

## Aspergillus: friend or foe?

### Update on clinical disease and laboratory diagnosis

Dr Renu Vohra

#### Introduction

Aspergillus species are saprophytic fungi that play an essential role in recycling environmental carbon and nitrogen. Without their activity much of the land surface of the earth would become inundated by persisting vegetable matter. They are vital members of the complex polymicrobial activity that converts dead plant material into humus and in this way the activities of aspergilli are predominantly “friendly” towards man. Considering the ongoing exposure of man to ubiquitous potentially infective airborne conidia, very rarely does clinical disease occur.

Although *A.fumigatus* is responsible for 90% of all the invasive disease, other pathogens in this genus include *A.terreus*, *A.niger* and *A.flavus*. *Aspergillus sp* are readily cultured from respiratory specimens, however, airway colonisation is frequent and hence its presence may not necessarily be predictive of underlying disease.

*Aspergillus sp* are generally regarded as weak pathogens. In immunocompetent hosts they are associated with allergic forms of the disease such as farmer’s lung, a clinical condition observed among individuals exposed repeatedly to conidia, or, aspergilloma, an overgrowth of fungus on the surface of pre-existing lung cavities of patients treated with tuberculosis. However, with increasing number of immunocompromised patients in the last 10 years, *A.fumigatus* has become the most prevalent airborne fungal pathogen, causing severe and usually fatal invasive infections in these hosts.

#### CLINICAL DISEASE

Normal host defences protect most people from *Aspergillus* infection. An efficient mucociliary stream, which clears inhaled airborne conidia from the respiratory tract provides the first line of defence. Polymorphonuclear leukocytes are the main effector cells in providing defence against hyphal forms of aspergillus.

#### Classification of the diseases caused by Aspergillus

- 1 Allergic aspergillosis
- 2 Aspergilloma
- 3 Invasive aspergillosis

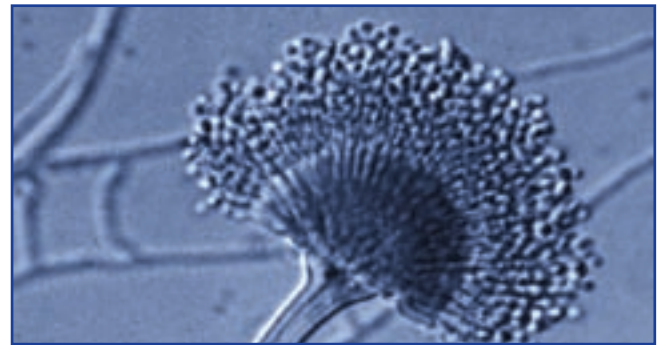


Figure 1: *Aspergillus terreus*

#### ALLERGIC ASPERGILLOSIS

Allergic aspergillosis can manifest as allergic asthma, extrinsic allergic alveolitis and allergic sinusitis. They occur following repeated exposure to conidia or antigens of aspergillus in absence of mycelial colonisation. In most cases removal of the patient from the environmental source results in clinical improvement and therefore will not be discussed in detail in this article.

However, allergic bronchopulmonary aspergillosis (ABPA) is currently the most severe allergic complication of aspergillus species and occurs in patients suffering from atopic asthma or cystic fibrosis. ABPA occurs in 1-2% of asthmatics and 7-35% of cystic fibrosis patients. The immunopathology of ABPA is not known exactly, but represents a reaction to the aspergillus conidia that are inhaled by the atopic individual. The fungus then grows non invasively within the bronchi, releasing an antigen that causes host sensitisation and a subsequent immunologic reaction; type I, type III, and probably type IV hypersensitivity reaction.

For the diagnosis of ABPA there are major and minor criteria.

#### Major criteria include:

- Asthma
- Peripheral blood eosinophilia
- Immediate skin reactivity to *Aspergillus* antigen
- Precipitating antibodies against *Aspergillus* antigen
- Increased total serum IgE
- Transient or fixed pulmonary infiltrate
- Central bronchiectasis: This radiographic picture is detected late in the disease.

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### Minor criteria are:

- *Aspergillus fumigatus* in the sputum
- History of expectoration of brown plugs
- Delayed skin reactivity to *Aspergillus* antigen

All the above criteria are rarely fulfilled. The predictive value of several of these criteria, eg radiographic findings, eosinophilia or precipitins, depends on the group (cystic fibrosis or asthmatic patients) and age of patients.

### Treatment consists of:

- Avoidance of the allergen
- Control of the acute episode by corticosteroids
- Limit the progression of the disease
- Oral therapy with itraconazole is useful for those who are corticosteroid dependant

Untreated ABPA leads to pulmonary fibrosis and respiratory failure, although some patients have remissions.

