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CONCISE ARTICLE

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Survey of neonatal candidiasis in Greece

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Abstract In order to estimate the extent of neonatal candidiasis in Greece and to identify trends in clinical management, the present study was conducted using a questionnaire directed to Greek neonatologists and pediatric infectious disease specialists. The respondents represented 15 hospitals in the country's seven largest cities, which are currently the only Greek cities with neonatal intensive care units. Based on the responses, the incidence of neonatal candidiasis was determined to be 1.87 and 1.94 cases per unit-year for the years 2001 and 2002, respectively. Although a shift toward the isolation of non-*Candida albicans* isolates was noted, *C. albicans* was still the predominant pathogenic species. Deoxycholate amphotericin B remains the most frequently used antifungal agent in neonatal units nationwide.

Introduction

Invasive infections due to *Candida* spp. have become a major cause of morbidity and mortality in neonates, especially those with a very low birth weight (<1,500 g) [1, 2]. Indeed, neonatal candidemia has been the most prevalent form of candidemia during recent years [3]. A previous study performed in the pediatric and neonatal departments of our hospital showed that neonatal candidiasis had a frequency of 1% compared to 0.1% for all other pediatric departments, including oncology ($p<0.01$) [4]. Other investigators have reported higher frequencies, ranging from 3.2 to 4.8% for very low birth weight and from 5.5 to 9.8% for extremely low birth weight (<1,000 g) neonates [5, 6]. However, little is known about the frequency of the problem in Greece and how Greek physicians manage these serious infections in the neonatal population. To estimate the extent of the problem and to identify trends in the clinical management of neonatal candidiasis in Greece, the study presented here was performed.

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Materials and methods

In October 2003, 137 questionnaires were mailed to the same number of neonatologists and to pediatric infectious disease specialists practicing in hospitals throughout Greece. The forms contained questions regarding the number of cases of neonatal candidiasis seen during the previous 2 years, the species of *Candida* most frequently isolated, and the antifungal treatment most frequently administered. Some of the questions required a yes/no response while others required participants to select one of the following responses: always, usually, occasionally, rarely, or never. There were also some multiple-choice questions concerning the management of candidemia and candiduria.

Additionally, the following three hypothetical cases involving infection of extremely low birth weight infants were presented and participants were asked for their opinion on proper management. Case 1: An infant with a birth weight (BW) of 750 g and an estimated gestational age (GA) of 26 weeks is now 3 weeks old. His umbilical artery catheter and umbilical venous catheter have been in place for 10 days, he has been given steroids to wean him from the ventilator, and he has been treated for coagulase-negative *Staphylococcus* bacteremia with vancomycin for 10 days through a percutaneously inserted central catheter that is still in place. Now he has respiratory decompensation and a blood culture is growing *C. albicans.* Case 2: An infant with a BW of 750 g and a GA of 26 weeks is now 3 weeks old. He has been receiving imipenem plus vancomycin for 10 days because of sepsis. Now he has

new clinical and laboratory signs of sepsis; blood and cerebrospinal fluid cultures have been taken. Case 3: An infant with a BW of 750 g and a GA of 26 weeks is now 3 weeks old. He was doing well but recently was evaluated for sepsis and was given antibiotics. His blood and cerebrospinal fluid cultures are negative, but urine obtained by suprapubic aspiration is growing 10^4 cfu/ml of *Candida albicans*.

The questionnaires were mailed along with pre-addressed and stamped return envelopes. All of the completed questionnaires received by 31 January 2004 were included in the study. Responses were entered into an Excel database (Microsoft Corporation, Redmond, WA, USA) and analyzed using the statistical program Instat (Graphpad, San Diego, CA, USA). A p-value of ≤ 0.05 indicated statistical significance.

Results and discussion

Of the 137 questionnaires mailed to neonatologists and pediatric infectious disease specialists, 52 were returned (i.e., 38% of those mailed). The respondents represented 15 hospitals, five of which were university hospitals located in the seven largest cities in the country (i.e., Athens, Thessaloniki, Patras, Heraklion, Alexandroupoli, Ioannina, Larisa), which were also the only cities with neonatal intensive care units (NICU).

Of the respondents, 76.9% had cared for neonate(s) with systemic candidiasis during the previous 2 years. Candidiasis accounted for an average of 1.87 cases per unit-year for 2001 and 1.94 cases per unit-year for 2002. Identification of *Candida* isolates to the species level at the local laboratory could be obtained by 90.4% of respondents. The species of *Candida* isolated affected the therapeutic decisions made by 62% of physicians. In cases of invasive fungal infection, *Candida albicans* was the most commonly isolated pathogen followed by *Candida parapsilosis*, *Candida tropicalis* and *Candida glabrata.*

Deoxycholate amphotericin B was the primary antifungal agent used by 71.2% of respondents. Liposomal amphotericin B and fluconazole were used as first- or second-line therapy by 51.9 and 3.8% of respondents, respectively.

