. Immunosuppression includes methylprednisone 500mg IV given at the time of reperfusion for each lung (two doses for bilateral transplantation, which equals 1 g in total). It is followed by a reduced dose of methylprednisone IV on days 1 and 2 after surgery. From day 2 onwards, the dose of CsA is adjusted based on therapeutic drug monitoring (TDM). In case of renal dysfunction, lower target levels of C0 and C2 are used. If satisfactory levels are not reached within 3–4 days the drug has to be administered intravenously (IV), especially in the case of altered intestinal absorption. It is important to know that CsA has a low bioavailability and the IV dose is only approximately one-third of the oral dose. In event of insufficient absorption of MMF and steroids they are to be administered IV as well, until the clinical condition improves and oral administration is possible(7).

In KK immunosupression is started 2 hours before commencement of surgery as well, but with the first dose of ATG antimocytic globulin IV. Mycophenolate (MMF) is administered from Day 1 post-operatively for the rest of the patient`s life. Induction therapy is used in KK, too, using methylprednisolone intraoperativly with the same dosage and timeslots as in USZ. Instead of CsA, in the Lithuanian Hospital TAC is administered sublingually or orally as maintenance therapy. According to the table, USZ uses Prednison and KK uses Prednisolon, both liefelong. USZ only changes to Prednisolon, in case Prednison does not seem to be effective or overall immunosupression seems inadequate.

In KK, too, the drugs are administered as soon as possible orally. In case of decreased absorption the administration is switched to IV, until the absorption of the intestinal tract is sufficient(29).

10.3.2.2 INFECTION PREVENTION AND TREATMENT POST OPERATIVELY

LTRs are prone to infection because of the profound immunosuppression, that is the reason why the following treatments are very important (7).

10.3.2.3 ANTIVIRAL THERAPY

The table below shows the different approaches of KK and USZ in antiviral prevention and treatment strategies.

Table 2: Antiviral prevention: Differences in drug use between USZ and KK(7), (29)

Infective agent: CMV		
	USZ	**KK**
Medication	Low risk: valacyclovir	Gancylovir
	Intermediate and high risk*:	-
	Valgancyclovir	-
Duration (days post operatively)	twice a day post-op	Day 0-3
	Intermediate to high risk: Day 0-week 2 ganciclovir, Infinitely: Valgancyclovir***	-
Route of Admission	Low risk: PO	IV
	high risk: PO and Valgancyclovir IV	-
Infective agent: EBV		
	USZ	**KK**
Medication	high risk **:Valacyclovir	Valgancyclovir
	low risk : -	Valgancyclovir
Duration:	high risk: Twice a day, if not treated already with Valgancyclovir IV	-
Duration	low risk: -	-
Herpes simplex virus and varicella zoster	Same as CMV treatment	-

(*USZ: For CMV there is a classification for low intermediate and high risk patients, depending on whether or not the donor and/or the recipient were infected with CMV at the time of transplantation: D (donor) -/R (recipient) - : low risk; D- /R+ or D+/ R- or D+ /R+: intermediate, and high risk if D+/R- (7) **EBV high risk patient in USZ and KK: D +/ R-(7)(29)

***Reduce dosage in case of worsening renal function or cytopenia (7)

Table 2: The most notable differences can be found in the preventive treatment of CMV. While USZ has a classification system between high, intermediate and low risk patients, KK has no classifications for this pathogen and treats all patients equally with gancyclovir IV, from Day 0-3 post-operatively. In

USZ, high and intermediate risk patients are treated with gancyclovir initially (ICU) and then valgancyclovir. Valacyclovir is used in low risk patients as well 2x/day.

EBV is classified in high and low risk patients in both centres and treated with valacyclovir. The only difference is that in USZ high risk patients may be treated longer than 1 year, while in KK the maximum treatment period is 12 months.

Varicella zoster and Herpes simplex viruses are prevented with the same drugs that are effective for CMV.