## COLONISING ASPERGILLOSIS

This condition with the development of “fungus ball” results from colonisation of preformed cavities caused by other diseases like tuberculosis, sarcoidosis, and bullous emphysema. It occurs in 10-15% of patients with cavitating lung disease. Haemoptysis is a common symptom that results from disruption of blood vessels within the cavity which usually originate from the bronchial arteries. Most patients are asymptomatic and aspergilloma is detected on chest x-ray for evaluation of another pulmonary or allergic condition.

Radiologically a mobile intracavitary mass is usually seen in the upper lobes. CT scan may be required to demonstrate the presence of the mycetoma. The radiologic appearance is almost always pathognomic for aspergillosis. Diagnosis can be confirmed serologically by demonstrating a rise in titre of serum precipitins. *Aspergillus sp* may be cultured from the sputum in 50% of the cases, but as aspergillus is a contaminant in the sputum of many, its presence is therefore of not much help.

Specific therapy is not required for patients with asymptomatic aspergilloma. Approximately 10% of aspergilloma resolve spontaneously. However, in patients who present with massive haemoptysis surgery is required.

## INVASIVE ASPERGILLOSIS (IA)

This is a disease of the severely immunocompromised or neutropenic patients.

The average incidence of IA is found to be 5-25% in acute leukemics, 5-10% after allogenic bone marrow transplant (BMT), and 0.5-5% after cytotoxic therapy of blood diseases or autologous BMT and solid organ transplantation. Four types of IA have been described: 1) acute or chronic pulmonary aspergillosis, the most common type; 2) tracheobronchitis and obstructive bronchial disease seen predominantly in AIDS patients; 3) acute invasive rhinosinusitis and 4) disseminated disease

involving the brain and other organs. Clinical features of different types of IA depend on the organ localisation and underlying disease.

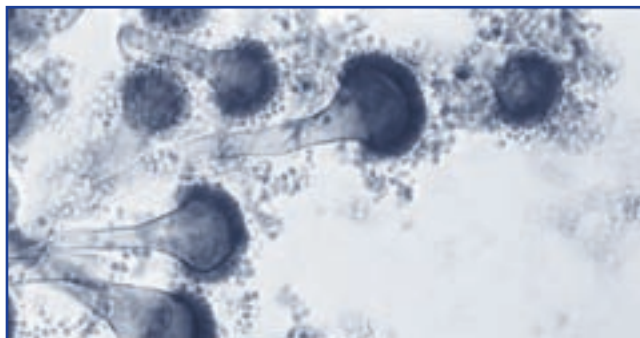


Figure 2: *Aspergillus fumigatus*

Features consistent with diagnosis of IA include 1) a positive CT scan 2) culture and / or histologic evidence of tissue invasion 3) detection of aspergillus antigen in serum. Radiographic features are very non-specific and heterogeneous. This may vary from single or multiple focal nodules to widespread and large infiltrates bilaterally. The diagnosis of invasive disease is frequently a presumptive one. The presence of pulmonary infiltrates in any febrile, granulocytopenic patient who is on broad spectrum antibacterial or who does not respond should signal the strong possibility of a fungal disease. Currently serological diagnosis is not recommended, however antigen detection by various methods may be helpful.

## LABORATORY DIAGNOSIS

Clinical condition	Laboratory diagnosis
APBA	Microscopy of sputum Culture Serology <b>Other tests</b> Total IgE level Peripheral eosinophilia
Aspergilloma	Microscopy Culture Serology
Invasive aspergillosis	Histopathology Culture Antigen detection <b>Other tests</b> Serology PCR

## ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

**Microscopy and culture:** On microscopic (KOH preparation) examination of sputum hyphal fragments will be seen and if there are mucus plugs present, branching hyphae will be seen within the plugs. Charcot-Leyden crystals (as a result of the breakdown of the eosinophils) are generally prominent. Culture of the sputum will grow *Aspergillus sp* in two thirds of patients, but

as *Aspergillus sp* is a contaminant in the sputum of many, its presence is suggestive but not diagnostic for ABPA.

**Serology:** Since titres in normal healthy people are low, infection can be correlated with rise in specific antibody titres. At QML Pathology an indirect hemagglutination (IHA) test is performed which detects total antibodies (IgG and IgM) to aspergillus.

A titre < 160 is regarded as normal.

A titre of 160 is regarded as equivocal.

A titre ≥ 320 is regarded as significant and indicates exposure to aspergillus.

