The Intensive Care Infection Score to predict microbial infection and its sequelae in critically ill lung and heart transplant patients.

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The aim of this study is to evaluate the predictive value of a blood cell derived score, ICIS, for microbial infection, its likelihood, its invasiveness (blood stream infection) and severity (septic shock or mortality) in patients after lung or...

Ethical review	Approved WMO
Status	Pending
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Observational non invasive

Summary

ID

NL-OMON40847

Source
ToetsingOnline

Brief title
ICIS

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
bloodstream infection, Sepsis

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: ICIS, ICU, Infections

Outcome measures

Primary outcome

The likelihood of microbial infection and its invasiveness (bloodstream infection). On the basis of the collected data the investigators, blinded to the study results, will decide after completion of the study whether a proven local infection or not was present from day 0-7 after inclusion. In case of disagreement a third party will be consulted. Source and likelihood of infection will be based on criteria defined at the International Sepsis Forum Consensus Conference.

Secondary outcome

1.Septic shock. The SIRS criteria according to the ACCP/ SCCM consensus conference criteria of: a body temperature >38º C; a heart rate of >90 beats/ min; a respiratory rate > 20 breaths/ min or mechanical ventilation or white cell count (WBC) of < 4.0 x 109/L, will be used. When SIRS and a probable/ proven infection or BSI was present, patients will be classified as having sepsis. Shock will be defined by a systolic arterial pressure of < 90 mm Hg or mean arterial pressure (MAP) < 70 mm Hg for at least one hour despite adequate fluid resuscitation or requirement of vasopressor support to maintain MAP, from day 0 to 7.

2. All cause mortality refers to day 28 (within ICU of hospital mortality after inclusion and ICU mortality).

3. The effect of immunosuppressive medication on the intensive care infection

score will be analyzed.

Study description

Background summary

Microbial infection in the ICU may lead to sepsis and other harmful sequelae. Fear of under treatment contributes to ordering tests and prescribing antibiotics, before results of cultures become available, while overtreatment carries the risk of bacterial selection and overgrowth by induction of resistance. Infectious complications remain on of the most important causes of morbidity and mortality in lung and heart transplant patients. There are numerous reasons why those patients have a heightened predisposition to infection. One of those reasons is the usage of immunosuppressive medication to prevent graft dysfunction. The immunosuppressive medication interferes with the immune system giving a higher risk for developing infections. The systemic inflammatory response syndrome (SIRS) criteria, including elevated white blood cell counts (WBC) may not accurately predict microbial infection and the common use of C-reactive protein (CRP) to predict infection, severity and outcome in critically ill patients is controversial. Therefore reliable verification of a systemic microbial infection is still the most challenging issue.

The host response to a microbial infection invariably starts with the activation of the innate immune system. Consequently, it is reasonable to focus on cell specific haematological information and methods aimed at detecting an early response to systemic infection. Among activated innate immune cells in the fist line of pathogen defense, polymorphonuclear neutrophils (PMN) form 50-60% of all circulating leukocytes. Once at the site of infection, neutrophils release a variety of toxic products to kill and clear invading pathogens by the process of phagocytosis, degranulation and generation of reactive oxygen metabolites. Such immune reactions are easy to viualize morphologically and are therefore measurable. When activated, neutrophils produce and secrete macrophage inflammatory protein 1 (MIP-1) and other pro-inflammatory cytokines resulting in recruitment, differentiation and activation of antigen-presenting cells such as monocytes/ macrophages. Besides various cytokines, soluble bacterial molecules and whole bacteria are well known stimuli for receptors at the surface of macrophages. Once bacteria are incorporated by phagocytosis, monocytes and macrophages unleash stored bactericidal agents and lysosomal enzymes to eliminate pathogens. Monocytes and macrophages are involved in inflammation induced anemia due to retention of iron, resulting in an immediate decrease in haemoglobin synthesis and content in reticulocytes. The difference in haemoglobin content between immature