10.3.2.4 ANTIFUNGAL THERAPY: PREVENTION AND TREATMENT

Table 3: Antifungal therapy: Differences between drug use in KK and USZ(7)(29)

Aspergillus spp		
	USZ	**KK**
Medication (treatment)	Caspofungin	-
Duration (days post op)	Day 0- at least for 2 weeks	-
Medication (prevention)	Itraconazol Day 5- lifelong	Itraconazol Day 5- 3 months
Pneumocystis jirovecci		
	USZ	**KK**
Medication	Trimethoprim-cotrimoxazol	Trimethoprim-sulfametroxazol
Duration (days post op)	Start: Day 0 (lifelong)	Start: Day 5 (lifelong)

Table 3: Fungal organisms such as Aspergillus are treated in USZ with Caspofungin and in KK with Itraconazol both are lifelong therapies, however unlike the Swiss centre, KK starts treatment of Aspergillus on Day 5 instead of Day 0 post operatively. Pneumocystis jirovecci is covered by similar medications in both centres, with the same duration and onset of treatment as described above in both treatment facilities.

10.3.2.5 ANTIBACTERIAL THERAPY

Table 4: Antibacterial therapy: Differences of drug use between USZ and KK(7) (29)

Prophylactic treatment		
	USZ	**KK**
Medication	Piperacilin-tazobactam or meropenem	Piperacilin-tazobactam
Duration (days post op)	Start: Intraoperatively Continued for 3-4 weeks	Day 0-5
Route of admission	IV	IV
Pseudomonas aeruginosa		
	USZ	**KK**
Medication	Dual antibiotic strategy on basis of previous antibiogram: Piperacillin-tazobactam or meropenem and ciprofloxacin, or aminoclycoside (tobramycin) or colistin	Piperacillin-tazobactam or ciprofloxacin
Duration	Start: According to pre -operative respiratory tract swap culture results	Start: When detected
Route of admission	IV ex.: ciprofloxacin po	IV
Multiresistant PSA		
	USZ	**KK**
Medication	Triple antibiotic strategy: colistin or tobramycin (or rarely taurolidine) added to dual antibiotic strategy	-
Duration	postoperatively, duration at least 2 weeks, generally longer (3-4 weeks).	-
Route of admission	IV ex.: colistin IV (early) or inhaled (late)	-
PSA or Burkholderia cepacia complex in cystic fibrosis patients		
	USZ	**KK**
Medication	Taurolidine	-
Duration (Days post op)	Day 0-week 4	-

Route of admission	Inhaled	-
Clostridium spp		
	USZ	**KK**
Medication	Metronidazole empirically	-
Duration	2x a day until infection subsides and repeated sampling is negative	-
Route of admission	p.o.	-
Staphylococcus aureus		
	USZ	**KK**
Medication	-	Vancomycin
Duration	-	2x d until infection subsides
Route of admission	-	PO
Pronounced leucocytosis with clostridial infection (only in case of hypogammaglobulinanemia)	**USZ**	**KK**
Medication	Immunoglobulins	-
Route of admission	IV	-

Table 4: Most remarkable differences in antibacterial therapy are seen in the pseudomonas aeruginosa (PSA) infection treatment: USZ takes respiratory tract cultures pre-operatively and treats patients with a dual antibiotic strategy based on antibiotigram results. In KK patients are treated empirically (piperacillin-tazobactam or ciprofloxacin), whenever the infection is detected.

Furthermore, there is no routine treatment for multiresistant PSA or Burkholderia cepacia complex in cystic fibrosis patients in KK. KK has no a routine treatment option for Clostridium spp infections. However, KK has a set treatment plan for staphylococcus aureus infections: Vancomycin 2x per day PO until there are negative cultures. In USZ there is no premeditated treatment plan for this pathogen.

Both centres administer the same medications as prophylactic treatment, but USZ starts administrating intra operatively until week 3 or 4 post operatively, while KK administers the prophylactic antibiotics from day 0-5 post operatively.

10.4 MOST REMARKABLE DIFFERNCES BETWEEN USZ AND KK TREATMENT GUIDELINES AND CONDUCTION OF POST TRANSPLANTATION CARE

10.4.1 DIFFERNCES IN WARD RONDS AND OBSERVATION SCHEDULE

- USZ: A team of an ICU physician, thoracic surgeon and a transplant physician, who work as a team together every day.
- They consult the patient twice a day, to obtain a cross functional picture of the patient`s status.
- As a team, it is less likely to miss early symptoms and signs of complications, i.e. infection or early graft rejection reaction.
- KK: The responsible doctors visit the LTR only once per day, separately from each other. Only if the status of the patient declines, they will form a team.
- There is no transplant physician, but a pulmonologist, who consults the LTRs instead.

