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The Contribution of Growth Rate to the Pathogenicity of *Candida* spp.

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***Abstract*—**Fungal infections are becoming more common and the range of susceptible individuals has expanded. While *Candida albicans* remains the most common infective species, other *Candida* spp. are becoming increasingly significant. In a range of large-scale studies of candidaemia between 1999 and 2006, about 52% of 9717 cases involved *C. albicans*, about 30% involved either *C. glabrata* or *C. parapsilosis* and less than 15% involved *C. tropicalis*, *C. krusei* or *C. guilliermondii*. However, the probability of mortality within 30 days of infection with a particular species was at least 40% for *C. tropicalis*, *C. albicans*, *C. glabrata* and *C. krusei* and only 22% for *C. parapsilopsis*. Clinical isolates of *Candida* spp. grew at rates ranging from 1.65 h^{-1} to 4.9 h^{-1}. Three species (*C. krusei*, *C. albicans* and *C. glabrata*) had relatively high growth rates (μ_m > 4 h^{-1}), *C. tropicalis* and *C. dubliniensis* grew moderately quickly (≈ 3 h^{-1}) and *C. parapsilosis* and *C. guilliermondii* grew slowly (< 2 h^{-1}). Based on these data, the log of the odds of mortality within 30 days of diagnosis was linearly related to μ_m. From this the underlying probability of mortality is 0.13 (95% CI: 0.10-0.17) and it increases by about 0.09 ± 0.02 for each unit increase in μ_m. Given that the overall crude mortality is about 0.36, the growth of *Candida* spp. approximately doubles the rate, consistent with the results of larger case-matched studies of candidaemia.

Keywords*—Candida* spp., candidiasis, growth, pathogenicity.

I. Introduction

CANDIDIASIS is becoming more common for at least two reasons. First, species other than *Candida albicans* are more frequently encountered [3] and widespread resistance to current antifungal agents (such as fluconazole) has developed. Second, the range of susceptible individuals has expanded; for example those living with HIV-AIDS or recovering from major surgery, premature babies and the elderly are particularly at risk of infection [6]. It has been estimated that invasive candidiasis (IC) affects 72-228 per million population each year and the excess mortality rate attributable to IC has been estimated to be 10-49% [8].

Early antifungal treatment may reduce mortality, but if delayed the risk increases [11, 12], which has prompted the suggestion that prophylactic antifungal treatment may be justified in some circumstances. It is also likely that undiagnosed IC contributes to mortality, but identifying the infective species may delay treatment by 2 to 3 days [15-17] which also contributes to mortality.

At least two factors contribute to the mortality associated with *Candida* spp. infection. First, the more commonly a particular species is encountered, the more likely it is that infection with that species will be reported. Second, the greater the burden of the pathogen carried by an individual, the greater the risk of mortality [11]. Both of these factors relate to the growth of the pathogen.

Growth is characterised by a growth rate (μ_m), a lag time (λ) and a maximum amount (A_{max}), which are themselves interdependent [21]. From this we infer that the more rapidly a pathogen grows, the more likely it is that an infection will eventually prove fatal. This inference is supported by both *in vitro* and *in vivo Candida* spp. infections [24-26] and by experiments with pathogenic bacteria [29, 30]. However, in a study of 43 strains of *C. albicans*, MacCallum *et al.* [32] observed no correlation between growth rate in the cell culture medium RPMI and any measure of pathogenicity. *Candida* spp. differ considerably in pathogenicity. The results of several experimental studies [25, 33-38] can be summarised by specifying the relative pathogenicity of *Candida* spp. as *C. albicans* ≥ *C. tropicalis* > *C. glabrata* ≥ *C. krusei* > *C. parapsilosis* ≥ *C. guilliermondii*.

Here we develop a means of quantifying the contribution of growth rate to the pathogenicity of *Candida* spp. We use experimental measures of growth and relate them to large-scale epidemiological reports of *Candida* spp. infection and the mortality associated with such infection. Of course, our work represents a first attempt, and it would be necessary to relate growth rate to the outcome of infections with each of many strains of each of the *Candida* spp. to substantiate our approach.

