VANISH: The evolution of pulmonary lesions on high resolution computed tomography scans in immunocompromised children with a suspected invasive fungal disease.

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Primary Objective: 1. The first objective of this study is to examine the evolution of pulmonary lesions on serial HRCT assessments in pediatric patients with possible or probable/ proven IA. The lesions will be measured three dimensionally and five...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON56261

Source
ToetsingOnline

Brief title
VANISH

Condition

- Other condition
- Fungal infectious disorders
- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
"Invasive pulmonary fungal infection" AND "fungal lung infection"

Health condition

Patiënten die een HSCT ontvangen

Research involving
Human

Sponsors and support

Primary sponsor: Prinses Máxima Centrum voor Kinderoncologie
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: CT-scan, Diagnostics, Invasive fungal infection, Pediatric oncology

Outcome measures

Primary outcome

1. Radiological imaging

The change in volume of the lesions on the serial HRCT scans will be used as primary endpoint. The volume of the lesions on day 7, 14, 28 and 42 (each) will be compared to the baseline scan on day 0. Secondly, the lesion volume of the follow up scans (t=7, t=14, t=28, t=42) will be compared to the precedent scan. This gives 7 pairwise comparisons in total. New lesions formed during the follow-up period will not be included in this endpoint.

2. Comparison of a new diagnostic test to the current SOC:

The novel method of cfDNA to detect IFD will be compared to the SOC diagnostics. Each test will give a positive or negative rest result for the detection of IFD for patient. The SOC will be done on both BAL fluid and blood and a positive rest result is defined as a probable/proven classification following the EORTC criteria.

Secondary outcome

For patients participating in main study objective 1:

We hypothesize that other radiologic markers will help differentiating in the probability of an IFD and in the course of the disease. With this study we want to explore and identify which radiological imaging characteristics are most sensitive for the course of the fungal disease.

Secondly, we hypothesize that the addition of a scan on day 7 will give an improved estimation for outcome and has an additional value in the fungal monitoring compared to a first follow up scan on day 14 (standard of care).

For patients participating in main study objective 2:
We hypothesize that molecular markers and host-derived markers (besides cf-DNA sequencing) are present in blood and BAL fluid that can be used in the detection or exclusion of fungal infections and can improve the standard diagnostic methods of fungal infections. The (follow-up) blood samples and BAL samples will be used to explore the measurement of therapy response by biological samples and additional molecular detection methods for IFD (besides cfDNA sequencing).
This study is the ideal setting in which new diagnostic molecular methods should be tested. The sample collection can be done with a minimal burden to the patient since a central line is placed and regular clinical blood checks are indicated. The study includes the population for which improved diagnostic tools is most valuable. Testing this novel technique in a broader population

hopefully leads to improved fungal diagnostics that can benefit future patients

within the same population.

Study description

Background summary

Invasive fungal disease (IFD) remains an important cause of morbidity and mortality in children with hemato-oncological malignancies. The incidence of IFD in pediatric oncology patients varies widely between studies and ranges between 1.7- 35%, depending on the type of malignancy. In paediatric immunocompromised patients, the most common IFD is invasive aspergillosis (IA). Persistent neutropenic fever in the presence of radiological abnormalities on a HRCT of the lungs suggestive of IFD often leads to antifungal therapy as timely treatment in those patients who do have a IFD is important for survival. For patients with IA initial combination therapy with voriconazole/isavuconazole plus liposomal amphotericin B (L-AmB), or voriconazole/isavuconazole plus an echinocandin is recommended. Definitive diagnosis of IA however is cumbersome and even after invasive microbiological investigation most cases of suspected IA remain possible or probable according to the EORTC/MCG criteria. Consequently, radiological assessment of the lung is an important component in the management of IA and continuation, or adaptation of antifungal treatment relies heavily on sequential analysis of Computed Tomography (CT) scans. Evolution of CT scan images of patients with IA has been studied poorly. The volume of Aspergillosis lesions from 30 adult patients with probable or proven IA increased significantly from day 0 to day 7 and decreased from day 7 to day 14. Moreover, sequential analysis of lesion volumes seems to predict outcome more precisely than comparison to baseline images. Any increase in CT volume between day 7 and day 14 was a sensitive marker of a lethal outcome.
In addition, a mixed pattern of a reduction of the initial lesions and the appearance of new lesions has been described on CT scans, it has been suggested that this mixed response is the result of a combination of an azole-resistant and azole-susceptible infection.
More knowledge of the evolution of pulmonary lesions in order to determine therapeutic response in children with IA could hopefully lead to earlier de-escalation of combination therapy or prevent unnecessary escalation of antifungal treatment. Focusing on the reduction of antifungal agents is important as current treatments have side effects, drug interactions, high costs and emergence of resistance.
Besides the radiological assessment, microbiological is a pivot component of the IFD diagnostic workup. Although progress has been made over the last decades, microbiological confirmation of a pulmonary IFD is hampered by the low sensitivity of diagnostic test. The SOC microbiological testing consists out of