As with any serology a four fold rise in antibody titre is regarded as diagnostic.

IgE antibody specific for aspergillus (IgE-Af) using *A. fumigatus* antigen is also performed at QML Pathology on request.

**Other tests that might be helpful:** Total serum IgE is usually elevated in patients with ABPA and full blood count reveals marked eosinophilia >1000 mm<sup>3</sup>. IgE levels are the best indicator of disease activity and should be monitored regularly. However, occasionally the total IgE level may remain elevated in a patient who has otherwise responded to prednisone.

**Colonising aspergillosis:** The diagnosis is made by microscopy and culture of appropriately collected material. Since, in both aspergilloma in a pre-existing lung cavity or within a paranasal sinus, air has ready access to the growing fungus, conidiation (spore formation) may occur so that a vesicle with associated conidiogeny (see figure 1 and figure 2) will identify the fungus as *Aspergillus sp*. More often, only non-diagnostic hyphal masses will be seen and specific diagnosis will depend upon culture of the fungus and microscopic morphology of the isolate.

## INVASIVE ASPERGILLOSIS

**Histology examination of biopsy material:** In paraffin sections, branching septate hyphae will be seen (see figure 3 and 4) and not uncommonly invasion of the pulmonary blood vessels. Much has been written in standard texts of Anatomical Pathology about septation, hyphal width and the angles at which hyphae branch. These features do clearly distinguish *Aspergillus* species from invasive fungi isolated from cases of "mucormycosis" (*Mucor*

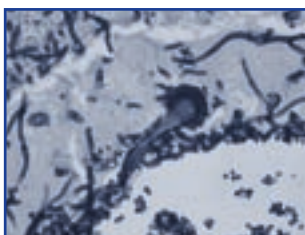


Figure 3 (left): Methenamine silver (GMS) stained tissue section showing *Aspergillus fumigatus* in lung tissue, note conidial heads forming in alveoli

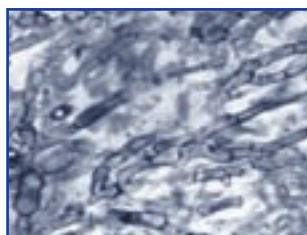


Figure 4 (right): Methenamine silver (GMS) stained tissue section of lung showing dichotomously branched, septate hyphae of *Aspergillus fumigatus*

species, *Rhizomucor species*, *Rhizopus species*. and others) which have much broader hyphae and are only sparsely septate. However, these morphological features cannot be relied upon to unequivocally identify *Aspergillus species* from *Paecilomyces species*, *Fusarium species* and *Penicillium marneffeii*. These fungi may cause invasive disease in patients with acquired immunodeficiency syndrome (AIDS) and other immunocompromised hosts.

**Culture of the biopsy material:** Fresh specimens, NOT placed in formalin, should be sent promptly to the microbiology laboratory. In this way the causative fungus can be identified by microscopic morphology and isolated efficiently. Culture is then also available for antifungal sensitivity testing which, although not as standardised as antibacterial sensitivity testing, can nevertheless be used as a guide to antifungal therapy in the particular patient.

**Antigen detection:** Not infrequently, invasive disease progresses to disseminated disease with a rapidly fatal outcome. Such patients will have aspergillus antigen in their bloodstream which can be detected using latex agglutination, ELISA, and radioimmunoassay. A commercial ELISA has been available for detection of galactomannan antigen. In studies so far the specificity of the galactomannan assay was 85% and sensitivity varied from 29% to 100%. There is however, considerable variation in performance. This variance is multifactorial and poorly understood. Despite the variance this assay is widely used in the management of patients at high risk of invasive disease. An increasing antigen ratio strongly indicates the presence of invasive aspergillosis. This rise can be detected by serial testing on patient's serum sample performed every 2-3 days.

**Other tests:** Serological monitoring is insensitive in most cases of immunosuppressed patients. The use of PCR assay for diagnosis is still under study. It is associated with both false positive and false negative results.

## Summary

Aspergilli are ubiquitous, and are common fungi in our local environment. In general, the good they do by helping to reduce dead plant material to humus far outweighs their occasional harm. But, in susceptible, immunocompromised patients they may cause serious and sometimes fatal disease.