II. Materials and Methods

Clinical isolates of *Candida* spp. were obtained from the culture collections of the Launceston General Hospital or the University of Tasmania and their identity was confirmed as previously described [39]. *Candida* spp. were grown in liquid YPD (2% (*w*/*v*) glucose, 1% (*w*/*v*) yeast extract, 2% (*w*/*v*) bacteriological peptone) in an orbital incubator (200 min^{-1}) at 37°C as described previously [40]. As the cultures were monitored repeatedly, exit cultures on MacConkey agar, blood agar and YPD agar plates were prepared to check for possible

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contamination. Growth was monitored by measuring the absorbance of the cell suspension at 600 nm (A_{600}) and the standard Gompertz model [41] was fitted to the growth data by nonlinear regression [42].

Epidemiological data were obtained from studies of candidaemia published between 1989 and 2006. For a study to be included we required that both the number of isolates and the mortality for several *Candida* spp. were reported.

III. Results

A. Growth of Candida spp.

The maximum growth rate (μ_m) of the seven *Candida* spp. ranged from 4.9 h^{-1} for *C. glabrata* to 1.5 h^{-1} for *C. parapsilopsis* (Fig 1). The the lag time (λ) ranged from 2.37 h for *C. glabrata* to 6.2 h for *C. parapsilosis* (Fig 1). The extent of the growth (A_{max}) was about 17 for *C. albicans* and *C. glabrata*, but only reached about 12 for *C. guilliermondii* and *C. tropicalis* (Fig 1). However, the early lag phase of the *C. guilliermondii* growth curve was not especially well modelled by the Gompertz function (Fig 1) and the lag time appeared to be under-estimated. Despite this, those species sometimes reported as less pathogenic (such as *C. guilliermondii* and *C. parapsilosis*) had and lower μ_m than those usually regarded as pathogens (*C. glabrata* and *C. albicans*, for example), as is apparent from Fig 2. As expected [21], the values of μ_m and λ varied inversely ($r = -0.954$, $p = 0.003$, excluding the data for *C. guilliermondii*). The data for *C. guilliermondii* did not lie on the same line as those of the other six species (Fig 2), perhaps because of the underestimation of λ. The values of A_{max} and μ_m were more weakly correlated ($r = 0.44$, $p = 0.32$).

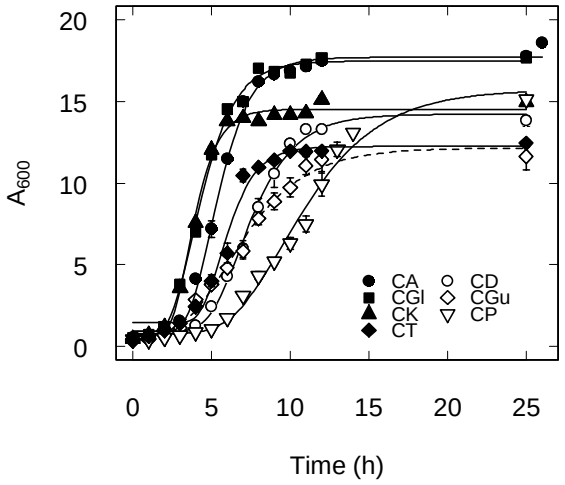

Fig. 1. Representative growth curves of seven *Candida* spp. The solid curves represent the fit of the Gompertz function to the data and the error bars represent ± SE for at least 3 replicates and where they are not visible they are hidden by the symbol. CA: *C. albicans*; CD: *C. dubliniensis*; CGl: *C. glabrata*; CGu: *C. guilliermondii*; CK: *C. krusei*; CP: *C. parapsilopsis*; CT: *C. tropicalis*.

