Early View

Research letter

Aspergillus colonisation in severe community-acquired pneumonia: not just a mere colonisation

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Aspergillus colonization in severe community-acquired pneumonia: not just a mere colonization

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To the editor:

Patients with severe community-acquired pneumonia (CAP) admitted to intensive care units (ICU) and mechanically ventilated are likely to develop invasive pulmonary aspergillosis (IPA) (1). While IPA is mainly reported in influenza (2) and SARS-CoV-2 pneumonia (3), it also occurs in CAP from other causes. It is associated with high mortality, exceeding 60% for Covid-19-associated IPA (4). However, little is known about patients presenting Aspergillus colonization in a context of severe CAP, and discrepancies are reported concerning its association with outcomes (5,6). Aspergillus colonization of the lower respiratory airways is commonly considered of little clinical significance (7) yet is associated with a poor prognosis in critically ill patients (5). Our study aimed to compare the number of ICU-free days at 90 days of follow-up for patients with severe CAP according to Aspergillus status: (i) absence of Aspergillus colonization, (ii) Aspergillus colonization, or (iii) IPA.

We conducted an observational retrospective study including patients admitted to 5 ICUs of the Dijon University Hospital (France) from January 1, 2015, to December 12, 2021, with a diagnosis of severe CAP. Inclusion criteria were: age > 18 years, admission to ICU with a diagnosis of CAP (clinical respiratory signs, new infiltrate on chest imagery within 48 hours following admission to hospital) with at least one test for Aspergillus (serum or alveolar antigen, bronchoalveolar lavage fluid (BALF) or tracheal aspirate culture or PCR) during the ICU stay. ICU stays for pneumonia were identified in the French hospital discharge database by primary diagnoses according to the International Classification of Diseases (ICD)-10 codes. The accuracy of the diagnosis was checked in individual medical files by a trained clinician, and patients were excluded if they did not meet the inclusion criteria. Cases were defined as having at least one of the following positive Aspergillus biomarkers: galactomannan index in serum > 0.5 and/or BALF > 1, and/or positive culture and/or PCR for Aspergillus from BALF or tracheal aspirate samples. We used the definition of IPA from Blot et al. to classify cases as colonization (definition not met) or putative IPA (definition met) (8). We included between 2 and 3 control patients per case randomly sampled from the cohort of CAP patients with a negative Aspergillus test and matched on ICU admission ± 14 days. SAPS-II scores were prospectively calculated at ICU admission and extracted from medical files. Demographic data were retrospectively collected from medical files. We defined 90 ICU-free days from admission as 90 minus the number of days in the ICU (range, 0-90 days); 0 ICU-free days were assigned if death occurred within those 90 days.

Study protocol and data collection were registered with the French national data protection authority and are in accordance with French and European regulations on data protection and patient information (Commitment of compliance MR004 n°2210228). Informed consent was waived given the non-interventional study design.

Bivariate comparisons were performed using mixed models (either, logistic, Poisson or linear according to the variable) between the 3 groups to take matching into account. ICU-free days at day 90 was
analyzed using a zero-inflated negative binomial model. This model contains two parts, a logistic regression for the excess zero (death) and a negative binomial regression for the count variable (ICU-free days excluding death), making it possible to analyze the effect of factors separately on each component of the outcome (9–11). To account for matching, a random effect on the matching identifier was added to the model. Models were adjusted on age and variables with a p-value < 0.2 in the bivariate analysis, and log-linearity was tested using splines and Akaike Information Criteria (AIC). A p-value < 0.05 was considered statistically significant. Analyses were performed using R (v4.1.3) and GraphPad Prism (v.9.1.1) software.

During the study period, 148 cases (115 colonized and 33 putative IPA) and 273 matched controls with severe pneumonia and negative Aspergillus biomarkers were included (Figure 1A). BALF or tracheal aspirate were performed in 95%, 98% and 100% of non-colonized, colonized and putative IPA patients respectively (p = 0.032). Median time from ICU admission to Aspergillus identification was 2 (0-11) and 5 (3-9) days for colonized and putative IPA patients, respectively (p = 0.112). Viral, bacterial and mixed etiologies were proven in 206 (49%), 101 (24%) and 35 (8%), respectively. Influenza and SARS-CoV-2 were the two most commonly detected respiratory viruses (27 (6%) and 162 (38%), respectively).

