



# Successful control of an outbreak of invasive aspergillosis in a regional haematology unit during hospital construction works<sup>☆</sup>

C.C. Chang<sup>a</sup>, A.C. Cheng<sup>a</sup>, B. Devitt<sup>b</sup>, A.J. Hughes<sup>a</sup>,  
P. Campbell<sup>b</sup>, K. Styles<sup>c</sup>, J. Low<sup>c</sup>, E. Athan<sup>a,\*</sup>

<sup>a</sup> Department of Infectious Diseases, Geelong Hospital, Geelong, Victoria, Australia

<sup>b</sup> Clinical Haematology Unit, Geelong Hospital, Geelong, Victoria, Australia

<sup>c</sup> Infection Prevention Unit, Geelong Hospital, Geelong, Victoria, Australia

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**Summary** We report the successful control of an outbreak of six cases of nosocomial invasive aspergillosis (IA) in our haematology unit coinciding with major hospital construction works. Infection control changes included unit relocation, impermeable barriers at construction site, face-masking and voriconazole prophylaxis of 18 further high-risk patients, none of which developed breakthrough IA. A multi-faceted pre-emptive approach involving clinicians, hospital management, engineering and building departments is essential in preventing nosocomial IA outbreaks. Crown Copyright © 2008 Published by Elsevier Ltd on behalf of The Hospital Infection Society. All rights reserved.

## Introduction

Invasive aspergillosis (IA) remains the leading infective cause of infectious mortality in most haematology and bone marrow transplant units.<sup>1</sup> Hospital building works is an established risk factor for invasive fungal infections (IFI).<sup>2,3</sup> Risk stratification for IFI by host-related factors is well-

established.<sup>4</sup> Less attention has been given to institutional risk factors such as the presence of construction works. We report an outbreak of six cases of IA in our haematology unit and describe the successful implementation of environmental measures and voriconazole prophylaxis.

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\* Corresponding author. Address: Department of Infectious Diseases, Geelong Hospital, Ryrie Street, Geelong, Victoria 3220, Australia. Tel.: +61 3 5260 3205; fax: +61 3 5260 3040.

E-mail address: [eugene@barwonhealth.org.au](mailto:eugene@barwonhealth.org.au)

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## Methods

### Setting

Geelong Hospital is a 406-bed regional referral centre in Victoria, Australia. The haematology–oncology service has been in existence for >20 years and manages ~40 patients annually with acute leukaemia, high-grade lymphoma and patients undergoing autologous stem cell transplantation. A small number of allogeneic transplantation recipients return to our centre following their transplantation elsewhere. Prior to this outbreak, fluconazole 200 mg daily was administered to patients with acute leukaemia undergoing induction or consolidation treatment and to patients receiving aggressive therapy for high-grade lymphoma. A search and chart review of medical records for haematology–oncology patients revealed no cases of IA (ICD-10 code B44.0) in the preceding eight years.

Ambulatory care occurs within a comprehensive day-oncology facility linked to the main hospital building by a 200 m open breezeway (Figure 1). The inpatient haematology ward is located on the sixth floor of the main building with five four-bed rooms and four single rooms. The inpatient ward is serviced by standard air filtration with pre-filters to remove large particulate matter using standard deep-bed filters, which are washed monthly and replaced annually. There is no high-efficiency particulate air (HEPA) filtration in the inpatient or day-oncology ward.

As part of the service expansion, hospital construction works in and around the vicinity of the day-oncology building commenced in early 2006. Major excavation and demolition works were planned for June 2006. A transfer of the day-oncology service to the main hospital building was to precede this; however, construction works unexpectedly ran ahead of schedule before this could occur.

