Candida auris, what do paediatricians need to know?

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ABSTRACT
The newly recognised and emerging fungal species, Candida auris, has caused worldwide invasive infections and has been implicated in difficult to control hospital outbreaks. Challenges are encountered in the correct identification of this fungus as commonly used phenotypic and biochemical methods fail to differentiate C. auris from other Candida species. Its resistance profile, over 90% of isolates are fluconazole resistant and 35% are resistant to amphotericin, confronts clinicians with the restricted arsenal of antifungals and concerns about optimal treatment. The very first C. auris isolate was recovered from a paediatric patient in retrospect. Although infections with the more antifungal-resistant Candida species are less frequently observed in paediatric patients, this seems to be different for C. auris infections.

INTRODUCTION
The emergence of Candida auris has received worldwide attention, not only from the scientific and clinical communities, but has as well been picked up by several public media channels. C. auris being reported as a ‘sometimes deadly and often resistant fungal infection’, a ‘superbug highly resistant to traditional drugs’ and C. auris sickness does’, makes clear that there is something to be feared from this newly recognised Candida species. The yeast C. auris was described for the first time in 2009 on recovery from the external ear canal of a Japanese patient.1 Subsequently, C. auris was recognised as causing chronic otitis media in 15 patients in Korea, including three paediatric patients.2 The earliest case to date was identified in retrospect by DNA sequencing of a Korean bloodstream isolate from a paediatric surgery patient in 1996.3 Since 2009, patients colonised and infected with C. auris have been reported from nearly all continents (except for Australia and Antarctica). C. auris has been shown to be a challenge to identify and treat, is capable to cause difficult to manage hospital outbreaks and reasons for its emergence is far from clear.4

The vast majority of infections caused by Candida species in the paediatric population are caused by C. albicans or C. parapsilosis, while the more antifungal resistant species as C. glabrata and C. krusei are less prevalent in comparison to Candida infections in adult patients.5 As the very first reports of C. auris infections are described in both neonates and children as well as adults, attention needs to be paid to its consequences for the management of Candida infections in the paediatric population.

CLINICAL EPIDEMIOLOGY
A literature search, restricted to publications in English, including publications up to 8 December 2017, was performed by using Medline/ Pubmed. At that moment, published clinical reports of C. auris infections originated from Japan, South Korea, India, Kuwait, Oman, South Africa, Venezuela, Panama, Colombia, Pakistan, Israel, Spain, UK, Canada and the USA describing 109 patients with candidaemia, 19 patients with chronic otitis media or otitis externa and 28 patients with other infections (including candiduria/urinary tract infections (n=16) and wound and soft tissue infections (n=6)).14.8-21 Real-time data from the Centers for Disease Control and Prevention show that new cases are reported on an almost weekly basis with a total of 243 clinical cases of C. auris infection in the USA.22 Public Health England shows a more episodic pattern in reported clinical cases (56 in total) with high increases during outbreaks.23 No paediatric patients have been reported in the UK (Dr E M Johnson, Public Health England, personal communication).

Ten out of the 18 publications described infections in adult patients only. Two publications did include paediatric patients but no details were given separately for the patients <18 years of age19 21 or age was not mentioned.21 Twenty-three paediatric patients have been reported in five case series published, of which 20 neonates and children suffered from a blood stream infection (18% of the total population).13 9 12 Three other paediatric patients suffered from chronic otitis media with positive ear swabs for C. auris.2 A table 1 summarises the clinical characteristics of those infections. Paediatric patients have only been reported in Asia and South America. Underlying conditions and risk factors are comparable to those known to render paediatric patients at risk for developing candidaemia and invasive candidiasis. Of the 20 paediatric patients with candidaemia due to C. auris, 14 were neonates and/or born prematurely. Older infants and children developed C. auris candidaemia during intensive care unit (ICU) admissions, postsurgery or with an underlying haematological malignancy. Antifungal regimens prescribed varied hugely with half of the patients receiving combination antifungal therapy with two or three antifungals. Mortality was 30% in paediatric patients with C. auris blood stream infections and lower compared with adult patients with mortality rates ranging from 30% to 60%. In contrast, during the C. auris outbreak in a large UK hospital, no attributable deaths were observed due to C. auris infections.2

