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Title:
Risk factors for candidaemia: A prospective multi-centre case-control study

Date:
2021-03-01

Citation:
Keighley, C. L., Pope, A., Marriott, D. J. E., Chapman, B., Bak, N., Daveson, K., Hajkowicz, K., Halliday, C., Kennedy, K., Kidd, S., Sorrell, T. C., Underwood, N., van Hal, S., Slavin, M. A. & Chen, S. C. A. (2021). Risk factors for candidaemia: A prospective multi-centre case-control study. Mycoses, 64 (3), pp.257-263. https://doi.org/10.1111/myc.13211.

Persistent Link:
https://hdl.handle.net/11343/276730

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Article type : Original Article

Original Article

Title

Risk factors for candidaemia: a prospective multi-centre case-control study

Running Title

Risk factors for candidaemia: a case-control study

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Abstract

Objectives

Candidaemia carries a mortality of up to 40% and may be related to increasing complexity of medical care. Here, we determined risk factors for the development of candidaemia.

Methods

We conducted a prospective, multi-centre, case-control study over 12 months. Cases were aged ≥18 years with at least one blood culture positive for *Candida* spp. Each case was

matched with two controls, by age within 10 years, admission within six months, admitting unit, and admission duration at least as long as the time between admission and onset of candidaemia.

Results

118 incident cases and 236 matched controls were compared. By multivariate analysis, risk factors for candidaemia included neutropenia, solid organ transplant, significant liver, respiratory or cardiovascular disease, recent gastrointestinal, biliary or urological surgery, central venous access device, intravenous drug use, urinary catheter, and carbapenem receipt.

Conclusions

Risk factors for candidaemia derive from the infection source, carbapenem use, host immune function and organ-based comorbidities. Preventive strategies should target iatrogenic disruption of mucocutaneous barriers and intravenous drug use.

Introduction

Candidaemia or bloodstream infection due to *Candida* spp. carries a high mortality, up to 40%, with attendant excess hospital stay and costs [1-6]. It is now, worldwide, amongst the most common hospital-acquired infections [1-3, 5, 7]. An increase in the frequency or incidence of candidaemia has been reported in a number of studies [3, 8] although the reasons for this are poorly understood.

A landmark case-control study examining risk factors for patients with candidaemia in hospitals identified prior haemodialysis, placement of a Hickman catheter, use of antibiotics and isolation of any *Candida* spp. (colonisation) from body sites other than blood as significantly associated with development of candidaemia [9]. Other studies in different patient groups have since identified similar risks [10-14]. Additional risks including neutropenia, indwelling urinary catheter (IDC) use, total parenteral nutrition (TPN), red cell transfusion, age >65 years, recent surgery, gastrointestinal (GI) cancer and solid organ malignancy with metastases were identified in some, but not, all studies [10-14]. Changes over recent years associated with altered patterns of risk and species distribution include an

aging population, multiple and complex co-morbidities, increasing use of fluconazole and other antifungal agents and use of broad-spectrum antibacterial agents [4, 15-19].

We had previously identified an increase of candidaemia from a population-based incidence of 1.81/10^5/year to 2.41/10^5/year and 0.21/1000 separations/year to 0.51/1000 separations/year across Australia over 10 years from 2004 to 2014 [3]. This was accompanied by an almost 2-fold rise in *Candida glabrata* candidaemia. We also observed that the majority of cases (55%) were attributable to a GI or urological source, rather than a central venous access device (CVAD) or intravascular source, and that source of candidaemia, a longer duration of antibiotic therapy, ICU, absence of prior surgery and host factors including age, severe organ dysfunction and haematological malignancy correlated with mortality [16]. Here we extend these observations via a prospective multi-centre study of contemporary risk factors for candidaemia in patients presenting to major Australian hospitals.