### Definitions

We assessed cases of IA according to European Organisation for Research and Treatment of Cancer (EORTC) definitions.<sup>5</sup> Proven IFI was defined as histopathologic or cytopathologic examination showing hyphae from needle aspiration or biopsy specimen with evidence of associated tissue damage, or a positive culture result for a sample obtained by sterile procedure from normally sterile and clinically or radiologically abnormal site consistent with infection. Probable IFI required at least one each of host factor and microbiological

criterion and one major (or two minor) clinical criteria from abnormal site consistent with infection. Possible IFI was defined as at least one host factor criterion and one microbiological or one major (or two minor) clinical criteria.

Galactomannan assays are not widely available in Australia outside of research studies. Polymerase chain reaction (PCR) for *Aspergillus* was performed at Westmead Hospital, Australia, using a nested qualitative real-time *Aspergillus*-specific PCR assay with a LightCycler (LC) system (Roche Diagnostics, Sydney, Australia).<sup>6</sup>

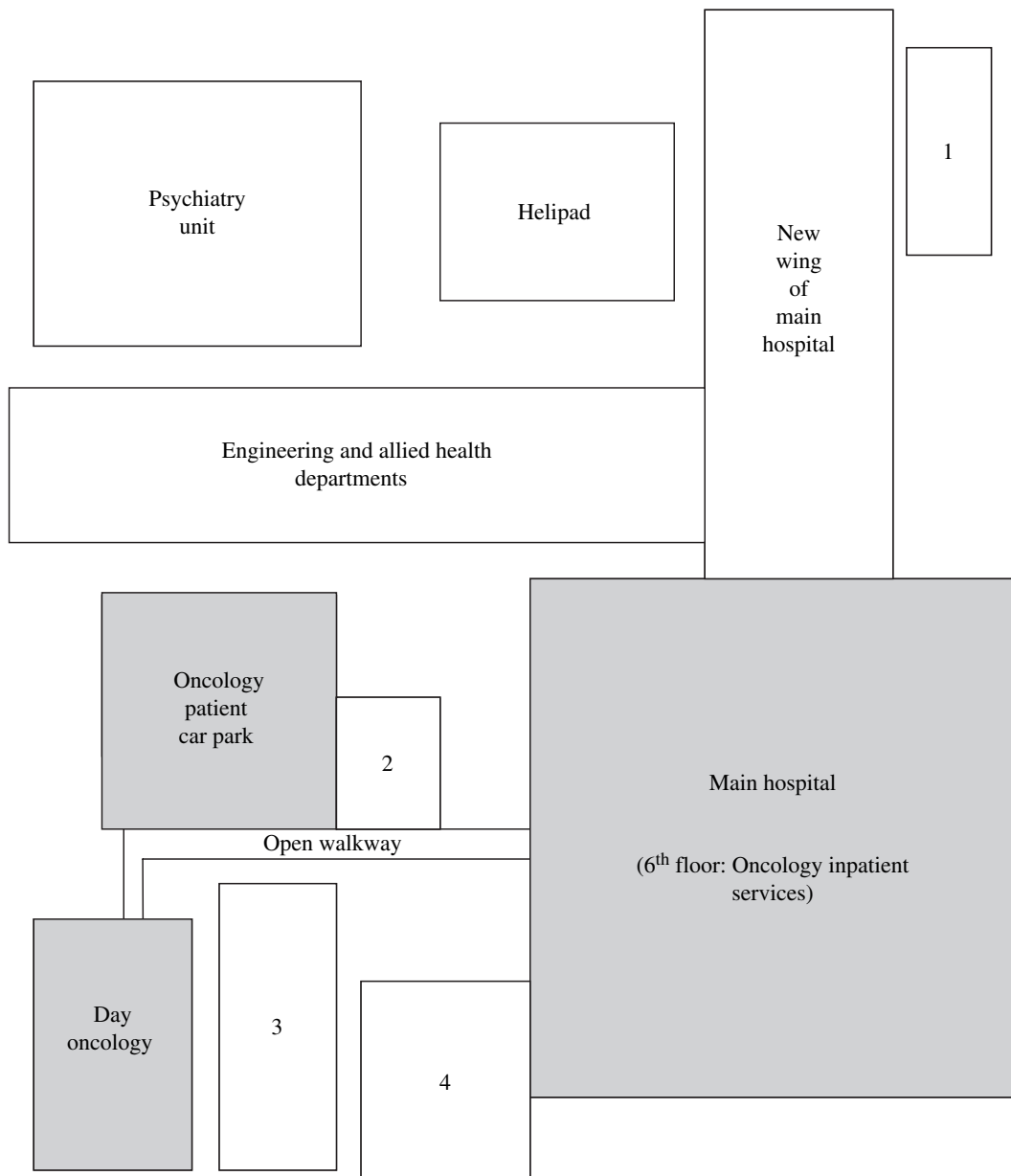
Following identification of the outbreak, cases were identified prospectively by active surveillance and supplemented by a review of hospital records of haematology patients treated prior to the outbreak. We considered patients as at high risk for IFI if they had acute leukaemia, were undergoing transplantation and those predicted to develop prolonged neutropenia. Air-sampling was performed using a MAS-100 air-filter (EMD Chemicals Inc., Merck Pty Ltd, Kilsyth, Australia) whereby 500 L of air was sampled for 5 min each, in the day-oncology unit, inpatient ward and pharmacy department, collected on horse blood agar and incubated at 37°C for 48 h.