As C. auris has been commonly misidentified as Candida haemulonii, a rare encountered Candida
species causing invasive infections.\textsuperscript{3,8,10,11,13} Paediatric patients with \textit{C. haemulonii} blood stream infections reported in the literature have been summarised in \textbf{Table 2}. The clinical characteristics are comparable to those described for \textit{C. auris} fungaemia and neonates and children with well-known underlying conditions and risk factors to develop invasive fungal disease are affected. Thirteen paediatric patients from Kuwait, Korea and Brazil have been described, including five premature neonates.\textsuperscript{5,24–26} \textit{C. haemulonii} infections have been more often described in infants and children (62\%) compared with \textit{C. auris} infections affecting mostly neonates (70\%). Half of the patients with \textit{C. haemulonii} infections were treated with combination antifungal therapy and the mortality rate was 30\%.

Due to the low numbers of paediatric patients described, it is difficult to draw meaningful comparisons with \textit{Candida} infections caused by other species, specific patient groups affected, geographic patterns and the outcome of the infections.

\section*{Identification and Susceptibility}
\textit{C. auris} isolates have been misidentified as a range of other \textit{Candida} species by using conventional phenotypic and biochemical methods. Most commonly, these isolates have been misidentified as \textit{C. haemulonii}, as \textit{C. auris} is phylogenetically closely related to the \textit{C. haemulonii} species complex.\textsuperscript{3,8,10,11,13} \textit{C. haemulonii} complex species are less frequently detected than \textit{C. auris}, although inaccuracies with the molecular identification of less common \textit{Candida} species prevents a robust insight into these infections.\textsuperscript{5} It is also possible that some of the reported isolates of \textit{C. haemulonii} are misidentified as \textit{C. auris}. It has been suggested that chromogenic agar is a low-cost method to differentiate between \textit{C. auris} and \textit{C. haemulonii} isolates.\textsuperscript{7} Molecular techniques are recommended to identify \textit{C. auris} to the species level. Matrix-assisted laser desorption ionisation–time of flight mass spectrometry is capable of providing an accurate identification to the species level once spectra for \textit{C. auris} are present in its database.\textsuperscript{7} The development of \textit{C. auris}-specific PCR assays allows for rapid identification and are of particular use during outbreak settings.\textsuperscript{7} Sequencing of genotypic loci and internal transcribed spacer domains of the rRNA provides the ability to differentiate between geographic clades.\textsuperscript{3,21} Genome sequencing has been shown to be useful in the identification of \textit{C. auris} but is often not an available technique in most laboratories and is less feasible for routine identification purposes.