Methods

This observational case-control study was performed at eight tertiary referral hospitals beginning in March 2014. Patients were identified through active laboratory surveillance over a period of 12 months. Periodic audits ensured complete case capture. Human research ethics and study oversight was approved through the Western Sydney Local Health District (HREC Ref: AU RED LNR14/WMEAD/112).

All consecutively presenting adults aged ≥18 years with at least one blood culture positive for *Candida* spp. were enrolled as cases. Episodes of recurrent candidaemia were excluded. Control patients (controls) for each case were matched for: (i) age within 10 years, (ii) admission date within six months, (iii) admitting unit (medicine, surgery or other) and (iv) a duration of admission at least as long as the at-risk period for cases (time between admission and onset of candidaemia); similar to criteria used previously [9, 11, 20]. The records of control patients were examined to ensure that they did not develop candidaemia during the admission of interest.

Data were collected on standardised case report forms at baseline (day 0), day 7 and day 30 after the initial positive blood culture (for cases) or post-admission (for controls). Data included patient demographic factors, ward of admission (medical, surgical or intensive care unit [ICU]), patient underlying conditions as recorded by the treating clinician (e.g. malignancy, organ or stem cell transplantation, connective tissue disorders, diabetes mellitus; see Table 1), predisposing factors (e.g. major surgery, central venous access device (CVAD) placement, indwelling catheter (IDC) present for at least 24 hours, haemodialysis, receipt of hyperalimentation (total parenteral nutrition, TPN), corticosteroids or other immunosuppressive therapies, major trauma and receipt of antibiotic agents [i.e. any antibiotic agent prescribed for >2 days before onset of candidaemia or in the study period for controls]) in the preceding 30 days prior to candidaemia (for cases) or prior to discharge, sepsis as previously defined [21], transfer from hospital or in-hospital death (for controls), and clinical outcomes at 30 days. Candidaemia was divided into inpatient and healthcare-associated (IHCA), outpatient healthcare associated (OHCA) and community-acquired (CA) as previous [16]. For patients in ICU, the Acute Physiology, Age, Chronic Health Evaluation II (APACHE II score), ventilation requirements and length of stay were also recorded.

Blood was cultured in automated systems, using BACTEC (Becton Dickinson, Sparks, MD, USA) or BacT/Alert 3D (bioMérieux, Marcy l'Etoile, France) platforms. *Candida* was speciated using matrix-assisted laser desorption/ionization- time of flight mass spectroscopy (MALDI-TOF MS) (Bruker Biotyper database v 3.1; Bruker Daltoniks, Germany) and/or by internal transcribed space (ITS) gene sequencing [22] at one of two mycology reference laboratories (Westmead Hospital, Sydney, New South Wales or SA Pathology, Adelaide, South Australia). Although the taxonomy of *Candida* spp. is changing, inclusion and nomenclature was retained in accordance with reference guidelines [23, 24]. Antifungal susceptibility testing was performed using the Sensititre (Thermo Fisher, Scientific, Cleveland, OH) method and interpretive MIC breakpoints or assignment of isolates as wild type (WT) or non-wild type (NWT) was made according to reference guidelines [23, 24].

Data were analyzed with R version 2.15.13 [25]. Antibiotics were grouped into classes in accordance with reference guidelines [26]. For univariate analysis of associations with candidaemia, continuous variables were compared with the student *t* test or non-

parametric equivalents as appropriate, and categorical variables, with the two-tailed chi-squared test with Yates continuity correction. A p value <0.05 was considered significant. Odds ratios (OR) and 95% confidence intervals for univariate analysis and/or credible intervals for multivariate analysis were calculated. A Bonferroni correction was performed. Bayesian conditional logistic regression analysis was performed using the rstanarm library with weakly informative priors for regularization, as this stabilized the estimate [27, 28].