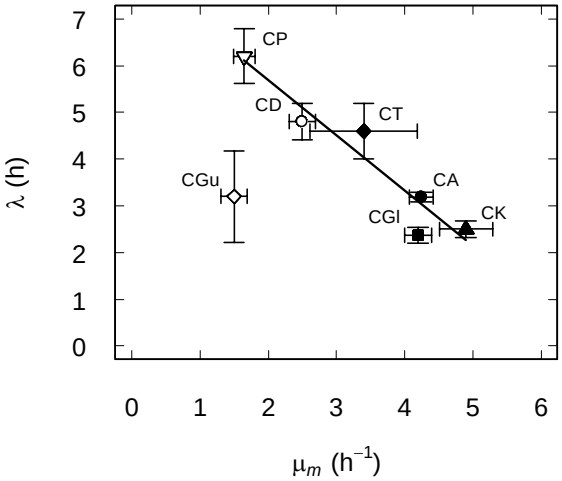

Fig. 2. Relationship between lag time (λ) and maximum growth rate (μ_m) for the seven *Candida* spp. Parameter estimates were obtained from the growth curves shown in Fig 1. Closed symbols indicate those species usually taken to be pathogenic and open symbols indicate those sometimes said to be non-pathogens. Error bars are ± 95% CI of the parameter estimate. The line is the least squares fit ($r = -0.954$, $p = 0.003$) to the data *without* considering the data for *C. guilliermondii* (CGu). The other species abbreviations are: CA – *C. albicans*; CD – *C. dubliniensis*; CGl – *C. glabrata*; CK – *C. krusei*; CP – *C. parapsilosis*; CT – *C. tropicalis*.

B. Epidemiology of Candida spp. infection

The pathogenicity of *Candida* spp. was assessed from seventeen large-scale epidemiological studies of candidaemia (referenced in Table I) involving a total of 9717 cases. As can be seen in Table I, 52% (range: 37.1–68.9%) of these isolates were *C. albicans* and the next two most significant species were *C. glabrata* (17%, range: 4.7–25%) and *C. parapsilopsis* (14%, range: 5.4–33.1%). However, the overall 30-day mortality rate among those infected with *C. albicans* or *C. glabrata* was about 40%, whereas only 22% of *C. parapsilopsis* infections resulted in mortality within 30 days (Table II). The number of cases involving *C. dubliniensis* or *C. guilliermondii* was very low (Table I) and so these data were combined with the 'other' species in the subsequent analysis (in Table II and Fig 3). These data were obtained in many countries, over more than a decade and no account was taken of underlying morbidity or antifungal resistance. Despite this, the data for each species are remarkably consistent, presumably reflecting the pathogenicity of each species.

IV. Analysis

The data in Table II represent the probability that an instance of candidaemia associated with an infection with species (i) of *Candida* is fatal (P(mortality| i)) and those in Table I are the probability that an instance of candidaemia is associated with species i (P(i| candidaemia)). The probability of mortality associated with candidaemia is

TABLE I
DISTRIBUTION OF THE *CANDIDA* SPP. ISOLATES REPORTED IN SEVENTEEN SURVEYS OF CANDIDAEMIA (1999-2006)

Study[a]	Number of isolates	Proportion of isolates (%)							
		C. albicans	*C. dubliniensis*	*C. glabrata*	*C. guilliermondii*	*C. krusei*	*C. parapsilosis*	*C. tropicalis*	other
Canada 1992-94 [1]	415	68.9	—	8.2	0.2	1.0	10.4	6.5	4.8
Europe 1997-99 [2]	2089	56.4	0.3	13.6	1.4	1.9	13.3	7.2	5.5
Europe/M. East 1992-94 [4]	248	48.8	—	9.3	—	8.9	11.3	11.3	10.5
Ireland 1999-03 [5]	66	50.0	1.5	18.2	—	—	21.2	6.1	3.0
Israel 1994 [7]	293	53.6	—	6.5	0.3	0.7	11.9	10.9	15.6
Italy 2000-03 [9]	94	40.4	—	12.8	2.1	3.2	22.3	16.0	3.2
Spain 1995-97 [10]	148	45.9	—	4.7	0.7	6.8	33.1	6.1	2.7
Spain 1995-99 [13]	124	50.8	—	16.1	—	—	25.8	6.5	9.7
Spain 1997-99 [14]	290	43.8	—	8.6	—	3.4	29.7	10.3	4.1
Spain 2002-03 [18]	345	51.0	—	8.0	—	4.0	23.0	10.0	4.0
Sweden 1998-99 [19]	186	67.0	—	15.7	0.5	1.0	7.3	2.1	3.6
Switzerland 1989-00 [20]	308	65.9	—	19.2	0.3	2.9	6.5	2.9	2.3
UK 1995-01 [22]	129	64.3	—	20.2	—	0.8	5.4	8.5	0.8
USA 1995-02 [23]	1890	53.8	—	18.8	—	2.4	11.4	11.1	2.5
USA 1995-97 [27]	1594	46.0	—	20.0	0.1	2.0	14.0	12.0	2.4
USA 1998-01 [28]	356	37.1	—	25.0	—	5.1	16.0	14.9	2.0
USA 1998-2000 [31]	1143	45.1	—	24.1	—	—	13.4	12.3	—
All[b]	9717	52.1	0.3	16.7	0.7	2.5	13.9	9.8	4.2