### Outbreak description and management

An outbreak was declared on 23 June 2006 after the identification of a cluster of two proven, two probable and one possible diagnosis of IA over two months (Table 1). Urgent steps were taken including immediate relocation of the day-oncology services for high-risk patients to a vacant ward in the main hospital building on 4 July 2006 (Figure 2). Regular building site inspections were held to ensure that sites were sealed with impermeable barriers, doors and windows remained shut, and cleaning was adequate (e.g. wet mop surfaces, vacuum carpeted areas, debris removal). Patients in the haematology–oncology services were given written notification, advised to avoid building construction sites and to use N95 face masks when they were out of the inpatient ward while on hospital premises. The patient car park was relocated away from the construction site.

Weekly meetings were held between infection control, cancer services, hospital management, building and engineering departments to facilitate updates and communication. Air sampling in the inpatient facility, day-oncology and pharmacy did not reveal any fungal growth.

Construction works continued from June till November 2006. In view of the unprecedented high incidence, morbidity and mortality rate of



**Figure 1** Schematic outline of hospital layout. (1) Endoscopy suite; (2) finance department; (3) library; (4) staff lounge.

IFI, during this period, voriconazole prophylaxis (loading 400 mg for two doses followed by 200 mg twice daily orally) was administered to patients stratified as 'high risk' by their treating clinicians. Patients receiving vinca alkaloids and cyclophosphamide were administered thrice-weekly prophylactic liposomal amphotericin at 3 mg/kg in place of voriconazole due to potential pharmacokinetic interactions. Those intolerant to amphotericin B were administered fluconazole and vigilantly monitored for development of IFI. Three patients received amphotericin B prophylaxis.

None of the 18 patients placed on voriconazole or amphotericin B prophylaxis developed IFI. However, one man aged 75 years with chronic lymphocytic leukaemia treated with methylprednisolone and rituximab, not stratified as high-risk, was diagnosed with disseminated IA at post mortem after presenting with confusion and fevers on 9 July 2006.

Day-oncology was relocated to the new facilities on 11 December 2006 after completion of construction works and five negative on-site air-samples were obtained. Fluconazole 200 mg daily