Results

There were 132 unique incident cases of candidaemia. Data were available for 118 (89%) episodes (118 patients) and these were matched 1:2 to 236 controls. Overall, the median patient age in years and interquartile range (IQR) for cases was 62 years (52-75) and for controls was 65 (52-75). Candidaemia was identified a median of 11 days from day of admission (IQR 4-20) for 98 cases (83% of 118) that were IHCA, a median of 1 day (IQR 0-3) for 13 cases (11% of 118) that were OHCA and 0 days (IQR 0-2) days for 7 cases (6% of 118) that were CA. The median duration of admission of control patients was 18 days (IQR 6-36). Overall, there were 201 (57%) patients admitted to a medical unit and 153 (43%) to a surgical unit. An intravascular source was attributable for 39 (33%) of candidaemia cases. Mortality at 30 days was 31% (36/118) for cases, and 16% (38/236) for controls (OR2.3, 95%CI 1.4-3.9, p = 0.002).

Candida albicans caused 47 (40%) episodes of candidaemia, followed by *C. glabrata* complex (n=35, 30%), *C. parapsilosis* complex (12, 10%), *C. tropicalis* (10, 9%) and *C. krusei* (3, 2.5%). There was one case each due to *C. lusitaniae* and *C. lipolytica*. Six (5%) cases were multi-fungal - *C. albicans* and *C. glabrata sensu stricto* in 2 instances and one instance each of *C. albicans* and *C. bracariensis*, *C. albicans* and *C. nivariensis*, *C. albicans* and *C. parapsilosis sensu stricto*, and *C. albicans, C. parapsilosis sensu stricto* and *C. tropicalis*. There were no isolates of *C. auris* as confirmed by reference laboratories.

Comparison of co-morbidities, predisposing factors and other characteristics of candidaemia cases with controls are summarised in Table 1. There were 48 cases (41%) and 39 controls (17%) admitted to ICU (p<0.001) and the median APACHE II score for cases (18, IQR 15-26),

was higher than that of controls (17, [IQR 11-22]; p=0.05). Significantly more cases met criteria for sepsis than controls (84 (71%) compared with 35 (15%), p<0.05). The median length of stay was 8 (IQR 3-15) days for cases and 6 (IQR 2-16) days for controls; these differences were not statistically significant.

Multiple underlying patient co-morbidities were associated with candidaemia; 90 (76%) cases had one or more co-morbidity compared with 131 (56%) controls (p<0.001). By univariate analysis, liver disease (12, 10% vs 5, 2%, OR 5.2, 95%CI 1.7-19.3, p<0.001), cardiovascular disease (23, 20% vs 24, 10%, OR 2.1, 95%CI 1.1-4.2, p=0.02) and renal disease (15, 13% vs 12, 5%, OR 2.7, 95%CI 1.1-6.6, p=0.02), but not solid organ transplantation, solid organ malignancy or diabetes mellitus, were significantly more common amongst cases (Table 1).

A total of 113 (96%) cases had one or more predisposing factors compared with 162 (69%) control patients (p<0.05) (Table 1). The strongest associations with candidaemia were hyperalimentation (21, 18% vs 11, 5%, OR 4.4, 95%CI 1.9-10.5, p<0.001), GI surgery (29, 25% vs 13, 6%, OR 5.6, 95%CI 2.7-12.2, p<0.001, an *in situ* CVAD (87, 74% vs 93, 39%, OR 4.3, 95%CI 2.6-7.3), urological instrumentation (16, 14% vs 7, 3%, OR 5.1, 95%CI 1.9-15.2, p<0.001), a urinary catheter (74, 63% vs 99, 42%, OR 2.3, 95%CI 1.4-3.8, p<0.001) and neutropenia (16, 14% vs 15, 6%, OR 2.3, 95%CI 1.0-5.2, p=0.03) (Table 1).

Amongst cases with a CVAD, this was *in situ* for a median of 7 (IQR 3-16) days compared with a median of 11 (IQR 6-21) days for controls. TPN receipt occurred for a median of 13 (IQR 5-20) days and 10 (IQR 6-14) days for cases and controls, respectively. Duration of an IDC/ drainage device was also similar for cases (median of 6 (IQR 3-18) days and controls (for a median of 6 (IQR 4-13) days). There was no association between duration of the above three clinical variables and development of candidaemia.