A dash indicates that no data were reported for this species.
[a]Each study is specified by geographical location, the range of years and the reference.
[b]The percentages are weighted by the number of isolates reported.

TABLE II
MORTALITY WITHIN 30 DAYS ASSOCIATED WITH *CANDIDA* SPP. INFECTION REPORTED IN SEVENTEEN SURVEYS OF CANDIDAEMIA (1999-2006)

Study[a]	Number of deaths	Proportion of deaths given infection with a particular species (%)					
		C. albicans	*C. glabrata*	*C. krusei*	*C. parapsilosis*	*C. tropicalis*	other[b]
Canada 1992-94 [1]	188	49.0	44.0	—	26.0	44.0	50.0
Europe 1997-99 [2]	667	38.5	45.0	—	25.9	41.4	—
Europe/Mid. East 1992-94 [4]	97	40.5	60.9	45.5	17.9	50.0	19.2
Ireland 1999-03 [5]	25	48.3	50.0	—	21.4	—	30.0
Israel 1994 [7]	59	30.4	43.8	—	—	33.9	21.1
Italy 2000-03 [9]	36	21.1	50.0	—	33.3	60.0	25.0
Spain 1995-97 [10]	64	43.5	40.0	80.0	31.1	25.0	—
Spain 1995-99 [13]	49	38.7	40.0	—	15.6	—	—
Spain 1997-99 [14]	114	47.2	36.0	60.0	31.4	23.3	—
Spain 2002-03 [18]	150	47.0	50.0	46.0	28.0	59.0	—
Sweden 1998-99 [19]	57	35.0	38.0	—	0.0	—	7.0
Switzerland 1989-00 [20]	133	46.3	—	—	—	—	37.0
UK 1995-01 [22]	45	38.6	30.8	100.0	14.3	27.3	0.0
USA 1995-02 [23]	741	36.6	50.1	58.7	27.9	43.1	—
USA 1995-97 [27]	558	38.5	36.7	34.6	18.7	42.5	—
USA 1998-01 [28]	92	31.0	27.0	0.0	14.0	28.0	0.0
USA 1998-2000 [31]	409	40.0	36.0	—	18.0	40.0	—
All[c]	3484	39.4	41.4	48.7	21.6	38.4	26.6

[a]Each study is specified by geographical location, the range of years and the reference.
[b]The 'other' species also includes *C. dubliniensis* and *C. guilliermondii*, which were under-represented in Table I.
[c] The percentages are weighted by the number of deaths reported.

$$P(\text{mortality}\,|\,\text{candidaemia}) = \sum_i P(i\,|\,\text{candidaemia}) \times P(\text{mortality}|\,i), \quad (1)$$

where the summation is taken over all the *Candida* spp. and the individual terms on the right hand side are the contributions of each species to the mortality associated with candidaemia.

The log of the odds of mortality given infection with species i increased linearly with growth rate (Fig 3). The slope and intercept of this relationship can be related to the contribution of growth rate to the mortality associated with candidaemia and the probability mortality associated with the underlying condition (see the Appendix). From Fig 3, a unit increase in the growth rate of *Candida* sp. is associated with

an increase in the probability of mortality of 0.09 ± 0.02 and the underlying probability of mortality is 0.13 (95% confidence interval: 0.10, 0.17).

