# supplementary materials

**Article Title:** A Ten-year Retrospective Study of Invasive Candidiasis in a Tertiary Hospital

**Journal:** *Mycopathologia*

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## Supplementary table 1

**Supplementary Table 1**. Common risk factors for neonates to acquire candidemia.

|  |  |
| --- | --- |
| Risk factors | Neonates (n=9) |
| Male  | 6 (66.7) |
| Age (days) | 14.4±9.6 (range: 0-28) |
| Premature  | 8 (88.89) |
| Perinatal conditions |  |
| Gestational age (weeks) | 31.5±2.4 (range:29-37) |
| Birth weight (g) | 1528.3±281.9 (range: 1090-1920) |
| Maternal age (years) | 34.7±2.1 (range:32-38) |
| Maternal disease |  |
| Gestational diabetes mellitus | 1 (11.1) |
| Infections  | 1 (11.1) |
| Fetal intrauterine distress  | 3 (33.3) |
| Premature rapture of fetal membrane | 3 (33.3) |
| Hemoglobin (g/L) | 131.1±17.1 (range:107-166) |
| Albumin (g/L) | 29.0±4.8 (range:21-37) |
| Neonatal respiratory distress syndrome | 3 (33.3) |
| Hydrocephaly  | 1 (11.1) |
| Iatrogenic factors |  |
| Corticosteroids/ immunosuppressant | 0 |
| Use of CVC | 9 (100.0) |
| Mechanical ventilation | 8 (88.9) |
| Candida Score | 1.2±1.2 |
| Sepsis  | 2 (22.2) |
| Surgery  | 1 (11.1) |
| TPN | 6 (66.7) |
| Multi-focal colonization | 0 |
| Normally distributed variables are presented with mean±standard deviation while categorical variables are presented with the patient number (percentage, %). Abbreviations: CVC: Central venous catheter; TPN: Total parenteral nutrition. |

## Supplementary table 2

**Supplementary Table 2**. The unsterile sites detected with *Candida* colonization.

|  |  |
| --- | --- |
| Colonization sites | Frequency  |
| Sputum/ BALF/ tracheal secretions | 28 |
| Urine  | 20 |
| Pharynx  | 4 |
| Skin  | 1 |
| Drained abdominal fluid (tube placed for over 24h) | 3 |
| Abbreviations: BALF: Bronchoalveolar lavage fluid. |