Antibiotic use was more common in cases (105, 89%) compared with controls (179, 76%) (p=0.003). By univariate analysis carbapenem receipt was strongly associated with development of candidaemia (32, 27% vs 23, 10%; p <0.001, OR 3.4, 95%CI 1.8-6.5) as was receipt of extended spectrum beta-lactams, first or second generation cephalosporins and

glycopeptides (Table 1). Administration of prophylactic antifungal therapy was more common in cases (16, 14% in cases vs 15, 6% in control patients; p=0.03)

On multivariate analysis (Table 2 and Figure 1), the strongest associations were GI surgery (p<0.001; OR 39.8, 95%CI 9.4-243), underlying liver disease (p<0.001; OR 37.0 95%CI 6.1-301) and an *in situ* CVAD (p<0.001; OR 6.0, 95%CI 2.4-16.9). Haematologic malignancy and SCT were not significantly associated even though they were considered in the model.

Discussion

This multi-centre matched case-control study demonstrates that both host, and patient-modifiable factors are associated with candidaemia. Compared with earlier studies [9-14], our findings highlight the importance of prior GI or urologic surgery as well as complex co-morbidities. The association of candidaemia with severe organ dysfunction (definitions in Table 1) and with carbapenem use in this study add strength to recent data describing the changing epidemiology [20, 29]. Amongst notable predisposing risks for candidaemia that may be modifiable (for example by removal of device) or mitigated (using prophylactic antifungals or addressing other risk factors), were recent GI, hepatobiliary or urological surgery, the presence of a CVAD, or IDC and use of carbapenems. Unlike previous studies, the data herein included all patients with *Candida* bloodstream infection, rather than focusing on a specific subgroup [11-13].

Disruption of body systems typically colonised by *Candida* spp. has consistently been associated with candidaemia. The GI system, particularly the upper GI tract, is a recognised habitat of *Candida* spp. [30, 31]. Upper GI and liver disease, surgery and malignancy have previously been associated with candidaemia, as in our study, consistent with its origin from a GI source [12, 14, 32, 33].

Breaches in cutaneous barriers such as use of CVAD or a history of IVDU potentiate entry of *Candida* spp. into the blood stream [31, 34]. The use of CVADs is a well-documented risk factor for candidaemia [10, 14, 35, 36]. National efforts to reduce central line infections in Australia through infection prevention programs targeting hand hygiene and use of central line insertion bundles are likely to have led to greater attention to changing lines and a short

duration of CVC being left *in situ* in our data. There was a drop in proportion of candidaemia attributable to an intravascular source compared with previous data [16, 21, 37, 38]. With the caveat of this context, we observed no association between duration of CVAD *in situ* and increased risk of candidaemia.

The easily overlooked presence of a urinary catheter may be enough to disturb the genitourinary flora [13, 14]. This was the only risk factor in one of our patients. Candidaemia after ureteric instrumentation may in part be related to the formation of a biofilm on stents [39-41]. There are also reports in association with new agents for treatment of diabetes that cause marked glycosuria [42]. The urinary tract is being recognised as an increasingly important source of candidaemia and prompt removal of IDC when possible is key.

Antibiotics alter the microbiome, and a reduction in lactobacilli lead to reduced H_2O_2, bacteriocin-like compounds and IL-22 induced by tryptophan metabolites that otherwise inhibit fungal adhesion, growth and colonisation [34]. Receipt of antibiotics, including glycopeptides, aminoglycosides, metronidazole and beta-lactams has been associated with candidaemia [10, 13, 14, 35]. On multivariate analysis, only receipt of carbapenems was associated with candidaemia in the present study, adding weight to antimicrobial stewardship efforts and restriction of the use of this broad-spectrum antibiotic.