10.4.2 DIFFERNCES IN FLUID MANAGEMENT

- USZ: Fluid overload is an important factor in USZ that is treated carefully and precise instructions are given on how to reduce the fluid overload.
- KK: Fluid management is entirely in the hand of the ICU physician and is not discussed in detail in the treatment guidelines.

10.4.3 DIFFERENCES IN THE STABILISTATION PHASE MEDICATION

- USZ: CsA is measured initially daily, then 3–4 times per week.
- CMV and EBV viral load via PCR, as well as serum level of itraconazole are measured weekly in the first month after the transplant.
- Immunoglobulin levels are obtained once postoperatively before administration of IVIG
- KK: TAC is measured phase once a week.
- Itraconazole is not measured weekly during the first month
- Immunoglobulin levels are accessed once preoperatively and IVIG are not administered routinely
- Tacrolimus levels are checked during every visit in the ambulatory phase

10.4.4 DIFFERENCES IN THE STABILISATION ON THE WARD

- USZ: Patients are transferred to the transplant ward as early as day 2 post operatively.
- physiotherapy and mobilisation of the patient is conducted on the transplant ward
- KK: LTRs are not transferred from the ICU ward before week 1.
- When stable they are transferred to the regular cardiac surgery ward
- Afterwards they are transported to the pulmonology ward
- The patient starts rehabilitation after discharge from the hospital
- USZ: removal of suture material is postponed until week 3 postoperatively
- KK: Sutures can be removed from day 7 postoperatively and onwards
- Physicians do not wait for 3 weeks postoperatively to remove sutures as a rule
- USZ: Patients, who previously required ECMO may have local wound healing complications at the sites of cannulation
- Sometimes conservative treatment is insufficient and surgical revisions have to be undertaken.
  KK: ECMO occurs hardly in KK transplant patients
- Patients who needed ECMO did not show local wound healing complications
- USZ: LTRs receive prophylactic IV heparin (generally 10000 IU/24h) from day 0 to the day of discharge

  KK: low molecular weight heparin is administered during the early post-operative phase in ICU, but it it`s administration is stopped when the patients are cleared from the ICU

10.4.5 DIFFERENCES IN CHEST IMAGING CONTROL

- USZ: there are daily routine check-ups for primary graft dysfunction on chest X-ray
- KK: Primary graft dysfunction is rarely encountered, therefore there are no routine check –ups for this specific syndrome

10.4.6 DIFFERENCES IN IMMUNOSUPRESSION THERAPY

- USZ: They use CsA as maintenance therapy and they reserve TAC for rare situations as a second-line CNI.

  KK: They use TAC as maintenance therapy, while CsA is reserved for rare situations.
- USZ: Start of immunosuppressive medication is administered 2 hours before anaesthesia is initiated with an oral dose of CsA

- KK: Start of immunosuppression is 2 hours before commencement of surgery as well, but with the first dose of ATG antimocytic globulin IV (induction therapy)
- USZ: Induction therapy is employed consisting of basiliximab on both day 0 and day 4 post-operatively.
- KK: Mycophenolate is administered from Day 1 post-operatively for the rest of the patient`s life
- USZ: Steroids and mycophenolate (MMF) are instigated postoperatively. Both are continued postoperatively every 12 hours.
- KK: Prednisolone is administered from day 3 onwards for the rest of the patient`s life.
- USZ: does not administer prednisolone at all.
- USZ/KK: Prednison is used in both centres, but in USZ it is used for a longer period of time than in KK.

10.4.7 DIFFERENCES IN ANTIVIRAL THERAPY

- USZ: For CMV, there is a classification system between high, intermediate and low risk patients
- KK has no classifications for CMV, thus treating all patients equally with gancyclovir IV, from Day 0-3 post-operatively IV.
- USZ: High risk patients of EBV infections may be treated longer than 1 year
- KK: The maximum treatment period is 12 months. for EBV infections of high risk patients
- USZ: Varicella zoster and Herpes simplex are treated the same way as CMV
- KK: There is no notion, as to how the above mentioned pathogens are treated.