## Supplementary table 3

**Supplementary Table 3**. Risk factors by common infected *Candida* species.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Risk factors |  |  |  |  |  |  | *Candida* species |  |  |  |  |  |  |
| *C. albicans* (n=87) | P-value |  | *C. parapsilosis* (n=37) | P-value |  | *C. glabrata* (n=27) | P-value |  | *C. tropicalis* (n=26) | P-value |  | *C. krusei* (n=7) | P-value |
| Male | 58 (66.7) | 0.763 |  | 29 (78.38) | 0.122 |  | 15 (55.56) | 0.142 |  | 18 (69.23) | 0.862 |  | 6 (85.71) | 0.300 |
| Age | 67 (49-81) | 0.331 |  | 65 (32-73) | 0.558 |  | 73 (51-88) | 0.410 |  | 64 (39-78) | 0.526 |  | 66 (28-78) | 0.549 |
| Age>75 years | 29 (33.3) | 0.357 |  | 6 (16.22) | 0.040\* |  | 13 (48.15) | 0.026\* |  | 8 (30.77) | 0.932 |  | 2 (28.57) | 0.930 |
| Age<1 month | 8 (9.2) | 0.616 |  | 6 (16.22) | 0.193 |  | 4 (14.81) | 0.413 |  | 0 (0.00) | 0.061 |  | 0 (0.00) | 0.358 |
| Hemoglobin (g/L) | 102.0±21.9 | 0.034\* |  | 101.3±21.5 | 0.447 |  | 94.52±28.6 | 0.327 |  | 93.62±21.1 | 0.121 |  | 81.4±31.9 | 0.025\* |
| Hemoglobin<80g/L | 12 (13.8) | 0.018\* |  | 5 (13.51) | 0.195 |  | 12 (44.44) | 0.018\* |  | 9 (34.62) | 0.074 |  | 4 (57.14) | 0.018\* |
| Albumin (g/L) | 30 (28-35) | 0.507 |  | 30 (28-35) | 0.517 |  | 30 (27-36) | 0.493 |  | 32 (30-35) | 0.448 |  | 31 (28-35) | 0.546 |
| Albumin <25g/L | 6 (6.9) | 0.542 |  | 3 (8.11) | 0.982 |  | 1 (3.70) | 0.357 |  | 3 (11.54) | 0.502 |  | 1 (6.90) | 0.549 |
| Diabetes mellitus | 25 (28.7) | 0.711 |  | 8 (21.62) | 0.210 |  | 15 (55.55) | 0.002\*\* |  | 8 (30.77) | 0.932 |  | 2 (28.57) | 0.930 |
| Solid organ malignancies | 35 (40.2) | 0.001\*\* |  | 7 (18.92) | 0.152 |  | 6 (22.22) | 0.440 |  | 5 (19.23) | 0.262 |  | 1 (14.29) | 0.398 |
| Hematologic malignancies | 0 (0.0) | 0.002\*\* |  | 0 (0.00) | 0.102 |  | 0 (0.00) | 0.176 |  | 7 (26.92) | <0.001\*\*\* |  | 1 (14.29) | 0.295 |
| Organ failure | 47 (54.0) | 0.465 |  | 23 (62.16) | 0.464 |  | 18 (66.67) | 0.264 |  | 13 (50.00) | 0.448 |  | 7 (100.0) | 0.019\* |
| Heart failure | 27 (31.0) | 0.283 |  | 6 (16.22) | 0.090 |  | 10 (37.04) | 0.220 |  | 7 (26.92) | 0.961 |  | 3 (42.86) | 0.347 |
| Respiratory failure | 25 (28.7) | 0.068 |  | 17 (45.95) | 0.138 |  | 16 (59.26) | 0.005\*\* |  | 7 (26.92) | 0.323 |  | 1 (14.29) | 0.231 |
| Renal failure | 21 (24.1) | 0.649 |  | 10 (27.03) | 0.834 |  | 8 (29.63) | 0.611 |  | 6 (23.08) | 0.743 |  | 6 (85.71) | <0.001\*\*\* |
| Hepatic failure | 6 (6.9) | 0.631 |  | 2 (5.41) | 0.862 |  | 0 (0.00) | 0.155 |  | 2 (7.69) | 0.697 |  | 1 (14.29) | 0.348 |
| Other deep-seated bacterial infection | 38 (43.7) | 0.319 |  | 20 (54.05) | 0.374 |  | 18 (66.67) | 0.031\* |  | 13 (50.00) | 0.786 |  | 2 (28.57) | 0.305 |
| Pancreatitis  | 4 (4.6) | 0.849 |  | 0 (0.00) | 0.121 |  | 2 (7.41) | 0.517 |  | 2 (7.69) | 0.480 |  | 1 (14.29) | 0.243 |
| Iatrogenic factors |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Long-term hospitalization (≥90 days) | 11 (12.6) | 0.015\* |  | 12 (32.44) | 0.038\* |  | 9 (33.33) | 0.066 |  | 7 (26.92) | 0.358 |  | 0 (0.00) | 0.174 |
| ICU hospitalization | 39 (44.8) | 0.666 |  | 20 (54.1) | 0.135 |  | 17 (63.0) | 0.025\* |  | 3 (11.5) | <0.001\*\*\* |  | 2 (28.6) | 0.427 |
| Hematodialysis  | 5 (5.7) | 0.356 |  | 5 (13.51) | 0.133 |  | 2 (7.41) | 0.959 |  | 4 (15.38) | 0.109 |  | 0 (0.00) | 0.437 |