In addition to disruptions in the microbiome that allow a portal of entry for *Candida* spp., immune dysfunction plays an important role. Neutrophils are the most potent killers of *Candida,* the only immune cells able to inhibit the germination of *Candida* yeasts into hyphae, and neutropenia has previously been associated with candidaemia [14, 34]. Haematologic malignancy was non-significantly more common in cases than controls. Severe liver, cardiovascular or respiratory disease may also impact on immune dysfunction and this is yet to be clearly elucidated.

Whilst the use of antifungal prophylaxis is an attractive preventive strategy, fluconazole risks selecting non-*albicans Candida* spp. [43, 44]. Close attention to early removal of CVADs and urinary catheters when feasible will reduce potential sources of candidaemia, and early cessation of antibiotics is likely to assist. As we learn more about microbiome disruption

such as that occurring with GI surgery or broad-spectrum antibiotic therapy including carbapenems, interventions to restore healthy GI flora may be developed [45]. Likewise, for patients with urological interventions, knowledge of biofilm infection in stents and other indwelling urological devices may lead to new approaches to prevent candidaemia. In the future it may be possible to modify the microbiome as a preventative strategy.

Strengths of this study include its prospective multi-centre design, and builds on previous data focusing on contemporary microbiology and epidemiology [3, 16]. Limitations include the number of cases of candidaemia available to include, the small number with some of the predisposing factors, and enumerating patients with diabetes without characterising blood glucose control, which may have an impact on development of candidaemia though not evident in our data. The site of CVAD placement, reasons for commencement of antibiotic or antifungal therapy and data regarding bacteraemia and urine culture results were not collected. Despite the multivariate analysis which controlled for alternate factors such as ICU admission, it is possible that patients with unexplained sepsis due to candidaemia were more likely to receive carbapenems. This finding warrants further research in order to confirm the association.

In conclusion, our analysis demonstrates that development of candidaemia is associated with multiple factors relating to the source, chronic co-morbidities or to host immune function. Targeting mucocutaneous barrier disruption through new approaches involving prophylaxis, the microbiome, or biofilms offer potential strategies for reducing the incidence of candidaemia.

Conflicts of Interest Statement

Conflicts of Interest and Source of Funding: Sharon Chen, Monica Slavin and Debbie Marriott are on the Antifungal Advisory Boards of Gilead Sciences Inc., MSD Australia and Pfizer Australia. Sarah Kidd is on the Antifungal Advisory Board of Pfizer Australia, MSD Australia and Mayne Pharma. Tania Sorrell, Debbie Marriott, Monica Slavin, Sharon Chen

and Sarah Kidd have received untied grants from Gilead Sciences Inc., MSD Australia and Pfizer Australia. All other authors: none to declare.

This work was supported in part by an unrestricted grant from MSD Australia.

Acknowledgements

The authors would like to thank Catherine Ferguson, Royal Adelaide Hospital, Adelaide, SA and Kyle McDonald, St Vincent's Hospital, Sydney, NSW for their assistance with data collection.

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Table 1: Clinical characteristics of patients in cases and controls and univariate analysis