10.4.8 DIFFERENCES IN ANTIFUNGAL THERAPY

- USZ: Fungal agents such as Aspergillus are treated with Caspofungin; Start of drug administration is Day 0 post operatively.
- KK: Itraconazol is used to cover Aspergillus infections; Start of treatment is Day 5 post operatively
- USZ: For mixed infective agents Itraconazole or Amphotericin is used from day 5-7 post-operatively
- KK: They do not have an additional coverage for mixed infective agents

10.4.9 DIFFERENCES IN ANTIBACTERIAL THERAPY

- USZ: Pseudomonas aeruginosa: They take respiratory tract cultures pre-operatively and treat patients with a dual antibiotic strategy based on antibiotigram results.
- KK: Pseudomonas aeruginosa: Patients are treated empirically (piperacillin-tazobactam or ciprofloxacin), whenever the infection is detected.
- KK: Multiresistant PSA/Burkholderia cepacia complex: There is no routine treatment for multiresistant PSA or Burkholderia cepacia complex in cystic fibrosis patients
- KK: Clostridium spp: There is no routine treatment plan for infections Clostridium spp.
- USZ: Staphylococcus aureus: There is no notion of a premeditated treatment plan for this pathogen.
- KK: They have a set treatment plan for staphylococcus aureus infections
- USZ: Prophylactic treatment starts intra operatively until week 3 or 4 post operatively
- KK administers the prophylactic antibiotics from day 0-5 post operatively.

11. CONCLUSIONS

1. The comparison of post operative lung transplantation guidelines and treatment shows that chronic rejection (obliterative bronchiolitis) is the most significant cause of chronic allograft dysfunction and late mortality after lung transplantation. Obliterative bronchiolitis syndrome (BOS) develops in 48% and 76% of patients by year 5 and 10, respectively. A key issue of the successful lung transplantation is the establishment of adequate immunosuppression in order to prevent acute allograft rejection.

2. Calcineurin inhibitors (CNIs), cyclosporine A (CsA) and tacrolimus (TAC) are administered as immunosuppressive therapy. It is suggested that TAC may be superior to CsA in respect to bronchiolitis obliterans syndrome, lymphocytic bronchitis, treatment withdrawal, and arterial hypertension. There was no difference noted regarding mortality and acute rejection among patients treated with TAC and CsA. Many lung transplant centres make use of induction therapy starting in the peri-transplant period to grant improved immunosuppression. Bacterial infections cause around half of all infectious complication. One of the most hazardous infections is tuberculosis (TB), due to its more frequent occurrence (20–74 times) in lung transplant patients. Respiratory, non-herpes viral infections have become a serious problem. Thorough postoperative observation is vital for the management of lung transplant recipients in order to detect and treat rejection and infections as early as possible.

3. The most remarkable differences between KK and USZ are following: For immunosuppression both centres opt for induction therapy, but in USZ Basiliximab is administered, whereas KK uses ATG antimocytic globulin. In KK Prednisolone is administered from day 3 onwards for the rest of the patient`s life, but in USZ this medication is not administered at all. For viral infection prevention and treatment, namely CMV, there is a classification system between high, intermediate and low risk patients in USZ, however KK has no classifications for this pathogen and treats all patients equally with Gancyclovir IV. USZ opts for a preventive treatment strategy concerning Pseudomonas aeruginosa infections: Respiratory tract cultures are taken pre-operatively and patients are treated with a dual antibiotic strategy based on antibiotigram results. Patients in KK are treated empirically, whenever a Pseudomonas aeruginosa infection is detected. In USZ, there are no set treatment plans for staphylococcus aureus infections, while KK treats these infections with Vancomycin. Moreover, the prophylactic treatment in USZ starts intra operatively until week 3 or 4 post operatively, while in KK the administrations of the prophylactic antibiotics last from day 0-5 post operatively. During daily ward rounds the doctors of KK visit the LTR once per day, separately from each other, while in USZ a team of an ICU physician, thoracic surgeon and a transplant physician visit the patient twice per day. Additionally, there is a pulmonologist instead of a transplant physician, who consults the patients in KK.

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13. ANNEX

POST TRANSPLANTATION MEDICATION OF KK

Table 5: Immunosuppression therapy (29)

Medication´s name		**Route of admission and dosage**	**Time post LTx**	**Therapeutic drug monitoring**
ATG antitimocytic globulin		Induction therapy 1,5 mg/kg/d IV	1mg/kg/d 10 to 14 days	
Basiliximab alternative drug				
Methylprednisolone		500mg iv per lung	Intraoperatively 2 day 125mg Iv every 12h 4 doses	
Maintenance:	Tacrolimus		Day 1	Measured 1h before next dose: 10 to 15 ng/ml during first 6 months, 24 months: 8 to 10ng/ml after 24 months: 6 to 8 ng/ml
Alternative Cyclosporine	Not used, tacrolimus			
Prednisolone				Begins 3rd day post op per os 1st 3 months 20 mg per day per os day 3- 3 to 6 m: 15 mg 6 to 12 months 10 mg per day 12 to 18 months 7.5 mg. Lifelong 5 mg per day
Mofetil mycophenolat				Pod 12 g per day, if TAC used: lifelong
Alternative: Azathioprine				

