Journal of Infection (2014) 69, 284–292

BIAM British Infection Association

www.elsevierhealth.com/journals/jinf

Aspergillus in the lower respiratory tract of immunocompetent critically ill patients

Maxime Lugosi [a,i,j], Corinne Alberti [b], Jean-Ralph Zahar [c], Maité Garrouste [d,j], Virginie Lemiale [a], Adrien Descorps-Desclère [e], Jean-Damien Ricard [f], Dany Goldgran-Tolédano [g], Yves Cohen [h], Carole Schwebel [i], Aurélien Vésin [j,k], Jean-François Timsit [i,j], Elie Azoulay [a,*]

[a] *Medical Intensive Care Unit, Research Group on Acute Respiratory Failure in Hematology and Oncology Patients, Saint-Louis Hospital and Paris 7 Denis Diderot University, Paris, France*
[b] *Epidemiologic Clinical Unit, INSERM, Robert Debre Hospital and Paris 7 Denis Diderot University, Paris, France*
[c] *Bacteriological-Virological Unit, Necker Hospital and Paris 5 René Descartes University, Paris, France*
[d] *Intensive Care Unit, Saint-Joseph Hospital, Paris, France*
[e] *Surgical Intensive Care Unit, Antoine Béclère Hospital, Clamart, France*
[f] *Intensive Care Unit, Louis Mourier Hospital, Colombes, France*
[g] *Intensive Care Unit, Gonesse Hospital, Gonesse, France*
[h] *Surgical Intensive Care Unit, Avicenne Hospital and Paris 13 University, Bobigny, France*
[i] *Grenoble 1 University, Medical Intensive Care Unit, Albert Michallon University Hospital, Grenoble, France*
[j] *Grenoble 1 University, Albert Bonniot Institute, Team 11: Outcome of Airway Cancers and Mechanically Ventilated Patients, Grenoble, France*
[k] *Biostatistical Department, Outcomerea Organisation, Paris, France*

Accepted 8 April 2014
Available online 9 June 2014

KEYWORDS
Aspergillus;
Mechanical ventilation;
ARDS;
Bacterial infection;
Immunocompromized

Summary *Objectives:* To shed light on the meaning of *Aspergillus*-positive lower-respiratory-tract samples in non immunocompromized critically ill patients.
Methods: Multicentre matched case-control (1:5) study. We used prospectively collected data to identify risk factors for *Aspergillus*-positive specimens, as well as outcomes in *Aspergillus*-positive patients.
Results: 66 cases (5 with definite invasive pulmonary aspergillosis (IPA), 18 with probable IPA, and 43 colonisations) were matched to 330 controls. In the multivariate conditional logistic

* Corresponding author. AP-HP, Hôpital Saint-Louis, Medical ICU; Université Paris-Diderot, Sorbonne Paris-Cité, Faculté de médecine; 1 avenue Claude Vellefaux; 75010 Paris, France. Tel.: +33 142 499 421; fax: +33 142 499 426.
E-mail address: elie.azoulay@sls.aphp.fr (E. Azoulay).

http://dx.doi.org/10.1016/j.jinf.2014.04.010

model, independent risk factors for at least one Aspergillus-positive respiratory-tract specimen were worse SAPSII at admission [OR, 1.10; 95%CI, 1.00—1.21], ARDS [OR, 2.64; 95%CI, 1.29—5.40]; long-term steroid therapy [OR, 4.77; 95%CI, 1.49—15.23]; steroid therapy started in the ICU [OR, 11.03; 95%CI, 4.40—27.67]; and bacterial infection [OR, 2.73; 95%CI, 1.37—5.42]. The risk of death, compared to the controls, was not higher in the cases overall [HR, 0.66; 95%CI, 0.41—1.08; $p = 0.1$] or in the subgroups with definite IPA [HR, 1.60; 95% CI, 0.43—5.94; $p = 0.48$], probable IPA [HR, 0.84; 95%CI, 0.28—2.50; $p = 0.76$], or colonisation [HR, 0.58; 95%CI, 0.33—1.02; $p = 0.06$]. In cases who received antifungal therapy, mortality was not lower than in untreated cases [HR, 0.67; 95%CI, 0.36—1.24; $p = 0.20$].