## References

- Jean-Paul Latgé. *Aspergillus fumigatus and Aspergillosis*. Clinical Microbiology Reviews.1999; April 12(2):310-350
- Miller WT: *Aspergillosis; A disease with many faces*. Seminars in Roetgenology vol XXXI,1996; Jan 1: 52-56
- Mennink-Kersten MA, Donnelly JP, Verweij PE. *Detection of circulating galactomannan for the diagnosis and management of invasive aspergillosis*. Lancet Infect Dis. 2004; Jun;4(6):349-57.
- Eaton T, Garrett J, Milne D, Frankel A, Wells AU. *Allergic bronchopulmonary aspergillosis in the asthma clinic*. A prospective evaluation of CT in the diagnostic algorithm. Chest. 2000; Jul;118(1):66-72.



## Doctors' Notice Board

**Dr Terrence Holt** would like to announce that he has commenced his Gastroenterology practice at:

Terrace West Endoscopy Centre,  
18 Limestone St, Ipswich, Qld, 4305.

Ph: (07) 3812 1426

**Dr Anders Taylor** has recently returned from overseas after completing a fellowship in Interventional Cardiology and has set up a full-time private practice at Greenslopes Private Hospital. Dr Taylor has trained in all aspects of coronary intervention, including intravascular ultrasound. His interests include angioplasty, ischaemic heart disease and general cardiology.

A member of the Heart Care Partners Group, Dr Taylor is happy to be of service to both private and veteran patients on an inpatient or outpatient basis.

Appointments: (07) 3394 3100

Fax: (07) 3394 3118

**Dr Margaret Kidd** would like to announce that she has retired as of 25 March 2005. She would like to thank everyone for their referral support over the past 25 years in which she has practiced at Wickham Terrace, Sunnybank and Sherwood.

**Dr Andrew Nielsen** (MBBS FRANZCP), Psychiatrist, has commenced at the Toowong Specialist Centre / Toowong Private Hospital, PO Box 822, 496 Milton Rd, Toowong 4066. He has a special interest in cognitive behavioural therapy (CBT), as well as general adult psychiatry. For appointments phone Liz on (07) 3721 8011.

**Dr Peter Ganter** (FRANZCOG) is currently accepting referrals for private obstetrics, gynaecology and infertility. He will begin consulting from rooms at Watkins Medical Centre, Wickham Tce as of April 2005. He has clinical privileges at most major metropolitan hospitals.

Dr Ganter has been in private practice in the Redlands area for the past 3 years but is relocating his practice to metropolitan Brisbane in order to further his interest in infertility services (Queensland Fertility Group Associate). Dr Ganter will continue to service the Redlands area by running regular clinics from his Cleveland Rooms. All enquires please phone (07) 3821 6626.

**Dr Gordon Senator** will be relocating as of the 4th April, 2005 to

Suite 7, Brockway House  
82 Queen Street

Southport Qld 4215

Ph: (07) 5531 0297

Fax: (07) 5531 0337

He will continue Friday sessions at John Flynn Gold Coast Medical Centre (Suite 2B).

Dr Senator would like to take this opportunity to thank you for your support and assure you of continuation of that support into the future.

**Dr Andrew Ives** is pleased to announce his commencement of practice in plastic and reconstructive surgery on the Sunshine Coast. He will be joining Dr Mark McGovern at Vie Institute from 31st March. For all appointments please phone 1800 080 001.

Vie Institute for Beauty and Longevity

17/35 The Esplanade

Maroochydore Qld 4558

Ph: (07) 5479 2922

Fax: (07) 5443 4292

**Dr Glynis Jones** (MBBS FRACOG), Gynaecologist, would like to announce the relocation of her practice to:

Shailer Park Specialist Centre

70 Bryants Rd, Loganholme

as of 16th March, 2005. Ph: (07) 3801 5055

**Dr Judith Goh** (MBBS, FRANZCOG, PhD CU), Urogynaecology and Pelvic Reconstructive Surgery, would like to announce the relocation of her practice to:

Shailer Park Specialist Centre

70 Bryants Rd, Loganholme

as of 16th March, 2005. Ph: (07) 3801 5055

**Dr Philip Jumeau**, ENT and Head & Neck Surgeon, would like to announce he has opened rooms at Cairns Private Hospital where he will see both private and public patients. Dr Jumeau's interest is in all areas of ENT including paediatrics, sinonasal disease, laryngeal pathology, ear disease, airway & snoring surgery, salivary gland and thyroid surgery. Please feel free to fax or mail along your referrals or contact him for ENT advice. Patients need to call to make an appointment.

Cairns Private Hospital

199 Abbott St, Cairns QLD 4870

Ph: (07) 4051 0890, Fax: (07) 4051 1132

# QML Pathology Charity Ball

## Thank you for your support

After missing out on the opportunity to be part of a QML Pathology Charity Ball in 2004, over 300 members of the medical community jumped at the chance to attend this year's Ball held at the Hilton Hotel on Saturday, February 26th.