Table 6: Antibiotic therapy(29)

Infective agent	**Medication´s name**	**Route of admission and dosage**	**Time post LTx**
Prophylactic	Piperacillin Tazobactam	Iv 3.5 g/kg 3 to 4 x per day	0 -5 or 7d
Staphylococcus spp.	Vancomycin*	1g 2x d IV	
Pseudomonas	Piperacillin tazobactam ciprofloxacin	IV 3.5 g/kg 3 to 4x per day Ciprofloxacin: 400mcg 2xd IV	
Wait for microb. results and adjust in case of other inf.			

*Allergy linezolid 600mg per d IV

Table 6: Antiviral therapy (29)

Infective agent	**Medication´s name**	**Route of admission and dosage**	Time post LTx
CMV	Gancyclovir	5mg/kg iv 2x d	If CMV infection - 2-3 weeks – For CMV prophylaxis – 5 days
	Later – oral valganciclovir	900mg per day	If CMV infection – continue at least 3 months or CMV DNA becomes negative; For prophylaxis – continue at least 6 months, high risk 12 months

Table 7 : Antifungal therapy (29)

Infective agent	Medication´s name	Route of admission and dosage	Time post Ltx
Aspergillus	Itraconazole	100mg 2xd	5 day post op for 3 months
Pneumocystis Jirovecii	Trimetroprim/ sulfametoxazole	80/400 mg 3x w	5 day post op for life
	Alternative: Dapson	50 or 100mg per day	5 day post op
Candida albicans	No prophylaxis		
Toxoplasmosis	Pirimethamin and folic acid	25 mg every day/ 1mg per day	For 6 weeks

All doses are in dependence of renal clearance.

Table : Acute rejection treatment (29)

A0, A1 B1	No additional measures	
A2 (<3months post op)	Pulse therapy methylprednisolone	3 days 500mg iv 4 day: 0.5mg/kg per day decrease until maintenance dose
Recurrent rejection reaction	Pulse therapy	1000 mg iv for 3 days Day 4 the same as above
A2 (>3month op)	Repeat bronchoscopy and bronchial bioscopy after 1 month	
A3, 4 B2, B3, B4	Pulse therapy methylprednisolone	1000mg iv for 3 d , day for same
If rejection repeats	Change maintenance immunosuppression	Cyclosporine to tacrolimus azathioprine mycophenolat or give additionally basiliximab or atg

A: histological lung, b: bronchi

Table 8: Chronic rejection reaction (29)

No effective treatment	
Pulse therapy Methylprednisolone 500 or 1000mg IV depending on severity	Cyclosporine change to TAC, azathioprine, Mycophenolat or give additionally Basiliximab or ATG (usually not the case)
Give additionally ATG antitimocytic globulin or Basiliximab	Give Azithromycin 3x with 500mg tab
Last option: Retransplantation	

POST TRANSPLANTATION MEDICATION OF USZ

Table 9: Immunosuppression therapy (30)

Immunosuppression therapy:			**Therapeutic drug monitoring**	
Medication´s Name	**Route of admission and dosage**	**Time post LTx**	**C0 through levels (mcg/L)**	**C2 level (mcg/L)**
Basiliximab (Simulect®)	20 mg iv Induction therapy	Day 0 &4		
Cyclosporine A (Neoral® caps)	Approx. 4-6 mg/kgKG/day in two doses as initial dose per os	Every 12h	250-300	Week 1&2 1200 – 1800 Week 3: 1000-1200
Tacrolimus (Prograf®)	Approx. 0.1 mg/kg Initial dose per os	Every 12h	Weeks: 1&2: 15-20 >2 weeks: 12-15	
Mycophenolate Mofetil (CellCept®)	> 50 kgKG: 3 g/d	1,5 g per os every 12 h	(2-5)	
	< 50 kgKG: 2 g/d	1 g per os every 12 h	2-4	
Methylprednisolone	2x 500 mg Intraoperatively	IV		
	125 mg Early postoperative phase	Every day *		
Prednison®	0.5 mg/kgKG	Day 4-Week 4: every day		