| Long-term use of broad spectrum antibiotics | 24 (27.6) | <0.001\*\*\* |  | 22 (59.46) | 0.013\* |  | 16 (59.26) | 0.043 |  | 12 (46.15) | 0.605 |  | 2 (28.57) | 0.478 |
| Corticosteroids/ immunosuppressant | 7 (8.0) | 0.234 |  | 2 (5.41) | 0.228 |  | 1 (3.70) | 0.192 |  | 7 (26.92) | 0.005\*\* |  | 3 (42.86) | 0.006\*\* |
| CVC | 51 (58.6) | 0.154 |  | 27 (73.0) | 0.200 |  | 18 (66.7) | 0.749 |  | 19 (73.1) | 0.295 |  | 2 (28.6) | 0.047\* |
| Mechanical ventilation | 21 (24.1) | 0.012\* |  | 17 (45.95) | 0.068 |  | 15 (55.56) | 0.008\*\* |  | 8 (30.77) | 0.765 |  | 0 (0.00) | 0.056 |
| *Candida* Score | 1.4±1.2 | 0.283 |  | 1.46±1.17 | 0.869 |  | 1.55±1.22 | 0.283 |  | 1.42±1.36 | 0.516 |  | 1 (0-1) | 0.644 |
| Sepsis | 17 (19.5) | 0.296 |  | 10 (27.02) | 0.509 |  | 7 (25.93) | 0.691 |  | 9 (34.62) | 0.127 |  | 1 (14.29) | 0.578 |
| Surgery | 49 (56.3) | 0.003\*\* |  | 15 (40.54) | 0.559 |  | 7 (25.93) | 0.033\* |  | 9 (34.62) | 0.259 |  | 3 (42.86) | 0.916 |
| TPN | 40 (46.0) | 0.382 |  | 15 (40.54) | 0.774 |  | 15 (55.56) | 0.141 |  | 8 (30.77) | 0.187 |  | 2 (28.57) | 0.443 |
| Multifocal colonization | 6 (6.9) | 0.141 |  | 5 (13.51) | 0.485 |  | 6 (22.22) | 0.029\* |  | 2 (7.69) | 0.627 |  | 0 (0.00) | 0.358 |
| Antifungal-drug exposure |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Fluconazole  | 3 (3.4) | <0.001\*\*\* |  | 10 (27.0) | 0.050 |  | 9 (33.3) | 0.010\* |  | 7 (26.9) | 0.117 |  | 0  | 0.232 |
| Voriconazole  | 1 (1.1) | 0.001\*\* |  | 5 (13.5) | 0.250 |  | 3 (11.1) | 0.637 |  | 5 (19.2) | 0.041\* |  | 1 (14.3) | 0.597 |
| Amphotericin B | 1 (1.1) | 0.619 |  | 0 | 0.379 |  | 1 (3.7) | 0.360 |  | 1 (3.8) | 0.339 |  | 0 | 0.728 |
| Echinocandins  | 2 (2.3) | 0.073 |  | 3 (8.1) | 0.428 |  | 3 (11.1) | 0.162 |  | 1 (3.8) | 0.695 |  | 1 (14.3) | 0.295 |
| Sites |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood/CVC | 54 (62.1) | 0.002\*\* |  | 34 (92.0) | 0.003\*\* |  | 23 (85.2) | 0.114 |  | 19 (73.1) | 0.961 |  | 4 (57.1) | 0.347 |
| Drainage  | 20 (23.0) | 0.022\* |  | 1 (2.7) | 0.012\* |  | 2 (7.4) | 0.172 |  | 5 (19.2) | 0.673 |  | 3 (42.9) | 0.054 |
| CSF | 8 (9.2) | 0.002\*\* |  | 0 (0.0) | 0.145 |  | 0 (0.0) | 0.229 |  | 0 (0.0) | 0.239 |  | 0 (0.0) | 0.564 |
| Other puncture fluids | 5 (5.7) | 0.496 |  | 2 (5.4) | 0.653 |  | 2 (7.4) | 0.947 |  | 4 (15.4) | 0.076 |  | 1 (14.3) | 0.451 |
| Bone  | 2 (2.3) | 0.135 |  | 0 (0.0) | 0.474 |  | 0 (0.0) | 0.554 |  | 0 (0.0) | 0.563 |  | 0 (0.0) | 0.777 |
| 90-day all-cause mortality a | 22 (28.9) | 0.334 |  | 9 (25.7) | 0.318 |  | 11 (45.8) | 0.137 |  | 9 (40.9) | 0.377 |  | 1 (25.0) | 0.739 |
| Normally distributed variables are presented with mean±standard deviation and compared using two-tailed student t-tests; Non-normally distributed variables are presented with median (interquartile range) and compared using Mann-Whitney U tests; Categorical variables are presented with the patient number (percentage, %) and compared using chi-squared tests. Rare *Candida* species are not included in this table, including *Candida inconspicua*, *Candida kefyr*, *Candida lipolytica*, *Candida carpophila*, *Candida guilliermondii*. Mixed infection with two *Candida* species were analyzed in both *Candida* species groups. a Mortality data were available in 159 episodes including 76 episodes of *C.albicans* infection and 83 episodes of *C.*non-*albicans* infection.Abbreviations: CVC: Central venous catheter; CSF: Cerebrospinal fluid; TPN: Total parenteral nutrition. |