The log odds of species *i* infection in candidaemia is only weakly related to μ_m, but is more strongly related to $(A_{max}\lambda\mu_m)^{1/2}$ (Fig 4), which is the geometric mean of two measures of overall growth: A_{max} and $\lambda\mu_m$ [21]. From Fig 4, a unit increase in the growth *Candida* sp. is associated with an increase in the probability of infection of 0.2 ± 0.1 and the underlying probability of infection in the absence of growth is $<2.2 \times 10^{-6}$ (which is the upper limit of the 95% confidence interval estimated for this value). It is apparent from Fig 3 that *C. krusei* grows rapidly and is associated with a high *P*(mortality| *i*), however it is involved in only about 2.5% of infections (Table II, Fig 4) and so *C. krusei* infections are less common than might be expected given its growth is greater than *C. albicans*, *C. glabrata* and *C. tropicalis* (Fig 4).

The contribution of a *Candida* sp. to the log odds of mortality given candidaemia is also related to $(A_{max}\lambda\mu_m)^{1/2}$ (Fig 5). A unit increase in the growth of *Candida* spp. is associated with an increase in the probability of mortality of 0.2 ± 0.1 and the underlying probability of mortality is <0.01 (Fig 5). From (1) and the estimates shown in Fig 5, the overall *P*(mortality| candidaemia) can be estimated to be 0.37 ± 0.19 (± 95% confidence interval), to which *C. albicans* contributes about 0.2.

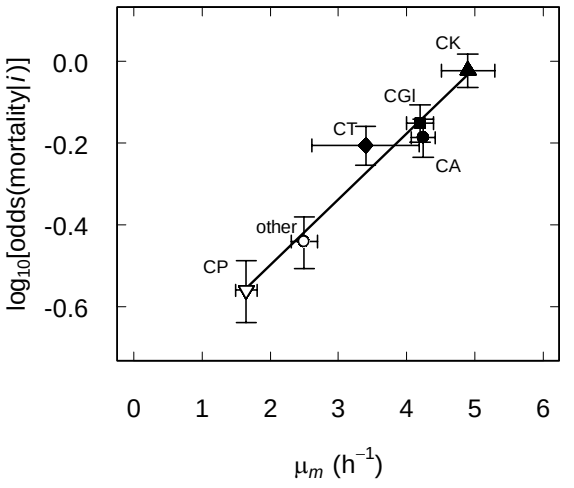

Fig. 3. Log odds of mortality within 30 days given infection with a particular *Candida* sp. (Table II) as a function of growth rate (μ_m, Fig 1). The solid line is the least squares fit to the data (r = 0.981, p < 0.001) and has a slope and intercept of 0.16 ± 0.03 h and -0.8 ± 0.1 (± 95% confidence intervals), respectively. Error bars are ± 95% confidence interval. Closed symbols indicate those species usually taken to be pathogenic and 'other' includes *C. guilliermondii* and *C. dubliniensis* as described in the text. CA: *C. albicans*; CD: *C. dubliniensis*; CGl: *C. glabrata*; CGu: *C. guilliermondii*; CK: *C. krusei*; CP: *C. parapsilopsis*; CT: *C. tropicalis*.

