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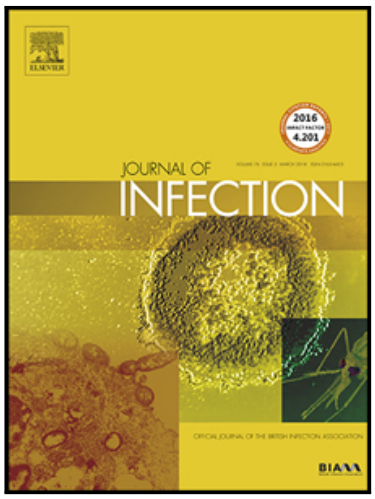

A retrospective multicenter analysis of candidaemia among COVID-19 patients during the first UK pandemic wave

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Title:

A retrospective multicenter analysis of candidaemia among COVID-19 patients during the first UK pandemic wave

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1000

Dear editor

It is with great interest that we read the recent article by De Francesco et al (1), who reported on chlamydia pneumoniae and mycoplasma pneumoniae co-infection in patients with COVID-19. Here, we report our experience with candidaemia co-infection with COVID-19. An increased incidence of candidaemia has been noted in patients with COVID-19 and

although patient characteristics, investigations and antifungal therapies have been described (2), to our knowledge, compliance with candidaemia management bundles has not (3).

Here, we present a retrospective review of candidaemias in adult patients (>17 years) with PCR proven COVID-19 between 1st March 2020 - 31st May 2020 across six acute London hospitals. All yeasts isolated from blood cultures were identified by matrix assisted laser desorption/ionisation-time-of-flight (MALDI-TOF) mass spectroscopy (Bruker Daltonik GmbH, Bremen, Germany). Antifungal susceptibility testing was carried out using broth micro-dilution in accordance with EUCAST guidelines (4). An episode of candidaemia was defined as blood culture growth of any *Candida* species.

Eleven patients with concurrent candidaemia and PCR-proven COVID-19 were identified during the study period; ten were male (90.9%), mean age 62 (33-77 years). Underlying comorbidities were predominantly cardiovascular (10/11). Two patients were immunosuppressed (see Table 1), but neutropenia was not identified.

Ten patients (90.9%) were admitted to an intensive care unit (ICU) prior to their candidaemia diagnosis. Of the ICU patients (n=10), all were intubated and ventilated, had an intravascular and urinary catheter and received inotropes. The non-ICU patient also had a urinary catheter. Nine (90%) of the ICU patients received haemofiltration. None of the patients in our cohort received total parenteral nutrition.

All eleven patients received broad-spectrum antibacterials. One patient received prior antifungal treatment in hospital with topical clotrimazole and oral terbinafine for a tinea infection.

The average number of days from PCR-proven COVID-19 to candidaemia was 14.8 days and from ICU admission to candidaemia, 15.5 days (range 6–24 days). Seven out of

eleven candidaemias (63.6%) were *C.albican*s, two (18.2%) *C.parapsilosis*, one (9.1%) *C. glabrata* and one (9.1%) *C.dubliniensis*. All isolates were fluconazole susceptible, except one (*Candida glabrata*), which showed intermediate susceptibility, although the patient was successfully treated with azole therapy through dose-optimisation.

An echinocandin was commenced for ten patients, as per local guidelines, pending susceptibility testing. One patient died prior to blood culture positivity and treatment. Four out of ten (40%) patients were switched to fluconazole to complete treatment. In line with recommended practice (3) six out of eleven patients (54.5%) had repeat blood cultures within 48 hours of treatment, eight (72.7%) patients had an echocardiogram, but only one (9.1%) had fundoscopy. Serum (1-3)-β-D-glucan(BDG) testing was performed in 54.4% (6/11) of patients; three were positive(see Table 1).

Intravascular catheters were removed for nine out of ten patients (90%), the last patient dying prior to candidaemia notification. Seven out of nine patients had line tips sent for culture; two were positive for yeasts. One line tip confirmed an identical *Candida* spp., and hence constituted a line infection, but no further identification was available for the second.

Four patients had prior colonization with yeasts; one with the same species as their candidaemia, no further identification was available for the remaining three. Five patients were not colonized and two had an unknown status following transfer from other secondary care providers, developing candidaemia shortly after transfer.

In concordance with Mastrangelo et al (1), there was a high 30-day mortality of 54.4% (6/11) in our patient cohort. The four surviving patients (36.6%) were discharged; average total length of stay 58 days (range 31-78 days). One patient was stepped down after nine weeks in ICU but remained an inpatient until the end of our study period.

Given the high mortality rate, it is important to identify and address modifiable risk factors in an attempt to prevent the occurrence of candidaemia. Firstly, all our patients received broad-spectrum antibacterials, a recognized risk factor for candidaemia (5,6). A recent study from Hughes et al (7) demonstrated a low frequency (3.2%) of early bacterial co-infection in patients hospitalized with COVID-19, suggesting early broad-spectrum antibacterials may not be warranted. Hence, antimicrobial stewardship initiatives to review unnecessary antibacterial use remain important.

Secondly, intravascular catheters are a well-recognised risk factor for candidaemia (5) and over 90% of our patients had these. The incidence of candidaemia observed warrants further consideration, and whilst not compared to pre-COVID-19 incidence (2), may potentially reflect pandemic unique challenges. Examples include increased ICU capacity, redeployment of less-experienced staff to ICU, challenges to aseptic technique with personal protective equipment (PPE), and patients requiring re-positioning to improve oxygenation, thus increasing possibility of line displacement/contamination. Improved aseptic intravascular catheter training focusing on PPE may be beneficial.

