Göteborg, 2019

Invasive fungal disease in immunocompromised hosts
with focus on diagnostics

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin,
Göteborgs universitet kommer att offentligen försvaras i aulan Järneken,
Kvinnokliniken, Östra Sjukhuset, Diagnosvägen 15, Göteborg
Torsdagen den 2 maj 2019, kl 13.00

av

Helena Hammarström
Leg. Läkare

Fakultetsopponent:
Professor Jan Sjölin
Institutionen för medicinska vetenskaper, Uppsala Universitet

Avhandlingen baseras på följande delarbeten

I. Hammarström H, Kondori N, Friman V, Wennerås C. **How to interpret serum levels of beta-glucan for the diagnosis of invasive fungal infections in adult high-risk hematology patients: optimal cut-off levels and confounding factors.** *Eur J Clin Microbiol Infect Dis.* 2015;34(5):917-25

II. Hammarström H, Stjärne Aspelund A, Christensson B, Heußel C.P., Isaksson J, Kondori N, Larsson L, Markowicz P, Richter J, Wennerås C, Friman V. **Prospective evaluation of a combination of fungal biomarkers for the diagnosis of invasive fungal disease in high-risk haematology patients.** *Mycoses.* 2018;61:623–632.

III. Hammarström H, Grankvist A, Broman I, Kondori N, Wennerås C, Gisslen M, Friman V. **Serum-Based Diagnosis of Pneumocystis Pneumonia by Detection of Pneumocystis jirovecii DNA and 1,3-β-D-Glucan in HIV-Infected Patients.** *Submitted* 2019.

IV. Hammarström H, Stjärne Aspelund A, Hansson L, Isaksson J, Kondori N, Riise GC, Wennerås C, Friman V. **Fungal colonization and tracheobronchitis following lung transplantation - impact on morbidity and mortality and utility of 1,3-β-D-glucan**. *In manuscript.*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICIN

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Invasive fungal disease in immunocompromised hosts
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ABSTRACT

Invasive fungal diseases (IFDs) are severe conditions affecting immunocompromised patients. The primary aim of this thesis was to explore different methods for diagnosis of IFD in different groups of immunocompromised patients. **Papers I** and **II** included patients with hematologic disorders. **Paper I** was a retrospective study evaluating two years of serial 1,3-β-d-glucan (betaglucan) testing. **Paper II** was a prospective study where samples were collected for the analysis of betaglucan, galactomannan, bm-gliotoxin (serum) and D-arabinitol/L-arabinitol (urine). The sensitivity of betaglucan and galactomannan was low early in the time course of IFD. The highest positive predictive value of betaglucan was obtained when using a cut-off level of at least 160 pg/ml and when testing patients upon clinical suspicion of IFD. Admission to ICU, previous administration of blood products and high serum triglyceride levels were associated with elevated betaglucan levels in patients without IFD. Betaglucan levels >800 pg/ml were highly indicative of IFD. Bm-gliotoxin could not be detected in patients with invasive aspergillosis. **Paper III** was a retrospective case-control study where frozen serum samples from HIV-infected patients and negative controls were analyzed for betaglucan and *Pneumocystis* PCR. *Pneumocystis* PCR in serum had a very high sensitivity and negative predictive value for the diagnosis of PCP. **Paper IV** was a prospective nationwide study on lung transplant recipients where serum and BAL-fluid samples were collected during the first post-transplant year for the analysis of betaglucan. Development of bronchiolitis obliterans syndrome (BOS) was assessed during a median 4.6 years of follow-up. Fungal colonization or tracheobronchitis had no impact on the development of BOS or on all-cause mortality. Betaglucan levels in serum were low while betaglucan levels in BAL fluid were elevated in patients with fungal tracheobronchitis. To conclude, betaglucan and *Pneumocystis* PCR in serum are useful diagnostic methods for different types of IFD although various issues need to be considered in order to determine their clinical applicability.

Keywords: invasive fungal disease, diagnosis, 1,3-β-d-glucan, hematological malignancies, hematopoietic stem cell transplantation, HIV, lung transplant recipients, bronchiolitis obliterans syndrome

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