**Table I** Summary of invasive aspergillosis cases

Case	EORTC definition	Underlying disease	Chemotherapy	Neutropenic days (<0.5)	Respiratory symptoms	CT chest	Microbiology/ molecular results	Outcome
1	Probable	De-novo AML	Cycle 1 consolidation FLAG-Ida	13	Moderate	Nodule and interstitial change	Sputum: <i>A. fumigatus</i> Delayed bronchoscopy negative.	Alive and in remission
2	Proven	Transformed AML	Induction FLAG-Ida	20	None	Small peripheral nodule	CT-guided biopsy: fungal hyphae resembling Aspergillus	Completed one cycle of reduced dose consolidation. Alive and in remission
3	Proven	De-novo AML	Induction Big-ICE	12	Mild	Small peripheral nodule	CT-guided biopsy: fungal hyphae resembling Aspergillus, and Aspergillus-positive PCR	Completed two cycles of consolidation. Alive and in remission
4	Possible	De-novo AML	Induction Big-ICE	23	Severe	Multiple bilateral nodules	Refused bronchoscopy and biopsy until 1 and 4 weeks post-empirical treatment (both negative)	Deceased with Gram-negative sepsis in second consolidation cycle
5	Probable	Advanced multiple myeloma	Thalidomide	65	Severe respiratory failure	Extensive bilateral interstitial change	Sputum: <i>A. fumigatus</i>	Palliated
6	Proven	CLL	Methylprednisolone and thalidomide	2	Mild (but severe neurological change)	CXR: RLL patchy change	Post-mortem: disseminated aspergillosis	Deceased. Day 6 admission despite antifungal treatment
7	Proven	DLBCL	R-CHOP and intrathecal methotrexate	5	None	Soft tissue mass in mediastinum	Hyphae seen on microscopy (not sent for culture). Aspergillus-negative PCR	Successfully underwent allotransplant

EORTC: European Organisation for Research and Treatment of Cancer; CT: computed tomography; FLAG-Ida: fludarabine; Ara-C: idarubicin, G-CSF; Big-ICE: idarubicin, high-dose Ara-C, etoposide; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; PCR, polymerase chain reaction; PET scan: positive emission tomography; AML: acute myeloid leukaemia; CLL: chronic lymphocytic leukaemia; DLBCL: diffuse large B-cell lymphoma; CXR: chest radiograph; RLL: right lower lobe.