Between the three groups, there were no significant differences in age (non-colonized: median (interquartile range) 66 (57-74); colonized: 67 (59-75); and IPA: 65 (57-73) years; p = 0.2), male sex ratio (69, 79 and 64%; p = 0.068), SAPS II score (43 (33-56), 48 (37-65), 45 (35-59); p = 0.05), mechanical ventilation (90, 91 and 97%; p = 0.356) or use of non-invasive ventilation (56, 54 and 61%; p = 0.790). In-hospital mortality and ICU-free days were significantly higher in colonized and IPA patients than in non-colonized patients (Figures 1B-C). After adjustment on age, sex, chronic cardiovascular and liver diseases, immunodepression, viral, bacterial origin of pneumonia and SAPS-II, we estimated a significantly higher probability of death at day 90 (logistic part of the model) for putative IPA patients compared to non-colonized patients (OR = 2.99; 95%CI [1.28; 6.98]) or to colonized patients (OR = 1.83; 95%CI [1.08 ; 3.09]) (Figure 1D). However, we did not observe a significant group effect for case patients compared to non-colonized patients when modeling ICU-free days using the negative binomial regression part of the model. Thus, the difference observed between groups for ICU-free days (cases: 0 (0-1) vs controls: 3 (0-18)) seems to be related to a higher death ratio rather than a longer ICU stay (Figure 1E).

Here we observed that the detection of Aspergillus in the lower respiratory tract of patients admitted to ICU for severe pneumonia was associated with high mortality, reaching more than half, irrespective of whether it was considered an invasion or a colonization. While our results could suggest that Aspergillus is harmful per se when it starts growing in the respiratory tract of this type of patient (12), this hypothesis remains unconfirmed due to numerous confounding factors. Aspergillus growth could be a mere reflection of underlying immunodeficiency or global severity, which in turn are associated with a poorer
prognosis. However, there were no significant differences in baseline characteristics between groups, and outcomes were adjusted on available potential confounders. As reported by Feys et al., SARS-CoV-2 impedes antifungal immunity by affecting the integrity of the epithelial barrier and decreasing anti-Aspergillus cellular immunity, mainly mediated by neutrophils (14).

The limits of our work include its case-control design and monocentric nature. We cannot exclude an immortal time bias since Aspergillus screening was not systematically performed upon admission, but both groups underwent Aspergillus testing with a median time from ICU admission that was not significantly different.

In conclusion, these data suggest that Aspergillus colonization may be a potential prognostic marker in patients with severe CAP. Its pathogenicity is still debated and needs to be further studied. Evaluating the benefits of antifungal therapies or immunomodulators such as recombinant interferon (IFN)-γ is one way to do so.
Conflict of interest: none reported.

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Figure legend:

Figure: Schematic representation of study workflow (A). Proportion of in-hospital mortality according to the 3 groups: non-colonized, colonized or invasive pulmonary aspergillosis (IPA) (B). Boxplots depicting ICU-free days at day 90 (C). Forest plot of odds ratio with 95% confidence intervals for in-hospital death (excess zero; estimated by the logistic regression part of the model) (D) and of adjusted incidence rate ratio with 95% confidence intervals for ICU-free days (excluding excess zero; estimated by the binomial regression part of the model) at day 90 for colonized and IPA patients compared to non-colonized patients (E).

Abbreviations: CAP: community-acquired pneumonia; ICU: intensive care unit; IPA: invasive pulmonary aspergillosis.
References


Figure

A

Admission in ICU for severe CAP + *Aspergillus* testing during ICU stay

<table>
<thead>
<tr>
<th>IPA classification</th>
<th>N=421</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-colonized (n=273)</td>
<td>Matched on ICU admission ± 14 days</td>
</tr>
<tr>
<td>Colonized (n=115)</td>
<td></td>
</tr>
<tr>
<td>Invasive Pulmonary Aspergillosis (IPA) (n=33)</td>
<td></td>
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</tbody>
</table>

B

In-hospital mortality

Non-colonized
Colonized
IPA

%  
34%  51%  58%

C

ICU-free days

Non-colonized
Colonized
IPA

days

D

In-hospital mortality

Colonized
IPA

adjusted Odds Ratio (95% CI)

E

ICU-free days (excluding death)

Colonized
IPA

adjusted Incidence Rate Ratio (95% CI)