Conclusions: In critically ill immunocompetent patients, risk factors for presence of Aspergillus in lower respiratory tract specimens are steroid therapy (either chronic or initiated in the ICU), ARDS, and high severity of the acute illness. Prospective studies are warranted to further examine these risk factors and to investigate immune functions as well as the impact of antifungal therapy on patient outcomes.

Introduction

The clinical spectrum of pulmonary aspergillosis depends on the level of immune competence.[1,2] *Aspergillus* invades the lungs in patients with immunological deficiencies, particularly those affecting the monocytes/macrophages and neutrophils.[3] Cooperation between these cells of the innate immune system and T lymphocytes is also required to control the spread of *Aspergillus*.[4] Thus, invasive aspergillosis has been reported chiefly in immunocompromised patients with either prolonged neutropenia due to induction chemotherapy for acute leukaemia or allogeneic stem cell transplantation. Furthermore, among patients in the intensive care unit (ICU), those with chronic obstructive pulmonary disease (COPD)[5—7] or sepsis followed by post aggressive immunosuppression, immunoparalysis or compensatory anti-inflammatory response syndrome (CARS)[8,9] are at high for aspergillosis. An international consensus panel convened by the European Organisation for the Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) developed diagnostic criteria for invasive aspergillosis in immunocompromised patients with cancer and haematopoietic stem cell transplantation.[10]

In the past decade, reports of *Aspergillus*-positive specimens found unexpectedly in critically ill patients have raised concern.[11—13] *Aspergillus* was recovered from the respiratory tract of ICU patients who had none of the classical host-related risk factors identified during the EORTC/MSG consensus conference.[11,14,15] Some of these patients clearly had invasive pulmonary aspergillosis (IPA).[16—18] However, criteria for distinguishing between invasive aspergillosis and *Aspergillus* colonisation remain controversial.[15,19,20] Clinical algorithms appropriate for ICU patients have been developed to assist in this diagnosis.[15,21,22] The diagnostic challenges are greatest in patients with *Aspergillus*-positive specimens but none of the recognised risk factors, that is, in immunocompetent patients.

In this study, our objective was to shed light on the meaning of *Aspergillus*-positive lower-respiratory-tract samples in immunocompetent ICU patients by performing a multicentre matched case-control study. We used prospectively collected data to identify risk factors for *Aspergillus*-positive specimens, as well as outcomes in *Aspergillus*-positive patients.

Methods

We conducted a matched case-control study using data collected in a prospective multicentre database (OutcomeRea®; www.outcomerea.org) from January 1996 to October 2009. This study was approved by our institutional review board (CECIC Clermont Ferrand — IRB n°5891; Ref: 2007-16); according to French legislation, the board waived the need for signed informed consent from patients included in the database. However, patients and their next of kin were asked whether they were willing to participate in the database, and none refused to participate.

OutcomeRea® database

OutcomeRea® is a high-quality database that has been described elsewhere.[23] Briefly, the database, fed by 12 French ICUs, contains data on admission features and diagnosis, daily disease severity, iatrogenic events, nosocomial infections, and vital status. Data for a random sample of at least 50 consecutive patients >16 years of age are entered into the database each year in each ICU. Each participating ICU chooses to select either consecutive admissions to all ICU beds during a single month selected at random or consecutive admissions to a randomly selected sample of ICU beds during the entire year.

The data-capture software automatically conducts multiple checks for internal consistency of most of the variables at entry into the database. Queries generated by these checks are resolved with the source ICU before incorporation of the new data into the database. At each participating ICU, data quality is assessed by having a senior physician from another participating ICU check a 2% random sample of the study data. A 1-day coding course is held annually with the study investigators and contract research organisation monitors.