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

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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 [1,3]. In recent years *C. gattii* has gained in prominence due to a sustained outbreak in British Columbia, Canada [4].

Incidence, diagnosis and management of cryptococcal infection has altered over time. Improved antiretroviral therapy has decreased the incidence of infection in the human immunodeficiency virus (HIV) cohort [5]. Access to cheap and accurate serological testing and screening of at risk populations has been found to be cost-effective [6]. 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 [7].

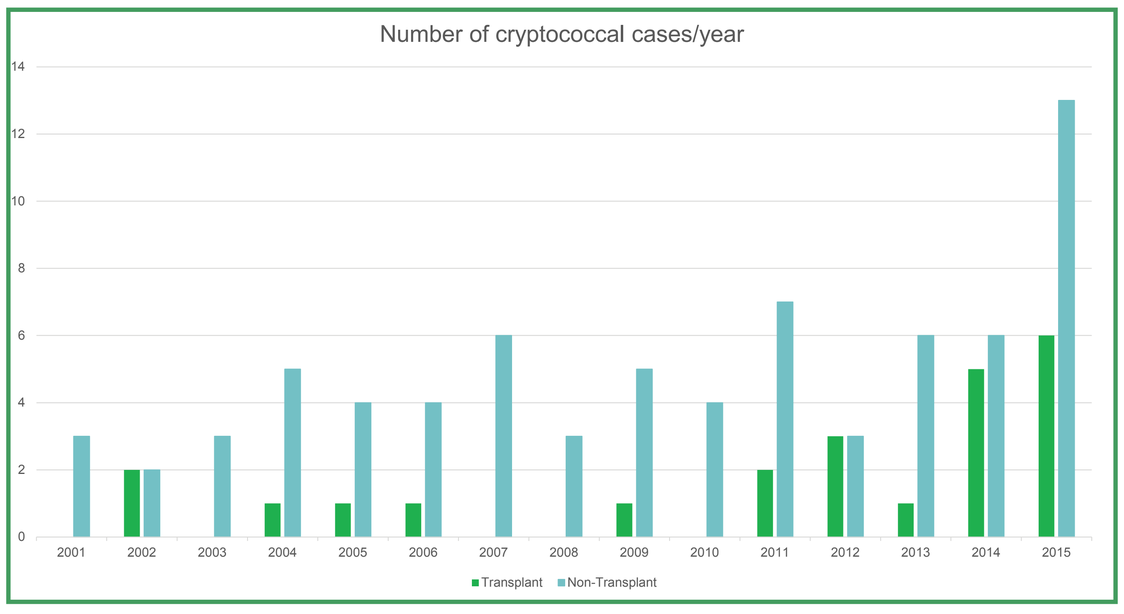
At our facility we have seen a trend towards increased incidence amongst our renal transplant cohort [8]. Analysis of this cohort revealed a much lower mortality rate compared with international data. Given this information we aimed to assess all cryptococcal infections managed at our facility from 2001-2015 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 cryptococcal antigen. Probable was defined as a positive serological cryptococcal titre. Statistical analysis was conducted using IBM SPSS Statistics Version 23.0 and Microsoft Excel.

RESULTS

Figure 1. Number of cases per year diagnosed and managed at our facility



102 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, Figure 1 [8]. Cryptococcal meningitis was the most common presentation of cryptococcosis with 58 of 98 patients (59%). With regards to species, 38/52 (73%) of identified isolates were *C. neoformans*, and 14/52 (27%) were C. gattii. Notably, 14/14 (100%) of *C. gattii* isolates were associated with meningitis, as compared to only 38/64 (59%) *C. neoformans* associated with meningitis (Fisher's exact test: p: 0.003). 13/14 (93%) were immunocompetent. Overall, *C. neoformans* is much more common with 82% total isolates compared with just 18% *C. gattii*, Table 1.

Figure 2. Time to diagnosis and missed diagnosis on multiple presentations

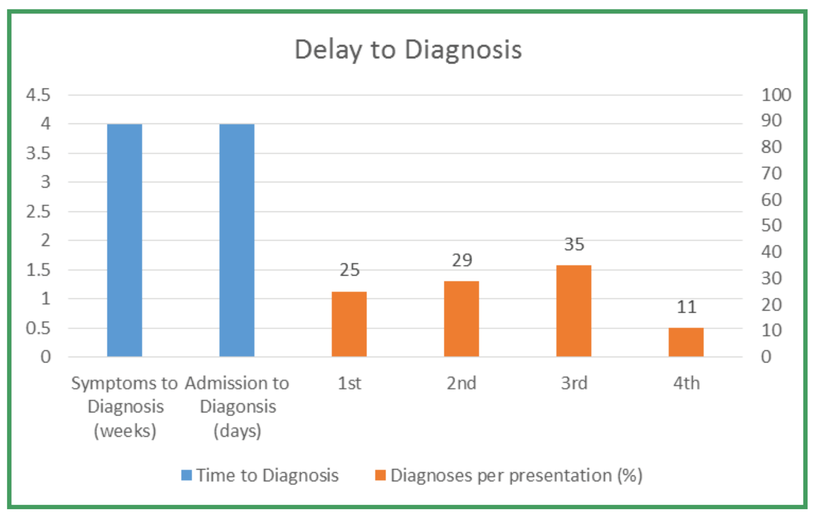


Table 1. Patient demographics & clinical variables comparing meningitis & non-meningitis cryptococcal infection