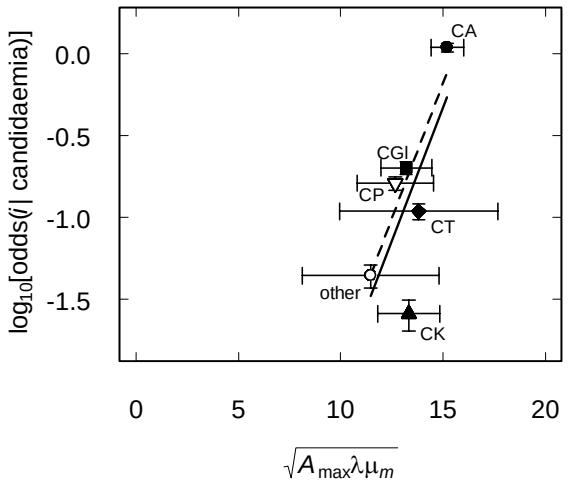

Fig. 4. Log odds of infection with with a particular *Candida* sp. (Table I) as a function of growth. The dashed line is the least squares fit to the data (r = 0.895, p = 0.04), neglecting that for *C. krusei*, and the solid line is the fit (r = 0.706, p = 0.12) including the *C. krusei* data; for either fit the slope and intercept are 0.3 ± 0.2 h and -5 ± 1 (± SE), respectively. Error bars are ± 95% confidence interval. Closed symbols indicate those species usually taken to be pathogenic and 'other' includes *C. guilliermondii* and *C. dubliniensis* as described in the text. CA: *C. albicans*; CD: *C. dubliniensis*; CGl: *C. glabrata*; CGu: *C. guilliermondii*; CK: *C. krusei*; CP: *C. parapsilopsis*; CT: *C. tropicalis*.

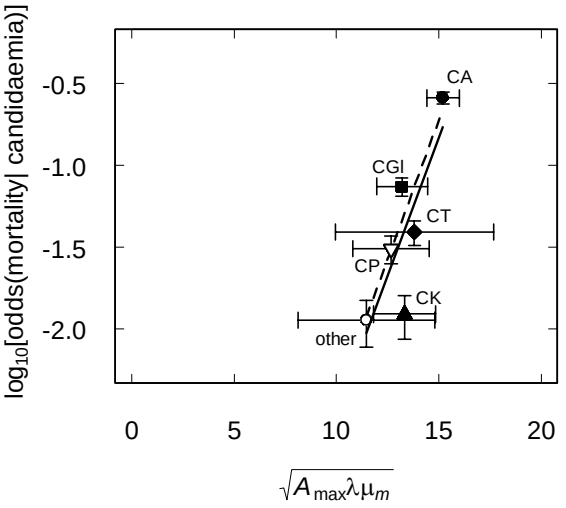

Fig. 5. Contribution of each *Candida* sp. to the log odds of mortality within 30 days given candidaemia (1) as a function of growth. The dashed line is the least squares fit to the data (r = 0.935, p = 0.02), neglecting that for *C. krusei*, and the solid line is the fit (r = 0.814, p = 0.048) including the *C. krusei* data; for either fit the slope and intercept are 0.3 ± 0.2 h and -6 ± 3 (± 95% confidence interval), respectively. Error bars are ± 95% confidence interval. Closed symbols indicate those species usually taken to be pathogenic and 'other' includes *C. guilliermondii* and *C. dubliniensis* as described in the text. CA: *C. albicans*; CD: *C. dubliniensis*; CGl: *C. glabrata*; CGu: *C. guilliermondii*; CK: *C. krusei*; CP: *C. parapsilopsis*; CT: *C. tropicalis*.

V. Discussion

The pathogenicity of *Candida* spp. depends on the rate of infection and on the virulence of the infecting species. We have shown that the log odds of mortality rises linearly with μ_m (Fig 3) and that the log odds of infection increases with the total growth (measured as the geometric mean of A_{max} and $\lambda\mu_m$, Fig 4). These observations are consistent with experimental reports [24-26]. However, MacCallum *et al.* [32] reported data for 43 strains of *C. albicans* from four different clades, that showed that there was no significant difference in the μ_m in RPMI of strains of differing pathogenicity or from different clades. It should be noted that the growth rates they reported were less than 10% (0.13-0.3 h^{-1} for cultures in RPMI) of that reported here for *C. albicans* (Figs 1 and 2).

Butler *et al*. [43] reported that *C. glabrata* lacked, and *C. guilliermondii* had fewer copies of, several of the genes that appear to be enriched in the genomes of other pathogenic *Candida* spp. Since *C. glabrata* is more likely to be isolated (Table I) and grows faster (Fig 1) than *C. guilliermondii*, the absence of these genes may not be consistent with a significant role for them as determinants of pathogenicity if mortality is associated with growth (Fig 5) and growth rate (Fig 3). Unfortunately, no complete genome sequence is currently available for *C. krusei*, which might provide further insight into the genetic basis for the disportionately low rate of infection reported for this species (Table I and Fig 4).