	Case (total n=118)	Controls (total n=236)	Odds ratio, 95% confidence interval	P value
Age >65, years	50 (42)	113 (48)	0.8 (0.5-1.3)	0.35
Male gender	66 (56)	140 (59)	0.9 (0.5-1.4)	0.57
Female gender	52 (44)	96 (41)	1.1 (0.7-1.8)	057
Admitting service				
Medical	67 (57)	134 (57)	1.0 (0.6-1.6)	1.00
Surgical	51 (43)	102 (43)	1.0 (0.6-1.6)	1.00
ICU admission	48 (41)	40 (17)	3.4 (2.0-5.7)	<0.001
Co-morbidities				
Haematologic malignancy	16 (14)	24 (10)	1.4 (0.7-2.9)	0.37
Stem cell transplantation (allogeneic or autologous)	0 (0)	4 (2)	0.0 (0-3)	0.31
Solid organ malignancy	25 (21)	33 (14)	1.7 (0.9-3.1)	0.09
Solid organ transplantation	5 (4)	4 (2)	2.6 (0.5-13.2)	0.17
HIV/AIDS	3 (3)	4 (2)	1.5 (0.2-9.1)	0.69
Diabetes mellitus	28 (24)	60 (25)	0.9 (0.5-1.6)	0.79
Renal disease	15 (13)	12 (5)	2.7 (1.1-6.6)	0.02
Liver disease	12 (10)	5 (2)	5.2 (1.7-19.3)	<0.001
Cardiovascular disease	23 (20)	24 (10)	2.1 (1.1-4.2)	0.02
Respiratory disease	8 (7)	11 (5)	1.5 (0.6-3.8)	0.46
Predisposing factors				
Gastrointestinal surgery	29 (25)	13 (6)	5.6 (2.7-12.2)	<0.001
Hepatobiliary surgery	7 (6)	4 (2)	3.6 (0.9-17.3)	0.05
Other surgery	22 (19)	33 (14)	1.4 (0.8-2.5)	0.28
Urological instrumentation	16 (14)	7 (3)	5.1 (1.9 – 15.2)	<0.001
Urinary catheter	74 (63)	99 (42)	2.3 (1.4-3.8)	<0.001
CVAD	87 (74)	93 (39)	4.3 (2.6-7.3)	<0.001
TPN	21 (18)	11 (5)	4.4 (1.9 – 10.5)	<0.001
Corticosteroids	20 (17)	23 (10)	1.9 (0.9-3.8)	0.06

Neutropenia	16 (14)	15 (6)	2.3 (1.0 – 5.2)	0.03
Intravenous drug use	12 (10)	12 (5)	2.1 (0.8-5.3)	0.11
Antibiotics				
Carbapenems	32 (27)	23 10)	3.4 (1.8 – 6.5)	<0.001
β-Lactam/β-lactamase inhibitor combinations	47 (40)	68 (29)	1.6 (0.0-2.7)	0.04
Cephalosporins, third or fourth generation	28 (24)	52 (22)	1.1 (0.8-1.9)	0.79
Cephalosporins, first or second generation	3 (3)	23 (10)	0.2 (0.1-0.8)	0.02
Glycopeptide	22 (19)	24 (10)	2.0 (1.2-4.0)	0.03
Aminoglycosides	8 (7)	20 (9)	0.8 (0.3-1.9)	0.68
Fluoroquinolone	7 (6)	13 (6)	1.1 (0.4-2.8)	1.00
Metronidazole	21 (18)	30 (13)	1.5 (0.8-2.8)	0.20

Figures represent number (%) unless otherwise indicated

Abbreviations: CVAD, central venous access device; ICU, intensive care unit; IQR, interquartile range; TPN, total parenteral nutrition.

Definitions: Cardiovascular disease, Severe congestive heart failure (symptoms at rest/inability to carry on physical activity without discomfort); Diabetes mellitus, Elevated HbA1c >6.5%; Liver disease, Biopsy proven cirrhosis with portal hypertension and/or past upper GIT bleeding due to portal hypertension and/or prior episodes of hepatic failure/encephalopathy/coma; Renal disease, On chronic haemodialysis or peritoneal dialysis; Neutropenia, neutrophil count of < 1.0 X 10^9 cells/L; Respiratory disease, Disease severely restricting exercise e.g. inability to climb stairs or do household duties and/or documented chronic respiratory hypoxia and/or pulmonary hypertension.