erythrocytes (formed after the onset of infection) and the mature erythrocytes (which were produced earlier) can therefore be used as an indirect early indicator for monocyte/ macrophage activation.
Plasma cells or lymphoplasmocytoid cells are also involved in the first line pathogen defense. Such antibody secreting lymphocytes (ASL) are not detectable in the peripheral blood of healthy individuals. Thus the presence of circulating ASL in a patient indicates an acute phase response to infection.
In addition to the activation of circulating immune cells, the bone marrow responds to systemic infection by releasing immature granulocytes into the peripheral blood. An increased immature/ total granulocyte ratio (i.e. a left shift in granulopoiesis) has been found to be related to bacteremia.
Because of the complexity of the pathophysiology of systemic inflammation and sepsis it a single parameter will have sufficient diagnostic accuracy for sepsis. Therefore, a combination of parameters constitutes a diagnostic score, the Intensive Care Infection Score (ICIS). This seems to be a more promising method of predicting microbial infection in the ICU. The activation parameters investigated consist of: a) fluorescence intensity of segmented neutrophils, b) fluorescence intensity of antibody secreting cells and c) haemoglobin concentration of newly formed red blood cells. In addition, two rapidly detectable bone marrow response: d) total mature neutrophil count and e) total immature granulocyte count. To generate the best sensitivity and specificity to predict microbial infection we will develop the ICIS score, which consist of above mentioned parameters, by using a score of 1 above the cut- off value for the best AUC, a score of 2 above the cut- off value with specificity above 85%, and a score of 4 above the cut off value with specificity above 95%. By adding all weighting values for all five parameter components the maximum possible ICIS score is.
Because immune suppression interferes with the natural host responses; inhibiting T-cell activation, T-cell mediated B-cell activation, T-cell and B-cell proliferation. It is not unreasonable to hypothesize interference with the ICIS score in predicting infection in this specific patient population. Assessing the influence of immunosuppressive therapy on the ICIS is essential to take steps to implement this clinical score in the treatment of this vulnerable patient population.

Study objective

The aim of this study is to evaluate the predictive value of a blood cell derived score, ICIS, for microbial infection, its likelihood, its invasiveness (blood stream infection) and severity (septic shock or mortality) in patients after lung or heart transplantation.

Study design

All patient who will undergo lung or heart transplantation can be included in the ICIS study. When a transplant has become available and is HLA suitable for

the receiver, the patient will be admitted into the hospital for the last routine checks prior to the transplantation. From this moment the patient can be included into the ICIS study, this day will be defined as day 0. At day 0 extra blood will be drawn from the patient (1 K3EDTA aliquots of 4.5 ml) in order to obtain the ICIS measurement.
The patient will be observed for a seven- day period after transplantation. The second measurement will be performed directly postoperative; this will be referred as day 1. In the next six days blood will be taken at 6 am in the morning when other routine blood laboratory measurements will be taken from the patient. Eight aliquots will be taken in total without the need for an extra venepuncture. At day 0 the ICIS measurements will be taken when other routine blood measurements are drawn from the patient. From day 1 until the end of the follow up period, blood will be taken from an arterial catheter that is routinely placed during the transplantation. An observational period of 28 days will be used to establish each patient*s discharge from the ICU or death (within ICU or hospital). In this period clinical and laboratory data obtained in the routine management of these patients will be collected. The results of the measured parameters will not be documented in the patient*s clinical records.
Patients of both sex and older than 18 years old who will undergo lung or heart transplantation are possibly eligible for this trial. Patients will be included into this trial after they have given informed consent. Patients will be excluded if they have neutropenia, defined as leukocyte count less then 0.5x109/L.

Study burden and risks

Blood will be drawn several times from an arterial cathether which is routinely placed in this category of patients.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

All patients above the age of 18 years who will undergo lung or heart transplantation are possibly eligible for this trial.

Exclusion criteria

N.A.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL
Recruitment status: Pending

Start date (anticipated):	01-08-2014
Enrollment:	100
Type:	Anticipated

Ethics review

Approved WMO Date:	26-05-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL48406.078.14