Highly pathogenic *Candida* spp. are more commonly isolated from individuals with IC (Table I) and are more frequently associated with mortality than others species (Table II). Based on data from large-scale epidemiological studies (such as [2, 23, 27]), a relationship between the probability of mortality and the growth rate of *Candida* spp. can be established (Fig 3). One interpretation of these data is that the underlying probability of mortality is about 0.13 (95% confidence interval: 0.10-0.17), and that *Candida* infection increases the probability by 0.09 ± 0.02 for every unit increase in μ_m (Fig 3). As the most commonly isolated *Candida* spp. have growth rates of at least 2 h^{-1} (Fig 1), the infection at least doubles the underlying *P*(mortality| *i*). The probability of infection is also related to the growth of *Candida* spp. (Fig 4), but the amount, rather than the growth rate, of the pathogen is a more significant determinant of infection. Based on Fig 3, the relative pathogenicity of *Candida* spp. given an infection can be summarised as *C. krusei* > *C. glabrata* = *C. albicans* ≥ *C. tropicalis* > *C. parapsilosis*, but the relative infectivity is *C. albicans* > *C. glabrata* = *C. parapsilosis* > *C. tropicalis* > *C. krusei* (Fig 4). The overall pathogenicity of the *Candida* spp. is a combination of these two sequences.

Naturally, our analysis has at least two important limitations. First, the growth of the clinical isolates reported here may not be representative of the many strains of each *Candida* sp. (there are hundreds of strains of *C. albicans* alone [44]). Second, we arbitrarily chose to grow the *Candida* spp. in conditions that are quite different from those *in vivo*, although this can be justified in part by the limited μ_m reported when grown in RPMI [32]. Despite these limitations, the relationship between growth rate and P(mortality| *i*) (Fig 3) is highly significant (p = 0.003) prompting two tentitive conclusions: First, the emergence of a faster growing *Candida* sp. would pose a significant threat. An example of this is the relatively recent emergence of *C. krusei* [8], which has a growth rate only 15% greater than that of *C. albicans* (Fig 1) and is associated with a 10% greater P(mortality) (Table II). The low probability of mortality associated with *C. krusei* candidaemia (Fig 5 and Table II) is due to the low probability of infection with this species (Fig 4 and Table I). Of course, *C. krusei* has the potential to be a signficant pathogen if more infectious strains were to develop. Second, this analysis confirms the suggestion that the excess mortality rate attributable to IC is 10-49% [8], but that the range in this estimate is likely to be related, at least in part, to growth rate.

VI. Conclusion

The pathogenicity of *Candida* spp. is directly related to the growth rate of the infecting species. Infection is more closely related to the extent of growth (measured as $(A_{max}\lambda\mu_m)^{½}$) of the infecting species. The probability of mortality given candidaemia is also related to the extent of growth. We have estimated that an increase in growth rate of 1 h^{-1} is associated with an increase in the probability of mortality of 0.09 ± 0.02 over an underlying probability of mortality of 0.13 (95% confidence interval: 0.10, 0.17).

Appendix

Where the logarithm of the odds [45] is linearly related to a variable x (such as $x = \mu_m$ in Fig 3 and $x = (A_{max}\lambda\mu_m)^{½}$ in Figs 4 and 5), then

$$\log_{10}\left(\frac{P(\cdot)}{1-P(\cdot)}\right) = \alpha x + \beta\,, \tag{2}$$

where $P(\cdot)$ is the probability specified by the argument. This can be rearranged to yield

$$P(\cdot) = \left(1+10^{-\alpha x-\beta}\right)^{-1} \tag{3}$$

from which the underlying $P(\cdot)$, corresponding to a situation in which $x = 0$, is given by

$$P(\cdot \mid x=0) = \left(1+10^{-\beta}\right)^{-1} \tag{4}$$

and the contribution to mortality associated with a unit change in x is related to the maximum slope which occurs at $x = -\beta/\alpha$

$$\left.\frac{dP(\cdot)}{dx}\right|_{x=-\beta/\alpha} = \frac{\ln(10)}{4}\alpha\,. \tag{5}$$

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