Aspergillosis: nosocomial or community-acquired?

MARIE-CHRISTINE NICOLLE*, THOMAS BENET* & PHILIPPE VANHEMS†

*Service d’Hygiène Hospitalière, Épidémiologie et Prévention, Hôpital Edouard Herriot, Hospices Civils de Lyon, and †Équipe Épidémiologie et Santé Publique, CNRS, UMR 5558, Université de Lyon, Université Lyon 1, Lyon, France

Introduction

Ubiquitous worldwide, Aspergillus is associated with community or hospital-acquired (nosocomial) infections. Thus, it may be difficult to identify the respective contributions of these two environments to the risk of colonization or infection. After revisiting the risk of invasive aspergillosis (IA) from environmental exposure, this short review will focus on methodological questions related to the epidemiology of community or nosocomial IA. Clinical conditions, such as aspergilloma, allergenic diseases, including allergic bronchopulmonary aspergillosis and other localizations, will not be discussed [1].

Usually, hospital-acquired or nosocomial infections (NI) have been defined as infections with onset 48 hours after hospitalization and not evident at admission. For some infections, e.g., invasive fungal infections, this time period is highly debatable. Care-related conditions, such as exposure to invasive devices (i.e., mechanical ventilation, central venous or urinary tract catheterization) and treatments, facilitate infections by heightening impaired immunity. Regarding IA risk, extensive reviews have described factors associated with this infection and underlined that the risk is low for patients without immunodeficiency and outside any context of care [2,3].

Aspergillus species are ubiquitous organisms that can be found in every region of the world. Among about 185 Aspergillus species identified, only approximately 20 are involved in human diseases. Aspergillus fumigatus is the most common species that causes invasive infections (about 80%). Aspergillus flavus (15–20%) is a common isolate in sinusitis. The emergence of Aspergillus terreus and Aspergillus niger has recently been reported [1,4], and other Aspergillus species have been implicated anecdotally.

Reservoirs

Decaying vegetation is the primary ecological niche of Aspergillus fumigatus [5]. The organism occurs in outdoor
Transmission routes

In hospitals, additional reservoirs have been identified in false ceilings, roller-blind casings, fireproofing material and contaminated ventilation or inadequate filtration. This fungal organism also contaminates some hospital material, such as adhesive tapes, arm bands, plaster [6–9–12]. Some investigations have discovered opportunistic fungi in water from sinks and showerheads in some American or Norwegian hospitals. Water contamination by filamentous fungi is non-systematic and perhaps related to intake modality [13]. However, this source-reservoir is still being debated [5,14].

Natural history and incubation

While little is known about IA incubation [22], it has been historically defined by Sartwell [23] as the time period required for multiplication of the parasite organism within the host up to the threshold at which the parasite population is large enough to produce symptoms in the host. This definition remains valid today [24] and in this instance, the parasite is understood to be Aspergillus spp., mainly the inhaled conidia, which are the units with initial contact with the host while the symptoms are related to IA. Durations of the incubation period from 3 days to more than 100 days after hospitalization have been reported [25]. A cut-off of 7 days has often been used as an incubation period for fungal infections [26], but some studies have defined nosocomial IA as that which occurs from the first day after hospital admission [27] and others as that which is present 10 days after admission [28]. These definitions were used more for clinical plausibility and comparability between studies than based on systematic analysis of observational or experimental data. Indeed, the incubation period preceding IA is still unknown. Moreover, the potential impact of Aspergillus colonization before hospitalization on incubation remains an issue which is still broadly discussed [29,30]. Indeed, any invasive aspergillosis occurring during hospitalization is difficult to describe as hospital acquired or ‘hospital revealed’. Furthermore, the role of a previous colonization with Aspergillus needs further prospective observational studies taking into account the host (i.e., immunodepression, underlying disease) and environmental (i.e., airway ventilation, water exposures) characteristics related to the risk of IA.

Different approaches might bring some information on the issue of the incubation. Statistical modeling using back calculation could permit an estimation of the incubation period when a specific date of the exposure to Aspergillus spores can be documented (i.e., IA outbreak during building renovation) [23]. However, such estimations will be uncertain due to the heterogeneity of disease presentation.