\begin{table}
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\caption{Clinical epidemiology of published paediatric cases with \textit{Candida auris} infections}\\
\begin{tabular}{|c|c|c|c|c|c|c|}
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Patient number & Country & Sex/age & Underlying condition & Positive cultures & Localisation of infection & Treatment & Outcome \\
\hline
1 (Lee et al\textsuperscript{4}) & South Korea & F1 year & Traumatic respiratory arrest & Blood & Blood stream & FLU, removal CVC & Survived \\
2 (Chowdhary et al\textsuperscript{4}) & India & F3 days & Prematuritas, TEF, ICH, bacterial sepsis & Blood & Blood stream & Caspo & Died \\
3 (Chowdhary et al\textsuperscript{4}) & India & F10 days & Prematuritas, ELBW, bacterial sepsis & Blood & Blood stream & d-AMB & Survived \\
4 (Chowdhary et al\textsuperscript{4}) & India & F28 days & Pneumonia, late-onset sepsis & Blood & Blood stream & d-AMB & Survived \\
5 (Chowdhary et al\textsuperscript{4}) & India & F45 days & Meningitis, septic shock, cardiac defect & Blood & Blood stream & d-AMB & Survived \\
6 (Chowdhary et al\textsuperscript{4}) & India & M10 years & ALL, chronic kidney disease & Blood & Blood stream & none & Died \\
7 (Chowdhary et al\textsuperscript{4}) & India & F2 months & Short-bowel syndrome, intestinal perforation, pneumonia, bacterial sepsis & Blood, tip CVC & Blood stream & FLU, d-AMB, removal CVC & Survived \\
8 (Calvo et al\textsuperscript{5}) & Venezuela & F30 days & Prematuritas, sepsis & Blood & Blood stream & AmB, VORI & Died \\
9 (Calvo et al\textsuperscript{5}) & Venezuela & F13 days & Prematuritas, colon atresia, sepsis, abdominal surgery & Blood & Blood stream & VORI, AmB, Caspo & Died \\
10 (Calvo et al\textsuperscript{5}) & Venezuela & M17 days & Abdominal surgery, sepsis & Blood & Blood stream & FLU & Died \\
11 (Calvo et al\textsuperscript{5}) & Venezuela & F23 days & Prematuritas, septic shock & Blood & Blood stream & Caspo & Survived \\
12 (Calvo et al\textsuperscript{5}) & Venezuela & M18 days & Prematuritas, sepsis & Blood & Blood stream & FLU, VORI, Caspo & Died \\
13 (Calvo et al\textsuperscript{5}) & Venezuela & M2 days & Intestinal atresia, congenital heart disease, abdominal surgery & Blood & Blood stream & Caspo & Survived \\
14 (Calvo et al\textsuperscript{5}) & Venezuela & M12 days & NEC, HIE, sepsis, abdominal surgery & Blood & Blood stream & VORI, Caspo & Survived \\
15 (Calvo et al\textsuperscript{5}) & Venezuela & M11 days & Prematuritas, NEC, sepsis, abdominal surgery & Blood & Blood stream & AmB, Caspo & Survived \\
16 (Calvo et al\textsuperscript{5}) & Venezuela & F18 days & Prematuritas, abdominal wall defect, sepsis, abdominal surgery & Blood & Blood stream & VORI & Survived \\
17 (Calvo et al\textsuperscript{5}) & Venezuela & F14 years & Septic shock & Blood & Blood stream & VORI, Anidula, Caspo & Survived \\
18 (Calvo et al\textsuperscript{5}) & Venezuela & F10 days & Prematuritas, HIE, sepsis & Blood & Blood stream & FLU & Survived \\
19 (Calvo et al\textsuperscript{5}) & Venezuela & F2 months & Meningocele, congenital hydrocephalus, sepsis & Blood & Blood stream & VORI, Caspo & Survived \\
20 (Calvo et al\textsuperscript{5}) & Venezuela & F1 month & Prematuritas, RDS, sepsis & Blood & Blood stream & VORI, Caspo & Survived \\
21 (Kim et al\textsuperscript{6}) & Korea & Not available & Chronic otitis media & Ear & Ear & n.a. & Survived \\
22 (Kim et al\textsuperscript{6}) & Korea & Not available & Chronic otitis media & Ear & Ear & n.a. & Survived \\
23 (Kim et al\textsuperscript{6}) & Korea & Not available & Chronic otitis media & Ear & Ear & n.a. & Survived \\
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ALL, acute lymphoblastic leukaemia; AmB, amphotericin B; anidula, anidulafungin; caspo, caspofungin; CVC, central vascular catheter; d-AMB, amphotericin deoxycholate; ELBW, extreme low-birth weight; HIE, hypoxic ischaemic encephalopathy; ICH, intracerebral haemorrhage; FLU, fluconazole; NEC, necrotising enterocolitis; RDS, respiratory distress syndrome; TEF, trachea o esophageal fistula; VORI, voriconazole.
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Intrinsic susceptibility patterns for *C. auris* show elevated minimum inhibitory concentrations for all three classes of antifungals, the polyenes, the azoles and the echinocandins.27 Exact breakpoints as have been established for the common *Candida* species using the Clinical and Laboratory Standards Institute and the European Committee on Antimicrobial Susceptibility Testing methodologies have not been established.28 Antifungal susceptibility data for 54 *C. auris* isolates showed that 93% were resistant to fluconazole (≥32 mg/L), 54% to voriconazole (≥2 mg/L), 35% to amphotericin B (≥2 mg/L) and 7% to echinocandins (≥8 mg/L). Forty-one per cent of those isolates were resistant to greater than or equal to two classes of antifungals. Resistance to all three classes of antifungals was observed in two Indian isolates.29 Of the 13 *C. haemulonii* infections in paediatric patients, eight isolates (62%) showed amphotericin B resistance, two isolates (15%) showed resistance for fluconazole and two isolates (15%) showed resistance for voriconazole.26