Variable	All Patients (n (%), IQR)	Meningitis (n (%), IQR)	Non-meningitis (n (%), IQR)	P-value
Total No. of cases	98	58	40	N/A
Age	53 (42-63)	54 (45-63.5)	52 (35.75-63)	0.19°
Gender (Male)	71 (72)	43 (74)	28 (70)	0.65`
Aboriginal & Torres strait Islander	3 (3.1)	3 (5.2)	0 (0)	0.26*
Cryptococcal species				
1. *C. neoformans*	64/78 (82)	38/52 (73)	26/26 (100)	0.003*
2. *C. gattii*	14/78 (18)	14/52 (27)	0	0.003*
Comorbidities				
1. HIV	9 (9.2)	6 (10.3)	3 (7.5)	0.73*
2. Diabetes mellitus	22 (22.4)	11 (19)	11(27.5)	0.32`
3. Liver Disease	10 (10.2)	6 (10)	4 (10)	1.00*
4. Lung Disease	13 (13.3)	3 (5.2)	10 (25)	0.004`
Presenting symptoms:				
1. Fever	30 (31)	22 (38)	8 (21)	0.07`
2. Headache	49 (50)	39 (67)	10 (25)	<0.001`
3. Cough	27 (27.5)	10 (17)	17 (43)	0.005`
4. Vomiting	26 (26.5)	21 (36)	5 (12.8)	0.01`
5. Altered consciousness	30 (31)	24 (41)	6 (15)	0.007`
6. Diaphoresis	5 (5)	1 (1.7)	4 (10)	0.15*
Clinical findings:				
1. Neck stiffness	14 (14.4)	11 (19)	3 (7.7)	0.12`
2. Photophobia	8 (8)	7 (12)	1 (2.5)	0.13*
Delay to diagnosis				
1. Time to diagnosis from admission (days)	4 (1 - 8)	4 (1 - 7)	5 (1 - 12.25)	0.32°
2. Time to diagnosis from symptoms (months)	4 (2 - 8)	4 (2 - 8)	5 (2.75 - 12)	0.14°
3. Number of presentations	2 (1.25-3)	2 (1.25-3)	3 (1.25-3.75)	0.17°
Biochemical:				
1. Lymphopenia	52 (53)	34 (59)	18 (45)	0.18`
2. Cryptococcal serum titre	128 (32–512)	512 (128-2048)	64 (8-192)	<0.001
3. CSF WBC	23 (1 - 110)	51 (14 - 160)	1 (1 - 1)	<0.001°
4. CSF Protein (mg/L)	625 (422.5 - 1200)	875 (535 - 1475)	375 (267.5 - 530)	<0.001°
5. CSF Glucose (mmol/L)	3.2 (2.2 - 4.3)	2.0 (1.1 – 2.9)	3.5 (2.9 – 4.6)	<0.001°
Lumbar puncture opening pressure (cmH_2O)	24 (15.5 – 34)	29 (19.5-34.5)	12 (9-15.5)	0.003°
Length of admission (days)	30 (12.75 – 53.5)	44 (26.5 - 72)	9.5 (1.75 - 22.75)	<0.001°

* Fisher Exact test
` Pearson Chi-square
°Mann-Whitney U test

RESULTS

The introduction of the 2010 IDSA guidelines has altered management and outcomes. Only 9/53 (17%) of all patients received standard amphotericin B post 2010 guideline compared with 14/44 (43.2%) prior. 44/53 (83%) received an alternative formulation ($\chi 2(1) = 8.037$, $p = 0.005$). Notably, 17/23 (74%) of transplant infections occurred post-2010. When stratifying for non-transplant patients, 9/36 (25%) patients post-guideline received standard amphotericin compared to 18/37 (48.6%) of non-transplant patients pre-guideline (Fisher's Exact test $p = 0.05$). Management of transplant patients was not statistically significantly altered post-guideline with 1/7 (14.3%) receiving standard Amphotericin B compared with 0/17 post-guideline (Fisher's Exact test $p = 0.29$). Renal treatment complications were not statistically altered with guideline introduction ($\chi 2$ (1) = 0.09, $p = 0.76$). There was a significant association between guideline implementation and mortality. Only 3/49 (6.1%) deaths due to cryptococcus occurred post 2010 guideline as compared with 7/41 (17.1%) (Fisher's Exact test, $p = 0.049$). Length of stay has also changed with a median of 23 (IQR: 7.5-44) days vs. 36.5 (IQR: 15.5-76.5) prior to guideline introduction ($U = 902$, $z = -1.9$, $p = 0.056$).

DISCUSSION

Cryptococcal infection is an important mycosis in both immunocompromised and immunocompetent individuals [1,9]. 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 15-31% [9,11]. We report a lower cryptococcal attributed mortality of 9.1% 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%.

Unfortunately a major concern remains the delay to diagnosis of infection Figure 2. Only 25% of patients with cryptococcosis are diagnosed on 1st presentation. Our cohort is similar to a smaller report demonstrating 78% of patients required ≥3 visits to a physician prior to diagnosis [12].

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.

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Poster produced by Patient Safety & Quality Unit, Princess Alexandra Hospital, 2017