the time of infection. The extremely long period of neutropenia in some individuals can be explained by the refractory underlying malignancy. The clinical presentation in our patients was similar to that described in both children and adults, with skin, lung and blood as the main sites of infection.[4,7,10] Due to the limited data available in children, it is not surprising that pediatric-specific recommendations on the treatment of invasive fusariosis are mainly based on adult experiences.[1,6] Corroborating these recommendations, all patients in our study received voriconazole, given in most patients in combination with amphotericin B or an echinocandin. Unfortunately, no data on regular therapeutic drug monitoring of voriconazole were reported. A recent analysis demonstrated that there has been a 21% increase in survival rate of invasive fusariosis during the last decade, which was associated with a more frequent use of voriconazole or combination therapies, although European guidelines give only a weak recommendation for the use of combination therapy.[1,11] Posaconazole, recommended for salvage treatment of fusariosis (AII recommendation: moderate support of a recommendation for use, evidence from at least 1 well-designed clinical trial without randomization or from cohort studies), has not been used in our patient population, which may be due to the fact that the dosage of this compound is still unclear in patients younger than 12 years.[1] In addition to antifungal treatment, optimal management of patients with fusariosis may include surgical debridement of infected tissues (AIII recommendation: moderate support of a recommendation for use, evidence based on clinical experience) and reversal of the immunocompromised state (AII recommendation).[1] Notably, the role of granulocyte-colony stimulating factor (G-CSF) fluid and granulocyte transfusions in disseminated fusariosis is not well established, although the duration of neutropenia inversely correlated with survival.[1,4,12] In our case series, all 3 patients undergoing surgery survived, whereas out of the 7 patients receiving G-CSF fluid and/or granulocyte transfusions, 4 died (2 patients due to progression of malignancy, 1 patient each due to fusariosis and sepsis, respectively).

Response assessment on day 14 did not predict overall outcome. One of 3 patients with partial response on day 14 died due to fusariosis, whereas 1 out of 3 children with deterioration at that time survived. Out of the 4 patients with stable disease on day 14, 2 died (1 each due to then fungal infection and progression of leukemia, respectively). The overall survival of 50% was similar to both a literature review in children and larger case series in adults.[2–5,7]

Although the retrospective collection of uncontrolled data is a clear limitation of our analysis, this is to the best of our knowledge one of the largest series of children with disseminated fusariosis reported to date, which adds direct pediatric-specific evidence on how to manage this opportunistic infection.

REFERENCES

1. Tortorano AM, Richardson M, Roilides E, et al.; European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group; European Confederation of Medical Mycology. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: Fusarium spp., Scedosporium spp. and others. *Clin Microbiol Infect*. 2014;20(suppl 3):27–46.
2. Muhammed M, Anagnostou T, Desalermos A, et al. Fusarium infection: report of 26 cases and review of 97 cases from the literature. *Medicine (Baltimore)*. 2013;92:305–316.
3. Lortholary O, Obenga G, Biswas P, et al.; French Mycoses Study Group. International retrospective analysis of 73 cases of invasive fusariosis treated with voriconazole. *Antimicrob Agents Chemother*. 2010;54:4446–4450.
4. Campo M, Lewis RE, Kontoyiannis DP. Invasive fusariosis in patients with hematologic malignancies at a cancer center: 1998-2009. *J Infect*. 2010;60:331–337.
5. Horn DL, Freifeld AG, Schuster MG, et al. Treatment and outcomes of invasive fusariosis: review of 65 cases from the PATH Alliance(®) registry. *Mycoses*. 2014;57:652–658.
6. Groll AH, Castagnola E, Cesaro S, et al. Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or allogeneic haemopoietic stem-cell transplantation. *Lancet Oncol*. 2014;15:e327–e340.
7. Schwartz KL, Sheffield H, Richardson SE, et al. Invasive fusariosis: a single pediatric center 15-year experience. *J Pediatric Infect Dis Soc*. 2015;4:163–170.
8. Marty FM, Ostrosky-Zeichner L, Cornely OA, et al.; VITAL and FungiScope Mucormycosis Investigators. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. *Lancet Infect Dis*. 2016;16:828–837.
9. Tezcan G, Ozhak-Baysan B, Alastruey-Izquierdo A, et al. Disseminated fusariosis caused by Fusarium verticillioides in an acute lymphoblastic leukemia patient after allogeneic hematopoietic stem cell transplantation. *J Clin Microbiol*. 2009;47:278–281.
10. Litvinov N, da Silva MT, van der Heijden IM, et al. An outbreak of invasive fusariosis in a children's cancer hospital. *Clin Microbiol Infect*. 2015;21:268.e1–268.e7.
11. Nucci M, Marr KA, Vehreschild MJ, et al. Improvement in the outcome of invasive fusariosis in the last decade. *Clin Microbiol Infect*. 2014;20:580–585.
12. Kadri SS, Remy KE, Strich JR, et al. Role of granulocyte transfusions in invasive fusariosis: systematic review and single-center experience. *Transfusion*. 2015;55:2076–2085.

