Timing

Patient enrolment is planned to start in February 2011 and will continue until the target number of included patients is reached (~2000). As long as the study is active centres can register to participate. This will be probably until the end of 2013, depending on the inclusion rate (we aim for ~2000 patients).

Procedures

- An electronic newsletter will be send on a regular basis to all registered investigators. Herein we will update collaborators on the process of the project.
- The principal investigators will provide ongoing quality control on the collected data. Data analysis will be performed by Prof. Dr. S. Blot and Dr. N. Brusselaers.
- Study results will be published in international peer reviewed journals. Top includers can be invited as co-authors.
- At the end of the study a fee of € 25,00 will be reimbursed to the investigator for each eligible and completed patient that was included in the study from that respective centre. Therefore the investigators must sent an invoice to the coordinating centre by means of a *Asp*ICU2 invoice form which can be downloaded from the website.

Legal and ethical aspects

The study must be approved by each local Ethics Committee (EC). As this study is observational in nature, without any modification in the general management of these patients (local usual clinical practice) and data collection obtained from patient medical record, informed consent should not be requested. If required by any local EC, an informed consent will be provided. Each participating centre must fax the EC approval to the coordinating centre (Ghent University Hospital: +32 9 332 3895) prior to entering patient data.

Executive committee
Stijn BLOT, Nele BRUSSELAERS, George DIMOPOULOS, Jordi RELLO, Dirk VOGELAERS

Steering committee
Pierre BULPA, Benoit MISSET, Jose Artur PAIVA, Fabio Silvio TACCONE, Anne-Marie VAN DEN ABEELE, Koenraad VANDEWOUDE

Contact
Stijn.Blot@UGent.be

Confidentiality

No data identifying study subjects will be recorded in the web-based survey. Only the subject numbers will be recorded in the case report form. Study findings will be stored on a computer in accordance with local data protection laws. A center decodification list will be kept at each study center. Study findings will be stored in accordance with local data protection laws. If the results of the study are published, the subject's identity will remain confidential. The medical secret and the legal demands concerning the private life are respected.

References

1. Lin SJ et al. Clin Infect Dis 2001; 32:358-366.
2. Rello J et al. Clin Infect Dis 1998; 26:1473-1475.
3. Vandewoude K et al. J Hosp Infect 2004; 56:269-276.
4. Nivoix Y et al. Clin Infect Dis 2008; 47:1176-1184.
5. McNeil MM et al. Clin Infect Dis 2001; 33:641-647.
6. De Pauw B et al. Clin Infect Dis 2008; 46:1813-1821.
7. Meersseman W et al. Am J Respir Crit Care Med 2004; 170:621-625.
8. Vandewoude K et al. Med Mycol 2006:S1-S6.
9. Vandewoude K et al. Crit Care 2006; 10:R31.

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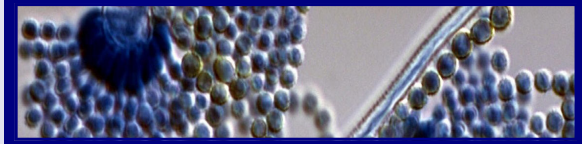

*Asp*ICU2

Information Booklet

Interested to participate?

Visit:

www.aspicu2.org

Endorsed by

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What is *Asp*ICU2?

This is a **multicenter web-based observational survey to assess the burden of Aspergillus and other fungi in critically ill patients**. *Asp*ICU2 is a follow-up study of the initial *Asp*ICU project in which emphasis was given to the clinical relevance of *Aspergillus*-positive cultures in critically ill patients. As such, the scope of AspICU2 is expanded to various types of invasive fungal disease (IFD) with accent on general epidemiology, especially incidence of the problem and risk factor identification in critically ill patients.

Background

The prognosis of IFD in critically ill patients is particularly poor. Mortality rates range from ~20% to 95% depending etiology, infection site, underlying disease, and associated organ failure [1-4]. Favorable evolutions in modern medicine have lead to greater acute phase survival, and as such, to an increasing pool of patients at risk for opportunistic infections. Therefore, it is assumed that the incidence of IFD is rising [5]. However, there remain important uncertainties about the true incidence and delineation of IFD. This is mainly due to substantial diagnostic uncertainty. According to the criteria defined by the European Organization for Treatment and Research of Cancer / Mycoses Study Group (EORTC/MSG), IFD is categorized according to the degree of certainty of the diagnosis [6]: (1) proven, (2) probable, and (3) possible IFD. A proven diagnosis requires histopathologic and/or mycological evidence of IFD. Probable IFD is defined as the combination of host factors[1] (immunocompromized status), clinical features (including suggestive imaging[2]) and positive mycology, either on direct (culture, microscopy) or indirect tests (detection of galactomannan or Beta-D-glucan). A diagnosis of possible IFD is reached in patients with host factors and clinical features, but without positive mycology.

[1]Host factors for IFD include (one of the following): (1) Recent history of neutropenia ($<0.5 \times 10^9$ neutrophils/L [<500 neutrophils/mm^3] for >10 days) temporally related to the onset of fungal disease. (2) Receipt of an allogeneic stem cell transplant. (3) Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for 13 weeks. (4) Treatment with other recognized T cell immunosuppressants, such as cyclosporine, TNF-a blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogues during the past 90 days. (5) Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency).

[2]CT scan demonstrating dense, well-circumscribed lesions, with or without Halo sign, air crescent sign, or cavity.