## Supplementary table 4

**Supplementary Table 4**. In vitro resistance of the 212 yeast isolates to five antifungal agents in this study.

|  |  |  |  |
| --- | --- | --- | --- |
| *Candida* spp. (n=208)a | Drug resistance |  | Non-wild type  |
| FCZ (%) | VCZ (%) | AMB (%) | MICA (%) | CAS (%) |  | FCZ (%) | VCZ (%) | AMB (%) | MICA (%) | CAS (%) |
| *C.albicans* (n=98) | 4 (4.1) | 3 (3.1) | - | 3 (3.1) | 1 (1.0) |  | - | - | 0 | - | - |
| *C.parapsilosis* (n=44) | 1 (2.3) | 0 | - | 0 | 0 |  | - | - | 0 | - | - |
| *C.glabrata* (n=29) | 7 (24.1) | - | - | 3 (10.3) | 3 (10.3) |  | - | 17 (58.6) | 0 | - | - |
| *C.tropicalis* (n=27) | 10 (37.0) | 0 | - | 2 (7.4) | 2 (7.4) |  | - | - | 0 | - | - |
| *C.krusei* (n=8) | IR | 0 | - | 0 | 0 |  | IR | - | 0 | - | - |
| *C. guilliermondii* (n=1) | - | - | - | 0 | 0 |  | 0 | 0 | 0 | - | - |
| *C.kefyr* (n=1) | - | - | - | - | - |  | 0 | 0 | 0 | 0 | 0 |
| Variables are presented as number (percentage). aFour other isolates are not shown in this table including *Candida lipolytica*, *Candida inconspicua* and *Candida carpophila*, since the reference cut-off value to determine resistance has not been established due to its rarity. Abbreviations: AMB: Amphotericin B; CAS: Caspofungin; FCZ: Fluconazole; IR: Intrinsic resistance; MICA: Micafungin; VCZ: Voriconazole.  |