The annual event has a history of delivering a great time for all who attend, while raising much needed funds for local charities. This year was no exception. The beautifully decorated main ballroom played part to one of the most enjoyable balls in the event's seven year history.

Everyone had a great time, and why not? The sumptuous food, live music, glamorous dresses and electric atmosphere satisfied everyone's senses.

The 2005 ball raised a great deal of money for this year's beneficiaries: Montrose Access and DrugArm. The overwhelming generosity of the night's sponsors ensured that these worthy causes could continue offering the valuable services they do.

In a very timely association, the donation to DrugArm has ensured their MOSHPIT van will remain active, a service which will play an important part in the current attempts by local government to curb street violence in Brisbane city.

The night was hosted superbly by ex-Wallaby captain Nick Farr-Jones, who generously donated his time for the evening. Intertwining the evening's important message of support with anecdotes of past on and off-field exploits, Nick was an extremely personable MC, even offering himself as a dance partner as the formalities ended and festivities commenced.

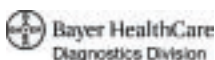
And there were plenty of reasons to dance. The great line up of entertainment had something for everyone. If the evening's band Zion wasn't enough, the operatic trio from Opera Queensland was certainly a highlight. Then there was the chance to win one of ten great raffle prizes ranging from a spa pamper package to a weekend at Palazzo Versace, which had punters scrambling for their winning ticket. There was even a signed Wallabies guernsey up for grabs, funnily enough ending up in the hands of the only Scotsman in the room.

Thank you to all who attended this year's Charity Ball. Your generosity has made a valuable contribution to the local community, and your attendance ensured the evening was once again a tremendous success.

### PLATINUM SPONSOR



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## COLLECTION CENTRE NEWS

For the convenience of our doctors and patients, we have listed the latest changes to QML Pathology's network of clinics:

### CLINIC CHANGES

#### **Arana Hills (07) 3351 4255**

20 Nepean Ave  
Mon – Fri 7.30am – 5.00pm  
Sat 8.00am – 12noon

Please contact your local branch or Brisbane Liaison for further information on (07) 3840 4943.

## And the winner is...

During the recent Australian Association of Practice Managers conference on 5th March, we once again ran the popular 'crossword' competition. By completing a simple crossword focussing on QML Pathology's services attendees were able to enter a competition to win one of two great prizes. As in the past, first prize was a pair of polar bear soft toys and on this occasion, second prize was a beautiful hamper of food and drink.



This year's winners were:

### **1st Prize – Polar Bears**

Karma Hodason  
Holy Spirit Northside Hospital

### **2nd Prize – Basket**

Carmel Dileo  
The Knee and Sports Medicare Centre

**Congratulations to our winners and thank you to all who attended and took part in the competition.**

## Anti-D Update

With the introduction of prophylactic anti-D during pregnancy (refer May 2004 Newsletter), a large number of anti-D antibodies are being detected. By inclusion in the clinical notes, that a patient has been given anti-D (the date it was given can also be advantageous), sample processing and result turnaround can be greatly improved. The testing process for anti-D determination is much shorter and less complex if scientific staff have the clinical information that an injection has been given prior to testing.

## April/May Events...

### **Cairns Division of General Practice – Healthy Kids and the GP Team**

**Date:** 23-24 April  
**Venue:** Sheraton Hotel, Port Douglas  
**Topics:** Paediatric and adolescent patient presentation in General Practice  
**Contact:** Peta Wilkinson  
**Phone:** (07) 4052 1699

### **RACGP Postgraduate Weekend**

**Date:** 30 April – 1 May  
**Venue:** Gold Coast International, Surfers Paradise  
**Topics:** Mental Health, Gynaecology, Dermatology, Plastic Surgery, Paediatrics, Cardiology  
**Contact:** Your registration desk  
**Phone:** (07) 3871 1155

### **Capricornia Division of General Practice CPD Conference**

**Date:** 30 April – 2 May  
**Venue:** Rydges Capricorn Resort, Yeppoon  
**Topics:** Asthma, Immunisation, CVD, Palliative Care, Travel Medicine, Plastic Surgery  
**Contact:** Suanne Robertson  
**Phone:** (07) 4927 3182

## Warfarin Reminder

**Please remember** to register your new Warfarin Care Patients on **1300 795 355** **BEFORE** they present for testing.

NEW PATIENTS ONLY need to be registered.

If you need a new info pack/stiicker, please contact our Liaison department on (07) 3840 4943.

**QML Pathology.**



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