© 2011 ISHAM, Medical Mycology, 49(Suppl. 1), S24–S29
and of the difficulty in the determination of the period of acute exposure and the unknown status regarding previous colonization of the host [31]. Repeated testing of antigen or PRC after admission might also provide interesting results, even if the test has some detection limits [32,33]. Animal experimental models could help for the estimation of this delay because the exposure time is precisely known (when the animals are inoculated with \textit{Aspergillus} spores), and autopsies permit histopathological data on the nature of the infection. Several animal models have been developed [34,35] to explore the pathogenesis of aspergillosis disease, but they did not focus on incubation. The use of murine models could provide further information on this issue. Lastly, the natural history of the exposure to this invasive disease is difficult to assess as \textit{Aspergillus} spp. are commensal fungi. The probability of disease depends on individual immunity, the colonization of the respiratory tracts is not constant, and the inocula can vary over seasons or place [36]. These factors could lead to different incubation periods for the same etiologic agent but no formal argument can support this hypothesis.

On the other hand, the incubation period can be contributed to only by the community, only by the hospital or could be the result of these two environments. The identification of exposure sources needs appropriate protective measures for different settings. For simplification, disease progression can be divided into four stages, i.e., exposure, colonization, clinical disease onset, and possible dissemination (Fig. 1). This simplistic disease course should be discussed because proof of colonization warrants valid screening, and most investigations have focused on the time interval between presumed exposure and clinical disease onset [3–5]. However, for each stage illustrated in Fig. 1, we have to consider the risk factors or environmental determinants (the hospital or the community) impacting the host, including underlying disease with or without immunosuppression [2], genetic predisposition [37] and \textit{Aspergillus} virulence. Thus, the individual risk of IA could be modulated by community or hospital exposure and with treatment improvements, immunosuppressed patients could return to a satisfactory ‘normal’ life.

Disease progression from one stage to another should take the duration of each stage into account (Fig. 2). The analysis must consider not only the date of exposure and colonization but also the duration of these periods as they will represent the difference between the older date of exposure minus the closest date of exposure before onset. Similar calculations of colonization could be proposed, but are difficult in practice. Figure 2 depicts the theoretical distributions of durations of exposure, the durations of colonization and the distribution of time of IA diagnosis. Based on these theoretical distributions, it is obvious that we have to document if these periods occurred in the community or hospital. For each period distribution, both scenarios should be discussed to propose adapted investigations, as well as preventive and prophylactic measures.

### Causality: association between hospital stay and IA occurrence

Preventive measures against IA are contingent on hospital and community acquisition of the disease. It is also important to research causal criteria for hospital-acquired IA. A major issue is to assess if hospital stay is a risk factor for IA. The answer is not easy because; (i) \textit{Aspergillus} spores are present in hospital and community, (ii) many confounders can be linked to hospital stay, and (iii) the estimation of this risk has not been fully explored. For instance, acute leukemia patients hospitalized for induction chemotherapy undergo prolonged neutropenia, a well-known host-related factor for IA [3,25,38,39]. Is hospital exposure to \textit{Aspergillus} sufficient to cause IA? If neutropenia is a component of IA, is it a necessary cause? The same question arises for corticoid exposure, transplantation, mild immunosuppression, and other risk factors for IA [2,3].

To begin dealing with the association between hospital stay and IA occurrence, we can apply the causal perspectives defined by Hill [40]. First, the strength of the association is correlated with the relative risk of the outcome, i.e., IA incidence in hospitalized vs. non-hospitalized populations. Thus, IA incidence in the general population was 12.4/100,000 in 3 American counties between 1992 and 1993 [41], whereas it was much higher in hospitals [41–45]. In addition, the attack rate for patients with acute leukemia was most often between 5% and 25% [42,43]. However, no study has formally estimated the relative risk with and without hospitalization. Second, there is consistency in the association between hospitalization and IA occurrence. Indeed, a review found 53 outbreaks involving 458 patients [19] and several surveillance studies determined that IA cases were regularly diagnosed in hematological units.
Nosocomial vs. community aspergillosis