## Supplementary table 5

**Supplementary Table 5**. Association between risk factors and 90-day all-cause mortality.

|  |  |  |  |
| --- | --- | --- | --- |
| Risk factors | Univariate analysis |  | Multivariate analysis |
|  | OR (95% CI) | P-value |  | OR (95% CI) | P-value |
| Male | 0.84 (0.41-1.72) | 0.632 |  | 0.79 (0.26-2.39) | 0.674 |
| Age  | 1.02 (1.01-1.04) | 0.001\*\* |  | 1.01 (0.99-1.03) | 0.347 |
| Hemoglobin<80g/L | 0.92 (0.40-2.12) | 0.844 |  | 0.78 (0.20-3.08) | 0.720 |
| Albumin<25g/L | 1.32 (0.41-4.24) | 0.645 |  | 1.12 (0.21-5.85) | 0.893 |
| Diabetes mellitus | 2.00 (0.99-4.06) | 0.053 |  | 1.76 (0.64-4.81) | 0.273 |
| Solid organ malignancies | 1.25 (0.60-2.60) | 0.543 |  | 2.07 (0.62-6.93) | 0.239 |
| Hematologic malignancies | 1.25 (0.29-5.44) | 0.767 |  | 44.29 (2.38-825.37) | 0.011\* |
| Neutropenia  | 1.03 (0.25-4.29) | 0.967 |  | 38.31 (2.07-709.75) | 0.014\* |
| Organ failure | 8.86 (3.66-21.44) | <0.001\*\*\* |  | 2.62 (0.48-14.27) | 0.264 |
| Heart failure | 4.63 (2.21-9.67) | <0.001\*\*\* |  | 3.62 (1.18-11.10) | 0.025\* |
| Respiratory failure | 6.90 (3.31-14.38) | <0.001\*\*\* |  | 7.13 (1.94-26.21) | 0.003\*\* |
| Renal failure | 4.54 (2.14-9.63) | <0.001\*\*\* |  | 2.40 (0.79-7.30) | 0.122 |
| Hepatic failure | 0.87 (0.22-3.53) | 0.851 |  | 1.01 (0.15-6.64) | 0.994 |
| Other deep-seated bacterial infection | 2.13 (1.08-4.22) | 0.009\*\* |  | 0.31 (0.09-1.02) | 0.054 |
| Pancreatitis  | 0.68 (0.07-6.70) | 0.741 |  | 0.14 (0.01-2.70) | 0.191 |
| Digestive tract perforation | 1.52 (0.46-5.04) | 0.494 |  | 13.02 (1.46-116.29) | 0.022\* |
| Iatrogenic factors |  |  |  |  |  |
| Long-term hospitalization (≥90 days) | 1.66 (0.79-3.57) | 0.195 |  | 0.12 (0.03-0.58) | 0.008\*\* |
| ICU | 2.02 (1.04-3.97) | 0.039\* |  | 1.28 (0.44-3.72) | 0.656 |
| Hematodialysis  | 1.37 (0.77-2.42) | 0.287 |  | 0.48 (0.17-1.18) | 0.104 |
| Long-term use of broad-spectrum antibiotics | 3.43 (1.71-6.85) | <0.001\*\*\* |  | 5.30 (1.55-18.08) | 0.008\*\* |
| FCZ exposure | 2.49 (1.10-5.60) | 0.028\* |  | 0.99 (0.23-4.17) | 0.989 |
| Corticosteroids/ immunosuppressant | 0.91 (0.27-3.10) | 0.877 |  | 1.76 (0.29-10.83) | 0.543 |
| Central venous catheter | 0.88 (0.44-1.76) | 0.719 |  | 0.12 (0.03-0.55) | 0.006\*\* |
| Mechanical ventilation | 3.05 (1.52-6.10) | 0.002\*\* |  | 0.71 (0.19-2.59) | 0.602 |
| *Candida* Score | 1.44 (1.08-1.92) | 0.013\* |  | 1.43 (0.95-2.13) | 0.084 |
| Sepsis | 2.67 (1.26-5.65) | 0.011\* |  | 1.25 (0.39-4.00) | 0.709 |
| Surgery | 0.58 (0.29-1.15) | 0.121 |  | 1.16 (0.35-3.87) | 0.811 |
| Gastrointestinal surgery | 0.76 (0.36-1.58) | 0.459 |  | 1.70 (0.40-7.20) | 0.470 |
| TPN | 1.89 (0.96-3.71) | 0.064 |  | 3.30 (1.18-9.22) | 0.023\* |
| Multifocal colonization | 2.28 (0.85-6.14) | 0.103 |  | 0.77 (0.17-3.40) | 0.728 |
| Initial treatment |  |  |  |  |  |
| FCZ | 1 (reference) |  |  | 1 (reference) |  |
| VCZ | 0.80 (0.20-3.20) | 0.757 |  | 1.04 (0.12-9.34) | 0.970 |
| CAS | 2.98 (1.07-8.31) | 0.037\* |  | 3.02 (0.47-19.38) | 0.243 |
| MICA | 3.45 (1.14-10.38) | 0.028\* |  | 7.36 (1.20-45.02) | 0.031\* |
| Main treatment |  |  |  |  |  |
| FCZ | 1 (reference) |  |  | 1 (reference) |  |
| VCZ | 3.83 (1.11-13.30) | 0.034\* |  | 2.05 (0.25-17.02) | 0.382 |
| AMB | 1.10 (0.20-6.05) | 0.917 |  | 0.52 (0.05-5.20) | 0.576 |
| CAS | 3.29 (1.09-9.88) | 0.034\* |  | 0.83 (0.12-5.85) | 0.852 |
| MICA | 2.46 (0.73-8.31) | 0.146 |  | 0.52 (0.06-4.70) | 0.561 |
| Echinocandins + Azole | 2.74 (0.72-10.34) | 0.137 |  | 1.60 (0.14-18.35) | 0.382 |
| Note: 159 episodes with mortality data were included in the analysis. Abbreviations: AMB: Amphotericin B; CAS: Caspofungin; FCZ: Fluconazole; ICU: Intensive care units; MICA: Micafungin; OR: Odds ratio; TPN: Total parenteral nutrition; VCZ: Voriconazole. |