### EMERGENCE OF C. AURIS

Results from whole-genome sequencing studies suggest that *C. auris* has emerged near simultaneously in four or more locations rather than spreading from a single source.21 Sequencing of *C. auris* isolates in the UK have clearly shown that those isolates have several geographic origins and belong to at least three different clades.22 This suggest that *C. auris* isolates have been introduced into the UK from different locations.

But what has driven the emergence of this new *Candida* species? One of the explanations could be that *C. auris* has just not been recognised before, but this is not supported by retrospective reviews of large collections of *Candida* isolates. A thorough review of over 15 000 *Candida* isolates from four continents (SENTRY isolate collection) did not detect any *C. auris* isolate before 2009.21 Increasing antifungal selection pressures either in humans and/or animals and/or the environment may cause the emergence of a new multidrug-resistant *Candida* species. The availability of antifungals with an improved toxicity profile has contributed to an expansion in the prescriptions of antifungals for prophylactic and empirical use. Increased antifungal use in agriculture and in the clinical environment has led to well recognised emerging resistance among *Aspergillus fumigatus* (azole resistance) and *C. glabrata* (echinocandin resistance).30 However, selection by antifungal pressure alone seems to be less likely as non-albicans *Candida* species have been increasing since the introduction of fluconazole in 1990. Changes to the ecological niches of *C. auris* and intrinsic characteristics as numerous virulence attributes, thermotolerance and salt tolerance and aggregation into difficult-to-disperse clusters, may have allowed the emergence of this newly recognised species causing human infections and persistence in hospital environments.31 A number of molecular resistance mechanisms are well described for causing resistance to particular antifungals in several *Candida* species.28 As yet, molecular mechanisms resulting in antifungal resistance in *C. auris* need to be elucidated.

### CLINICAL MANAGEMENT

Based on susceptibility data, echinocandins seem to be the drug of choice as less than 10% resistance is reported.27,28 Micafungin showed increased efficacy in a murine study of *C. auris* candidaemia compared with fluconazole and amphotericin B.32 For the paediatric population, micafungin and caspofungin can be used while awaiting susceptibility testing results.33,34 Depending on the site of infection, alternative choices might be considered.3,28,33,34 Echinocandins have limited penetration in the cerebrospinal fluid and urine, and therefore other antifungal compounds should be used to treat central nervous system or renal tract infections.35 No recommendations can be made with regard to treatment with combinations of antifungals, as data are not available.

Consideration should be given to determine *Candida* isolates from mucosal surfaces and non-sterile sites to the species level and perform susceptibility testing. Particularly, in paediatric patients at high risk for developing invasive *Candida* infections, as these results may guide early and targeted treatment if a *Candida* infection is suspected based on clinical signs and symptoms. Even more so in premature neonates where a high percentage of false-negative blood cultures for *Candida* species has been described.36

An additional reason to be informed about colonising *C. auris* isolates in intensive care settings is to prevent transmission and to instal proper infection prevention and control measures. Several countries including the UK have released guidance documents with recommendations regarding clinical policies, isolation
of patients, contact precautions and cleaning of equipment and clinical environments.5 21

SUMMARY

C. auris infections have emerged as an important challenge in the management of already vulnerable paediatric patients including premature neonates, infants and children admitted to ICUs and those with underlying malignancies. Proper identification is challenging with conventional methodologies failing. Great concern exists how to control this emerging new Candida species showing multidrug resistance and being very well capable to persist in hospital environments. The increased number of cases detected worldwide is causing a global concern and research is urgently needed. Current research is addressing the many unanswered questions related to the emergence of this Candida species, its molecular resistance and virulence mechanisms and improved management options to minimise its impact on patient outcomes.

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