In addition, although we were unable to identify urinary catheters as a source in our cohort, they are a recognized risk factor for candidaemia (6) and all patients in our cohort had these.

One patient died prior to candidaemia notification. Time to blood culture positivity may be delayed, particularly for non-albicans candidaemias (8), and delay in treatment is known to increase mortality (9), therefore, non-culture-based diagnostics such as galactomannan antigen and BDG should be combine with clinical data to aid diagnosis (10). 54.4% (n=6) of the patients were tested for BDG, and of those, 50% (n=3) were positive.

Although not possible to demonstrate in this patient cohort, an early positive BDG may herald invasive fungal infection, enabling timely initiation of empirical antifungal therapy.

Guidelines for management of candidaemia recommend a care bundle, including repeat blood cultures at 48 hours, echocardiogram, and fundoscopy to identify disseminated infection. In our cohort, only 54.5 % (6/11) of patients had repeat blood cultures within 48 hours, 72.7 % (8/11) an echocardiogram and only 9.1% (1/11) fundoscopy. COVID-19 infection control concerns, patient positioning and PPE, with resultant challenges to ophthalmic examination, may account for the poor fundoscopy compliance, adding further weight to the need for COVID-19 specific practical training.

To conclude, during the ongoing COVID-19 pandemic it remains important to consider modifiable risk factors for candidaemia, non-culture based diagnositics to aid early diagnosis, as well as adherence to established treatment bundles.

Declarations

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Institute for Health Research. DAJ is also funded by a Cystic Fibrosis Trust Strategic Research Centre (SRC015) and a Wellcome Trust Collaborative Award (219551/Z/19/Z).

Ethics

Ethical approval was not required for this service evaluation and audit of practice.

Authors' contributions

SD, AR and NM designed the study methodology. SD, TE and XG collated the data. SD drafted the initial manuscript with all authors contributing significantly to revising this for submission. All authors agreed on the final version for submission to the journal.

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Potential conflicts of interests

SC has received a research grants from the Scientific Exploration Society.

EC has been paid for consultancy fees by bioMerieux.

SH reports personal fees from Pfizer and Shionogi.

DAJ holds share options in Pulmocide Ltd and has received research grants from Pulmocide Ltd, Gilead Sciences, Astellas and Pfizer. He has received speaker and consultancy fees from Astra-Zeneca, Pfizer, Gilead, and Astellas.

LSPM has consulted for DNAelectronics (2015-18), Dairy Crest (2017–2018), Umovis Lab (2020), bioMerieux (2013-2020), received speaker fees from Profile Pharma (2018) and

Pfizer (2018-2020), received research grants from the National Institute for Health Research (2013-2020), CW+ Charity (2018-2020), and Leo Pharma (2016), and received educational support from Eumedica (2016–2018).

NM has received speaker fees from Beyer (2016) and Pfizer (2019) and received educational support from Eumedica (2016) and Baxter (2017).

All other authors have no conflicts of interest to declare.

Availability of data and materials

The data analysed during the current study and further details on the assays are available from the corresponding author (SD; sarahdenny1@nhs.net) on reasonable request, as long as this meets local ethical and research governance criteria.

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Demographics	N=11
Age, years	62 (33-77)
Sex, male	10 (90.9%)
Past medical history	
Type 2 diabetes	8 (72.7 %)
Hypercholesterolaemia	8 (72.7%)
Hypertension	3 (27.3%)
Ischaemic Heart Disease	1 (9.1%)
Permanent Pacemaker	1 (9.1%)
Myaesthenia Gravis	1 (9.1%)
Previous solid organ malignancy	2 (18.2%)
Gastro-oesophageal Reflux Disease	1 (9.1%)
Benign prostatic hypertrophy	1 (9.1%)
Hypopituitarism	1 (9.1%)
Risk factors for candidaemia	
Immunosuppression	2 (18.2%) [a]
Broad spectrum antimicrobials	11 (100%)
Neutropenic	0 (0%)
Intensive care (ICU) admission	10 (90.9%)
Intravenous catheter - Average catheter day - Number of patients where catheter day unknown	10 (90.9%) 6.3 (3-9) 4 (40%)

Ventilated	10 (90.9%)
Inotropic support	10 (90.9%)
Haemofiltration	9 (81.8)
Urinary catheter	11 (100%)
Total parenteral nutrition	0 (0%)
Candida colonisation - Yes - No - Unknown	 4 5 2
Clinical course	
Days to candidaemia since COVID-19 diagnosis	14.8 (7-24)
Days to candidaemia since ICU admission	15.5 (6-24)
Repeat blood cultures taken at 48 hours	6 (54.5%)
Days to candidaemia clearance	2.3 (1-3)
Non-albicans candidaemia	4 (36.4%)
Beta-D-glucan performed - positive - negative	6 (54.5%) 3 (50%) [b] 3 (50%)
Galactomannan performed - positive - negative	5 (45.5%) 0 (0%) 5 (100%)
Intravascular catheter removed - culture confirmation of same Candida spp.	9 (90%) 1 (10%)
Echocardiogram performed - positive - negative	8 (72.7%) 0 (0%) 8 (100%)
Fundoscopy peformed - positive - negative	1 (9.1%) 0 (0%) 1 (100%)
Death at 30 days	6 (54.5%)
Values are reported as mean and range or frequency (%)	

a: One patient received 9mg prednisolone once daily plus 500mg mycophenolate mofetil twice daily for myasthenia gravis A second patient received hydrocortisone 10mg/5mg/5mg for hypopituitarism.

b: Positive results included values of 256 pg/ml, 154 pg/ml and 110 pg/ml

Table 1: Characteristics of patients with concurrent COVID-19 and candidaemia.