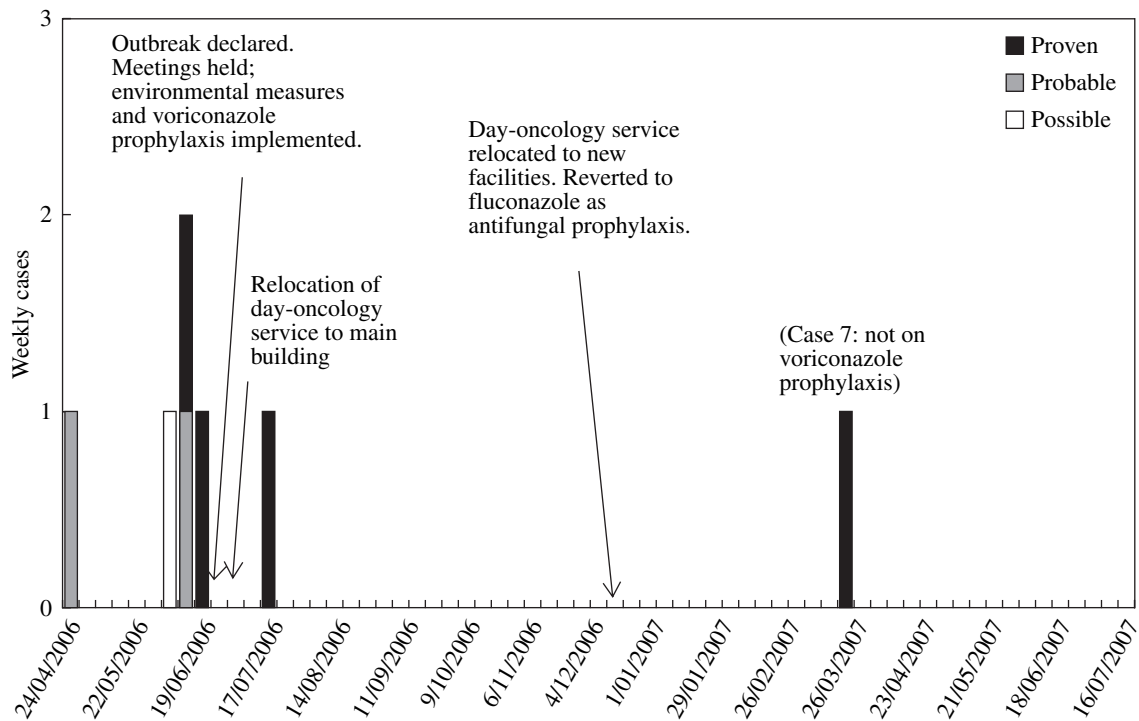


Figure 2 Timeline of invasive aspergillosis outbreak.

was re-established as routine antifungal prophylaxis. Three of the five patients involved in the outbreak remain alive at end of the current follow-up period, 31 July 2007. In March 2007, a further patient with non-Hodgkin's lymphoma was diagnosed with IA from a mediastinal biopsy – notably, part of his earlier chemotherapy coincided with the IA outbreak period.

## Discussion

Hospital building works are an ever-present phenomenon in modern-day healthcare.<sup>7,8</sup> Current guidelines call for management plans to be implemented during times of construction, and our experience highlights the need for communication between clinical, management and engineering services at the hospital.<sup>2,9–13</sup> Effective measures include relocation of high-risk patients, masking, wet cleaning, reducing unnecessary traffic through affected areas, environmental sealing of construction areas, advice to patients and air filtration.<sup>2,9,13,14</sup>

There are conflicting data on the efficacy of HEPA filters in outbreak control.<sup>15–17</sup> We did not elect to install HEPA filters during this outbreak. HEPA filters are complex to install and maintain, and suboptimal maintenance can lead to outbreaks of aspergillosis.<sup>7,11</sup> A meta-analysis of 16 controlled trials in high-risk haematology patients

demonstrated ambiguous findings, with a reduction in IFI but no difference in mortality, in studies with considerable clinical heterogeneity and evidence of publication bias.<sup>18</sup>

The role of air sampling for fungal spores also remains controversial. Outbreaks of IFI with negative air-sampling data have been described previously.<sup>8</sup> The incubation period for IFI remains unknown and single-point air-sampling may miss peaks in fungal spores. Further, the lack of standardized methods to perform air sampling makes interpretation difficult.

We used voriconazole as antifungal prophylaxis for high-risk patients during the outbreak in view of its activity against *Aspergillus* spp., its availability in oral and intravenous formulation and ease of dosing. Voriconazole as primary prophylaxis is yet to be supported by clinical trials, but it has clear efficacy against IA and in secondary prophylaxis.<sup>19</sup> This outbreak occurred prior to the publication of the posaconazole primary prophylaxis papers.<sup>20,21</sup>

Criteria for assessing patients at high risk of IFI are generally based on patient characteristics, such as underlying disease, degree of immunosuppression, chemotherapy utilised and duration of neutropenia.<sup>4,22</sup> It is important also to recognise environmental factors, reflected in the baseline institutional rate of IFI and modifying factors such as building works. We believe that the threshold for

antifungal prophylaxis should be lowered in the setting of hospital construction works. The relative convenience and safety of newer oral antifungal agents make this possible. Although we did not perform a formal cost analysis, the expense of these newer antifungal agents remains an issue (the cost of voriconazole alone for prophylaxis and treatment during this outbreak approached A\$160,000), but should be weighed against the high cost and morbidity associated with IA.

In conclusion, we report the first published experience of the use of voriconazole as antifungal prophylaxis in the setting of building works and an outbreak of IA. Hospital construction work is a clear risk factor for development of IFI. Clinicians, hospital management, building and engineering staff should have a strategic plan to reduce this risk. Ongoing vigilance and interdepartmental communication is important. The threshold for antifungal prophylaxis should be lowered. There is a pressing need for further research and management guidelines for prevention of IA in hospital building works.

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### Conflict of interest statement

None declared.

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