*Change mode of admission of steroids: iv to per os as soon as CNI-target levels are reached and the patient defecates regularly

Table 10: Antifungal Therapy (7)

Infective agent	**Medication´s name**	**Route of admission and dosage**	**Time post LTx**	
Pneumocystis jiruvecci	trimethoprim-cotrimoxazol (prophylaxis)	Tab per os Bactrim forte 1 Tabl Mo/Mi/Fr	Day 0 continued 3 times per week lifelong	Dose reduction for renal failure (1/2 Tabl)
Documented pre transplant *Aspergillus* infection of recipient/donor samples	Caspofungin*	IV 50 mg	Day 0 and continued daily 10-14 days	
Regular antifungal therapy (mixed infective agents)	Itraconazole*	200 mg per os twice daily	Starting Day 5 - 7 twice a day	Target level 0.5-1
	Amphotericin B	10 mg Inhalation	Starting Day 5 - 7wice a day	

*Transient overlap of the antifungal spectrum (itraconazole plus caspofungin): do not interrupt itraconazole transiently for reasons of interaction stability, maintaining a stable immunosuppression

Table 11 : Antibacterial therapy (7)

Infective agent	**Medication´s name**	**Route of admission and dosage**	**Time post LTx**
	Broad spectrum abx (piperacillin-tazobactam or meropenem)	IV, usually for 3-4 weeks	Intraoperatively
Pseudomonas aeruginosa	dual antibiotic strategy on the basis of previous antibiograms: piperacillin-tazobactam or meropenem + ciprofloxacin, an aminoglycoside (tobramycin) or colistin IV	IV colistin (1 Mio Units, piptaz 4.5g, mero 1g (each 8 hourly) and/or cipro p.o.(500mg twice daily)	
Multiresistant PSA	triple antibiotic strategy: : colistin or tobramycin, or taurolidine added to dual abx	IV inhaled colistin (2 Mio Units, 8-hourly)	4 weeks
PSA or Burkholderia cepacia complex	taurolidine exclusively in **cystic fibrosis**	4 mL 1% solution* inhaled	Day 0 until week 4
Clostridium spp	Metronidazole empirically	500mg per os	3x a day
	Exceptionally: oral vancomycin to avoid interaction with CsA.		
Pronounced leucocytosis with *clostridial* infection (IVIG).	Immunoglobulin	IV 10g	only if hypogammaglobulinaemia

*A 1% solution is replaced with a 2% solution, if well tolerated, and nasal and oral inhalation routes are alternated. This use is off label and not supported by large clinical trials, yet in USZ experience it has proven valuable.

Table 12: Antiviral Therapy prophylaxis (31)

Infective agent	**Donor (D)/recipient (R) infection status**	**Medication´s name**	**Route of admission and dosage**	**Time post LTx**
Cytomegalovirus	D- /R – (low risk)	Valaciclovir (Valtrex)	1000mg p.o.	Twice a day
	D-/R+ or D+/R+ or D+/R- (intermediate and high risk)	Ganciclovir (Cymevene)	250mg IV	Twice a day for first 2 weeks post transplantation
		Valganciclovir (Valcyte)	450mg p.o.	Infinitely - Dose reduction: worsening renal function, cytopenia
		Immunoglobulin gamma	IgG < 7.0g/l iv	Additional treatment in the setting of Hypogammaglobulinemia
		Foscavir*		For resistant CMV strains
Epstein Barr Virus	(D-/R+) high risk	Valaciclovir (Valtrex)	500mg	Twice a day (if patient is not treated with this medication already due to CMV)
	Passive immunoprophylaxis	anti-EBV antibodies (immunoglobulin gamma)	IV	rarely
herpes simplx virus (HSV) varicella-zoster virus		See CMV treatment		

*Foscavir: Check urine for presence of crystals 2x/week. Daily monitoring of Na, K, Mg, Ca, P during first days of treatment. When stable: check 2x/ week

Table 13 : Antiviral therapy monitoring and treatment (31)

Infective agent	**Viral load (IE/ml)**	**Mediacation´s name**	**Route of admission and dosage**
Cytomegalovirus	0 - <80	No adjustment	
	>80 , but no signs of infection	Valganciclovir	900 mg twice a day po
	>800 and/ or signs of infection	Ganciclovir	5mg/kg twice a day IV

Monitor CMV-PCR in all patients at every outpatient visit (inpatient: 1x/ week):