Galactomannan (GM) antigen testing, culture, and PCR testing on bronchial alveolar lavage (BAL) fluid or GM testing on serum. Ideally, new diagnostic test is able to detect IFD from minimally invasive obtained blood with high sensitivity and specificity. A promising novel method is the sequencing of cfDNA to detect microbial (e.g. Aspergillus spp.) in plasma. A proof-of-concept study (submitted) showed a high sensitivity and specificity in the detection of Aspergillus fumigatus. To confirm the potential of this new diagnostic method, it needs to be tested in a broader population and compared to the standard of care diagnostic work-up. This will include clinically relevant fungal pathogens, Aspergillus and non-Aspergillus species.
Over the last two years (2020-2021) 43 children were treated for a possible (n=19), probable (n=22) or proven (n=1) IA in the Princess Maxima Center. Three children died due to underlying disease progression not directly related to IA. Antifungal treatment was given for prolonged period of time (primary treatment and secondary prophylaxis) both for children with possible or probable/ proven IA. The objective of this study is to examine the evolution of pulmonary lesions on serial HRCT scans in pediatric patients with possible or probable/ proven IA by evaluating volume size of the lesions.

Study objective

Primary Objective:
1. The first objective of this study is to examine the evolution of pulmonary lesions on serial HRCT assessments in pediatric patients with possible or probable/ proven IA. The lesions will be measured three dimensionally and five scans per patients will be compared (day 0, 7, 14, 28, 42) and the evolution will be expressed as increase or decrease of volume compared to the baseline scan (day 0) and compared to the preceding scan. This will be done by measuring the volume size of (maximally five) pulmonary lesion(s).
2. The second objective of this study is to compare two diagnostic test. The sensitivity of two tests (SOC vs cfDNA sequencing) in the detection of IFD in blood will be compared.

Secondary Objective(s):
Secondary exploratory objectives of this study are:
- to identify other qualitative radiological markers that are sensitive in differentiating in the course of the fungal disease and corresponding clinical outcome
- The additional value of a scan on day 7 will be compared to the standard of care and evaluated.
- to collect blood and BAL to improve molecular detection (besides cfDNA) methods for pulmonary fungal infections
- To describe the proportion of patients in which new lesions appear during the treatment period and describe the evolution of these new lesions over time (mixed-effect)

Study design

The study is a prospective observational trial and will be executed at the Princess Máxima Center for pediatric oncology. Patients be included during a 3 years period.

Study burden and risks

To assess accurate radiological response an extra HRCT scan at day 7 will be performed compared to standard care. The burden of extra radiation will be minimal. A HRCT scan of the lungs takes approximately 5-10 minutes. The additional blood draw and collection of BAL poses a minimal additional burden, the blood draw will be done, as much as possible, simultaneously with standard care blood draw and only the residue of the bronchoalveolar washing (BAL) will be collected and stored. The total amount of blood draw will not exceed 0.8 mL/kg. This poses minimal additional burden for the patient.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)
Newborns

Inclusion criteria

Children from 0 up to and including 18 years with a hemato-oncological maligancy or post-HSCT and diagnosed with a possible, probable or proven invasive aspergillosis

Exclusion criteria

Refusal to give informed consent
For part 1: not able to give informed consent and patient is unable to undergo a HRCT scan without anaesthesia.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-01-2024
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	06-09-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	09-01-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-01-2025
Application type:	Amendment
Review commission:	METC NedMec

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	NL84319.041.23