## Supplementary table 6

There were 31 patients in this studies who did not receive any systematic antifungal drugs and were not included when comparing the drug effectiveness. The details for these patients, including their infected sites and other local treatment are listed below.

**Supplementary Table 6**. Information for patients who did not receive systematic antifungal drugs.

|  |  |  |  |
| --- | --- | --- | --- |
| Infected sites | Survived (n=20) | Died (n=8) | Missing outcome (n=3) |
| n | comments | n | comments |
| Blood related (n=15) | 10 |  | 4 |  | 1 |
| Blood (n=10) | 6 | 1. One patient acquired candidemia after surgery and recovered after changing a CVC.

2-4. Three patients acquired candidemia after surgery (two of the three received toe amputation for diabetic foot). However, no clinical abnormality was recorded in relation to fungal sepsis.5. One patient re-admitted for renal abscess 20 days later, but culture for the abscess was negative for *Candida* species.6. One patient was considered as acute abdomen induced candidemia and recovered after surgery. | 3 | 1-2. Two patients gave up and both died four days later;3. One patient died on the day when the culture result was obtained one day later. | 1 |
| CVC (n=1) | 1 | 1. The infection was hematodialysis-related and was cured by extubation.
 | 0 |  | 0 |
| Blood+CVC (n=4) | 3 | 1-3. Three patients acquired candidemia after surgery and recovered after extubation. | 1 | 1. One patient gave up and died 18 days later; | 0 |
| Drains (n=10) | 6 |  | 3 |  | 1 |
| Drainage after surgery (n=5) | 4 | 1-2. No clinical abnormality was recorded in these two patients regarding the intra-abdominal IC.3-4. Two patients with acute abdomen (one perforation and one ileus) recovered after surgery. | 0 |  | 1 |
| Abscess (n=3) | 1 | 1. One patient with an abdominal abscess recovered after effective drainage.
 | 2 | 1. One patient with a subcutaneous abscess recovered from antibiotics (Metronidazole) but died from STEMI afterwards.
2. One patient with an abdominal abscess died 12 days later.
 | 0 |
| Bile (n=2) | 1 | 1. The patient was diagnosed as acute cholecystitis and recovered after surgery and drainage.
 | 1 | 1. The patient died before the culture results came back.
 | 0 |
| CSF (n=1) | 1 | 1. The original culture of CSF in this patient was negative while enrichment culture was positive for *Candida* species. Thus, the patient was not considered IC clinically.
 | 0 |  |  |
| Other fluids (n=5) | 3 | 1. One patient with infection in synovial fluid recovered after TKA surgery.
2. One patient with encapsulated pleural effusion recovered after effective drainage.
3. One patient with a tracheo-esophageal fistula recovered after drainage.
 | 1 | 1. The patient did not add antifungal agents due to his hepatic failure, and died nine days later.
 | 1 |
| Abbreviations: CSF: Cerebrospinal fluid; CVC: Central venous catheter; STEMI: ST-segment elevation myocardial infarction; TKA: Total knee arthroplasty. |