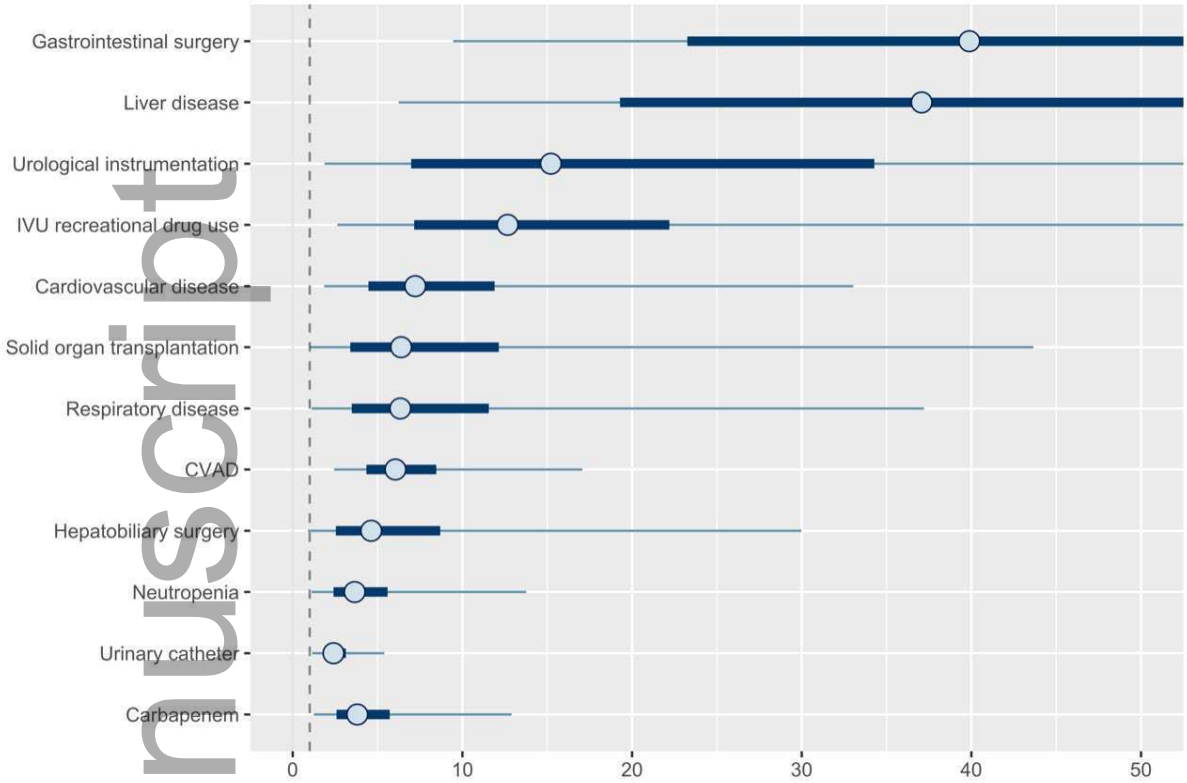
Table 2: Variables associated with candidaemia by multivariate analysis

Variable	OR	95% credible interval	"P-value"
Cardiovascular disease	7.2	1.8 - 32.6	0.001
Respiratory disease	6.4	1.1 - 37.3	0.02
Solid organ transplantation	6.4	1.0 - 43.3	0.02
Liver disease	37.0	6.1 - 301	<0.001
Hepatobiliary surgery	4.7	0.9 - 31.6	0.03
Gastrointestinal surgery	39.8	9.4 - 243	<0.001
Urological instrumentation	15	2.0 - 178	0.004
Urinary catheter	2.4	1.1 - 5.5	0.01
CVAD	6.0	2.4 - 16.9	<0.001
Intravenous drug use	12.6	2.5 - 69.6	0.001
Neutropenia	3.6	1.1 - 13.5	0.02
Carbapenem	3.8	1.2 - 12.8	0.01

CVAD; central venous access device

P-value is proportion of posterior distribution less than 1. It therefore is interpretable as the p-value of a one-sided test of the hypothesis that the OR is 1.

Figure 1: Factors associated with candidaemia on multivariate analysis



Odds ratios and 95% credible intervals for variables significantly associated with development of candidaemia compared with controls