Cryptococcal infections over a 15 year period at a tertiary facility & impact of guideline management

Gassiep I 1,2, Douglas J 1, Emeto TI 3,4, Crawley K 1,2 & Playford EG 1,2

1Department of Infectious Diseases, Princess Alexandra Hospital, Queensland Health, Australia
2School of Medicine, The University of Queensland, Brisbane, QLD, Australia
3Queensland Research Centre for Peripheral Vascular Diseases, College of Medicine and Dentistry, James Cook University, Townsville, Australia
4Public Health & Tropical Medicine, College of Public Health, Medical & Veterinary Sciences, James Cook University, Townsville, Australia

BACKGROUND
Cryptococcosis is an invasive fungal infection caused primarily by Cryptococcus neoformans and C. gattii species, associated predominantly with meningoencephalitis and more commonly diagnosed in the immunocompromised host 1,2. Discovery of the organism is attributed to Busse in 1894, however C. neoformans rose to infamy during the height of the HIV pandemic at a staggering incidence of 3.2% in sub-Saharan Africa 3,4. In recent years C. gattii has gained in prominence due to a sustained outbreak in British Columbia, Canada 5.

Incidence, diagnosis and management of cryptococcal infection has altered over time. Improved antifungal therapy has decreased the incidence of the human immunodeficiency virus (HIV) cohort 6. Access to cheap and accurate serological testing and screening of at risk populations has been found to be cost-effective 7. Management has changed with the advent of liposomal and lipid complex amphotericin B as well as the most recent 2010 Infectious Diseases Society of America (IDSA) treatment guidelines 8.

At our facility we have seen a trend towards increased incidence amongst our renal transplant cohort 9. Analysis of this cohort revealed a much lower mortality rate compared with international data. Given this information we aimed to assess all cryptococcal infections managed at our facility from 2001-2015 in order to determine potential increase in incidence, clinical and biochemical presentation, and comparison of outcomes prior to and after introduction of the 2010 IDSA guidelines.

METHODS
All potential cases of Cryptococcus infection were identified via the Queensland Health pathology service database AUSLAB, using search criteria for a positive cryptococcal antigen titre and or positive Cryptococcus microbiology culture results. A definitive case was a positive culture from tissue, blood, CSF or positive CSF Cryptococcus antigen titre 10

RESULTS
2010 potential cases were identified using the aforementioned methodology. 5 patients were not managed at our facility and were excluded from analysis. There appears to be a rise in incidence however this was not statistically significant in the transplant cohort and could not be accurately calculated at population level. 15

As might be expected, meningitis patients with positive CSF culture were more severely affected, more likely to have positive blood cultures, have a higher serum antigen titre and thus an increased mortality. Length of stay was not only greater in the meningitis cohort, but also when stratifying for CSF culture (13 days) 12.

Unfortunately a major concern remains the delay to diagnosis of infection Figure 2. Only 25% of patients with cryptococcal meningitis had their diagnosis confirmed within the first 3 days of admission. Figure 3. Mortality associated with cryptococcosis has been described between 25-35% 13. We report a lower cryptococcal attributed mortality of 9.9% over our study period. Death from C. gattii was 7% similar to 8.7% in British Columbia and lower than 13% previously reported in Australia 14. Since introduction of the 2010 IDSA guidelines mortality has markedly improved from 17.1% to 6.1%.

DISCUSSION
Cryptococcal infection is an important mycosis in both immunocompromised and immunocompetent individuals 15. This study demonstrates not only a potential for increasing incidence, but also highlights the Australian epidemiology of cryptococcal infection with both C. neoformans and C. gattii. As might be expected, meningitis patients with positive CSF culture were more severely affected, more likely to have positive blood cultures, have a higher serum antigen titre and thus an increased mortality. Length of stay was not only greater in the meningitis cohort, but also when stratifying for CSF culture positive vs. negative patients. In our cohort the IDSA guidelines appear to be associated with a shorter length of stay, decreasing the median admission time by 13 days.

Mortality associated with cryptococcosis has been described between 25-35% 13. We report a lower cryptococcal attributed mortality of 9.9% over our study period. Death from C. gattii was 7% similar to 8.7% in British Columbia and lower than 13% previously reported in Australia 14. Since introduction of the 2010 IDSA guidelines mortality has markedly improved from 17.1% to 6.1%

CONCLUSION
Cryptococcosis remains an important human infection affecting both immunocompetent and immunocompromised individuals. Delay in diagnosis remains a significant concern given the association with poorer outcomes. The deleterious effects of delay in diagnosis may in part be rectified with utilisation of the IDSA management guidelines which have improved mortality and length of stay at our facility.

REFERENCES