For the three case studies presented in the questionnaire, cases 1 and 2 described two neonates with proven and suspected candidemia, respectively. A single blood culture positive for *Candida* spp. led 98.1% of physicians to initiate immediate treatment. Deoxycholate or liposomal amphotericin B was the preferred therapy for candidemia in 94.6% of cases. In cases of candidemia, 96.3% of physicians chose to remove the central venous catheter immediately and administer an antifungal drug. Responses to the question asking for the recommended length of therapy for the management of candidemia varied widely, but the mean duration provided was approximately 3 weeks (Table 1).

For cases of candiduria, 91.1% of physicians chose to administer either deoxycholate or liposomal amphotericin B, and 33.9% of physicians preferred to repeat the culture before deciding to administer an antifungal agent. Again, the physicians' recommendations for the length of therapy varied greatly. Nevertheless, the mean duration of treatment recommended for candiduria was shorter than that for candidemia (13.6±6.6 days vs. 20.5±7.7 days, $p<0.0001$; Table 1).

Table 1 Physicians' responses to questions regarding the management of candidemia and candiduria in neonates

Type of therapy	Candidemia	Candiduria
Preferred first-line therapy		
Deoxycholate amphotericin B	71.2%	64.3%
Liposomal amphotericin B	23.4%	26.8%
Fluconazole	5.4%	7.1%
Other[a]	0%	1.8%
Immediate treatment after a single positive culture		
Yes	98.1%	66.1%
No, repeat the culture before deciding to treat	1.9%	33.9%
Removal of central vascular catheter		
Yes	96.3%	NA
No	3.7%	NA
Duration of treatment in days (mean±SD)	20.5±7.7	13.6±6.6*

NA not applicable
[a]Itraconazole or flucytosine
*$p<0.0001$

Neonatal candidiasis has become an important problem in recent years due to its increasing incidence. Neonates, especially those born prematurely, have many unique features and risk factors that make consensus regarding management difficult [6]. Although *C. albicans* remains the predominant species isolated from cases of neonatal candidiasis, there has been a shift toward the isolation of non-*C. albicans* spp. in most centers during the last decade [2, 7]. We have found a similar trend among cases of neonatal candidiasis in Greece. Data collected at our NICU in Thessaloniki between the years 1994 and 2000 showed a similar shift from *C. albicans* predominance towards the increasing isolation of non-*albicans* spp., especially *C. parapsilosis*: specifically, the incidence of *C. albicans* was 65.5%, followed by *C. parapsilosis* with 15.5% and *C. tropicalis* with 7%, and the rate of *C. albicans* isolation decreased annually throughout the study period [8]. Factors contributing to this shift include the increasing use of central venous catheters as well as total parenteral nutrition. Exposure of maternal and healthcare workers to azoles may also play a decisive role in the changing pattern of *Candida* spp., as could the use of antifungal prophylaxis in some centers [9].

The responses to our survey of neonatal candidiasis in Greece elucidate several areas of consensus and contro-

versy among physicians caring for such patients. One important point of consensus is the near-unanimous decision to immediately start antifungal therapy once a blood culture reveals a *Candida* sp.; however, controversy was apparent regarding the appropriate duration of treatment. The majority of respondents indicated deoxycholate amphotericin B was their drug of choice for treating neonatal candidiasis. In addition, the great majority of physicians agreed that removal of a central venous catheter should be attempted as soon as candidemia is detected and antifungal therapy should be started immediately [9–11]. Of interest is that one-third of the respondents elect to confirm a positive urine culture before initiating antifungal therapy.

Immediate treatment after a first blood culture positive for *Candida* spp. is essential, since delayed treatment pending the results of repeat blood cultures in cases of candidemia has been reported to increase dissemination to end organs and to increase mortality [12, 13]. Similarly, one-third of fungal urinary tract infections in preterm infants may include abscess formation, so treatment in cases of candiduria should not be delayed pending the results of repeat cultures [14]. The issue of empirically prescribing an antifungal drug immediately after a blood culture is drawn was not raised in the questionnaire.

The development and broad use of other antifungal agents such as lipid formulations of amphotericin B, fluconazole and itraconazole has not altered this practice; however, new antifungal agents, including the echinocandins, have entered the armamentarium against fungal infections in neonates [15]. Deoxycholate amphotericin B was used by 71.2% of respondents against candidemia and by 64.3% against candiduria; these choices were followed by liposomal amphotericin B and fluconazole as first- or second-line therapy. In a previous study [16], deoxycholate amphotericin B was also reported as the treatment of choice, but fluconazole and liposomal amphotericin B were used to some extent as first- or second-line therapy by 90 and 69% of respondents, respectively. Considering those and our findings together, deoxycholate amphotericin B remains the most widely used agent for the treatment of neonatal candidiasis. Careful monitoring of renal function, blood counts, and electrolytes is required in order to avoid adverse effects with this treatment [17].

In conclusion, our study found the incidence of neonatal candidiasis in Greece in the years 2001 and 2002 to be 1.87 and 1.94 cases per unit-year, respectively. Although there was a shift towards the isolation of non-*Candida albicans* isolates during the period studied, *C. albicans* was still the predominant pathogenic species. Deoxycholate amphotericin B remains the agent of choice for treating neonatal candidiasis in Greece. In order to establish effective and safe preventive and therapeutic antifungal protocols for neonates, multicenter randomized clinical trials need to be conducted.

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