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Problem outline

Diagnosing IFD in critically ill patients, according to the criteria stated above, is problematic due to a number of reasons. First, biopsy sampling might be contra-indicated in septic patients because of coagulation disorders. As a consequence, a diagnosis of 'proven IFD' is rare, with the exception of autopsy based cases. Second, current definitions of probable or possible IFD are only valid for immunocompromized patients as characterized by the classic host factors[1]. As such, in the absence of histological evidence of IFD, it is - per definition - impossible to diagnose IFD in non-immunocompromized patients, while, it is clear that IFD can occur in patients who lack classic host factors[1] [7-9]. Third, radiologic findings in mechanically ventilated patients are non-specific in the majority of cases [9] in contrast to the very strict definition of radiologic lesions compatible with IFD in the EORTC/MSG criteria only including "robust" signs (see footer[2]) [6]. Furthermore, the clinical relevance of positive mycology findings in the absence of compatible signs and classic host factors remains vague. Finally, galactomannan antigen detection by means of an indirect test on serum is of little value in non-neutropenic patients as circulating neutrophils are capable of clearing the antigen.

Objectives

The main objectives of *Asp*ICU2 are:

- to identify distinct risk profiles for IFD in critically ill patients,
- To define diagnostic categories for (non-immunocompromized) critically ill patients, and
- to estimate the burden of IFD in terms of incidence and outcomes.

Methods

Design. *Asp*ICU2 is a prospective, observational survey of patients with either a diagnosis or suspicion of IFD, or any positive mycology either with or without clinical signs of invasive infection.

Inclusion criteria.

- At least 18 years of age.
- Hospitalized at an intensive care unit (ICU).
- Patients should have a diagnosis or suspicion of IFD. It is not necessary that the IFD is "ICU-acquired". Patients admitted to the ICU with documented or suspected IFD are eligible as well. Every patient must meet at least one of the three basic entry criteria:

1) An autopsy-based diagnosis of IFD.

2) Any positive mycology (either on direct or indirect test) 'in vivo' sampled

3) Presence of risk profile for IFD[3] + signs of sepsis[4] + decision to start an antifungal agent[5]

In order to obtain a reliable snap shot of the epidemiology, all consecutive patients meeting one of the three entry criteria must be enrolled.

[3]Judgment of the risk profile is left at the discretion of the physician. Risk factors may include a wide range of underlying diseases or acute conditions (either specific or non-specific for IFD), and are not limited to the classic host factors as used in the EORTC/MSG criteria for defining IFD.

[4]Sepsis is defined as at least two of the following criteria in the presence of documented or presumed infection: (1) body temperature >37.9° C or <36.1° C; (2) heart rate >90 beats per minute; (3) tachypnea manifested by a respiratory rate of >20 breaths per minute, or hyperventilation indicated by a $PaCO_2$ <32 mmHg; (4) alteration in the white blood cell count >12,000/μL^{-1} or <4,000/μL^{-1} or 10% immature (band) forms.

[5]Only antifungal agents with mould activity are valid: either conventional or lipid-associated amphotericin B, an echinocandin, voriconazole, posaconazole, itraconazole, ravuconazole, or Mycograb.

Exclusion criteria.

- Patients with mycology findings exclusively positive for *Candida* species.
- Patients in whom empiric antifungal therapy is started because of the perceived risk of invasive candidiasis or candidemia. However, in patients with evidence of non-Candida fungal involvement, the additional presence of *Candida* positive cultures is not considered an exclusion criterion.

Data to be collected.

The data collection process is completely web-based. The case report form includes the following items:

0. Demographics & admission data

1. Diagnostic evaluation

1.1. Mycology :

1.1.1. Affected site

1.1.2. Type of sampling

1.1.3. Relevant diagnostic tools

1.1.4. Fungal identification

1.2. Clinical assessment

1.2.1. Acute conditions

- Compatible signs and symptoms
- Organ failure assessment

1.2.2. Underlying conditions / risk factors

1.2.3. Therapy related risk factors – iatrogenic risk factors

1.2.4. Life style risk factors

1.3. Medical imaging

2. Clinical decision

2.1. Initial antifungal therapy

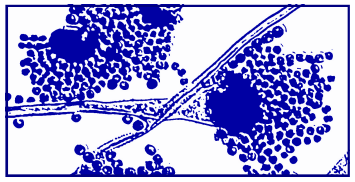
2.2. Antifungal therapy at completion of diagnostic work-out

3. Clinical outcome evaluation at 12 weeks

4. Autopsy evaluation (optional)

To start...

- Centres prepared to participate should register via the official website: www.aspicu2.org. A personal log-in can be made for each participating unit (per unit only one log-in will be made available; multiple ICUs per centre can register).
- During the registration process basic information about the ICU, antifungal formularium, and mycological techniques used in routine practice will be requested.
- Inclusion of patients can start from the time the centre is in line with local ethics committee regulations for observational trials.
- The minimum period of observation is 1 month. Yet, several periods are possible per centre, as long as each period takes at least 1 month. It is for example possible to register all patients in May 2011, September-November 2012 and one month more in December 2013.
- For every period all consecutive patients meeting at least one of the entry criteria are to be included.
- For every period the total number of ICU admissions should be recorded as well as the mean ICU stay. The latter is necessary to calculate incidence of IFD in ICUs.



Paper (pdf) version of the CRF can be downloaded from the study website