[43–45] or intensive care units [46]. Third, the specificity of hospital exposure is not a constant criterion because (i) it can lead to a wide range of NI [47], and (ii) IA has been observed without previous hospital stay [28]. Fourth, the temporality criteria were met in more than 50% of IA cases in 1 study [28], but other cases were obviously not related to hospital acquisition. Fifth, the observation of a correlation between *Aspergillus* environmental load and IA involved a biological gradient [48] but other studies did not find any correlation [20]. Moreover, simultaneous isolation of the same *Aspergillus* strain in hospital environments and patient samples [21,49] reinforces the biological gradient concept. Sixth, the association is plausible since the etiological agent is present in the hospital environment and progression of the infectious process is known [2,50]. Seventh, underlying diseases could interfere in the association between hospital stay and IA occurrence. Indeed, neutropenia, transplantation and other host-related factors could jeopardize coherence of the association [51,52] because of their interaction with IA risk factors. Experimental evidence suggested a link between environmental changes and decreased IA incidence in ‘protected rooms’ [53–55] or increased IA incidence during hospital renovations [17,18]. Finally, analogies with other pulmonary infectious diseases could be made, but the transmission route, reservoir and infectious process related to IA seem to be unique.

![Fig. 2](image_url) Environmental exposure and theoretical stages of invasive aspergillosis (IA).

<table>
<thead>
<tr>
<th>Causal criteria</th>
<th>Argument for nosocomial origin</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength</td>
<td>High incidence in hospitals</td>
<td>[28,42–46]</td>
</tr>
<tr>
<td></td>
<td>Low incidence in the general population</td>
<td>[41]</td>
</tr>
<tr>
<td>Consistency</td>
<td>Several reports on IA cases that occurred during hospital stay</td>
<td>[28,43–45]</td>
</tr>
<tr>
<td></td>
<td>IA outbreaks</td>
<td>[19]</td>
</tr>
<tr>
<td>Specificity</td>
<td>One cause (hospital stay) mainly has not a single effect (IA)</td>
<td>[47]</td>
</tr>
<tr>
<td></td>
<td>One effect has mostly 1 cause: most IA occur during hospital stay</td>
<td>[28]</td>
</tr>
<tr>
<td>Temporality</td>
<td>Most IA occur after hospital admission</td>
<td>[28]</td>
</tr>
<tr>
<td>Biological gradient</td>
<td>Correlation between hospital <em>Aspergillus</em> exposure and IA occurrence</td>
<td>[48]</td>
</tr>
<tr>
<td></td>
<td>Relationship between molecular strains isolated from the environment and from IA patients</td>
<td>[21,48,49]</td>
</tr>
<tr>
<td>Plausibility</td>
<td>A single known etiological agent</td>
<td>[2,3]</td>
</tr>
<tr>
<td></td>
<td>Exposure to colonization and disease in hospitals in a classical infectious disease transmission model</td>
<td>[50]</td>
</tr>
<tr>
<td>Coherence</td>
<td>Coherent, but interaction with underlying disease and disease history</td>
<td>[51,52]</td>
</tr>
<tr>
<td>Experimental evidence</td>
<td>Decreased incidence when controlling for hospital environmental exposure</td>
<td>[53–55]</td>
</tr>
<tr>
<td></td>
<td>Increased incidence during hospital renovation</td>
<td>[17,18]</td>
</tr>
<tr>
<td>Analogy</td>
<td>No data</td>
<td>-</td>
</tr>
</tbody>
</table>
Temporality and biological plausibility are important components of a causal association between hospital stay and IA. Moreover, strength of the effect and experimental evidence are strong arguments for hospital acquisition of IA. Indeed, several reports provided experimental evidence for such infections as quasi-experimental studies show decreased IA incidence when controlling for hospital environment (by positive pressure isolation or high-efficiency air filtration) [53–55]. Also, besides host-specific factors that can be linked with hospital stay and possibly with the hospital acquisition of IA [2, 3, 38, 39], hospitalization seems to constitute an independent risk factor for IA.

While exposure to Aspergillus spores is universal, many causal arguments for hospital acquisition of IA can be put forward (Table 1). However, the natural history of IA—from exposure to colonization and disease—is complex, and the precise place of hospital involvement in this process is still not directly known.

Acknowledgments
We thank Ovid Da Silva for editing this manuscript.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References


This paper was first published online on Early Online on 7 September 2010.