THE FIRST INFANT DEATH ASSOCIATED WITH HUMAN CORONAVIRUS NL63 INFECTION

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Abstract: Human coronavirus NL63 (HCoV-NL63) primarily infects the upper respiratory tract. However, it may cause severe lower respiratory tract infection, and the clinical course may be severe in immunocompromised patients. To our knowledge, child death due to HCoV-NL63 has not been reported. We present a fatal lower respiratory tract disease associated with HCoV-NL63 in a 7-month-old malnourished infant.

Key Words: death, fatal, human corona virus NL63, infant, lower respiratory tract infections

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Lower respiratory tract infection (LRTI) is an important cause of morbidity and mortality, especially among young children. It is estimated that 25–33% of deaths observed in children younger than 5 years of age are caused by acute respiratory infections and their complications.[1] In 80–90% of LRTI, the main agents are respiratory viruses.

Coronaviruses are enveloped viruses with a large plus-strand RNA genome. To date, 6 coronaviruses (HCoV-229E, HCoV-OC43, SARS-CoV, HCoV-NL63, HCoV-HKU-1 and MERS-CoV) that

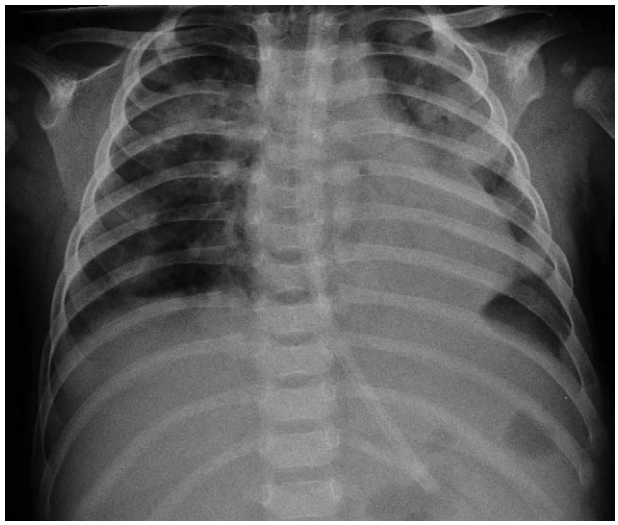

FIGURE 1. Bilateral widespread pulmonary infiltrates on second chest radiograph.

infect humans have been identified, 4 of which (HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU-1) circulate continuously in the human population. HCoV-NL63 was first isolated from the aspirate of a 7-month-old baby in early 2004.[2] Generally, HCoV-NL63 primarily infects the upper respiratory tract, typically causing mild upper respiratory infectious symptoms such as cough, rhinorrhea and fever. But the clinical course of HCoV-NL63 infection can be more serious in some risk groups. A study reported that an elderly Canadian patient infected with HCoV-NL63 died 5 days after the onset of disease.[3] Another study reported a fatal lower respiratory tract disease with HCoV-NL63 in an adult hematopoietic cell transplant recipient.[4] To our knowledge, child death associated with HCoV-NL63 has not been reported. Here, we present a fatal lower respiratory tract disease associated with HCoV-NL63 in a 7-month-old baby for the first time.

CASE REPORT

A 7-month-old boy [weight: 5.4 kg (<–2 standard deviations) and height: 58 cm (<–2 standard deviations)] was admitted to another emergency department with a 2-day history of lack of appetite, dyspnea and cyanosis. He was hospitalized. Laboratory investigations revealed hypernatremia (Na: 151 mEq/L), lymphocytosis (white blood cell: 35,000/μL with 65.7% lymphocytes) and decompensated acute metabolic acidosis. Bilateral pneumonic infiltrates were detected on chest radiographs. Intravenous fluids, antibiotics, oxygen inhalation and nebulized salbutamol were started. Respiratory distress of the patient worsened within a few hours, and he developed cardiopulmonary arrest. After 15 minutes of cardiopulmonary resuscitation, he was intubated and transferred to our pediatric intensive care unit.

He was admitted to our pediatric intensive care unit 2 hours after cardiopulmonary arrest. On the physical examination, he had cheilitis, brittle hair, thin and soft nail plates and pallor. He did not breathe spontaneously, was bradycardiac (70/min), and blood pressure could not be measured. The patient was connected to the mechanical ventilator. Dopamine, dobutamine and epinephrine infusions were started for refractory hypotension in addition to repeated 0.9% NaCl boluses, and blood pressure returned to normal levels. The first chest radiograph revealed bilateral linear pneumonic infiltration (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/C579). Laboratory investigations revealed hypernatremia (Na: 148 mEq/L), lymphocytosis (white blood cell: 30 K/uL with 55.6% lymphocytes), hypertransaminasemia (aspartate aminotransferase: 4202 U/L and alanine aminotransferase: 3056 U/L) and severe decompensated acute metabolic acidosis (pH: 6.8; PCO_2: 28.7 mm Hg; HCO_3: 5.9 mmol/L).

Bicarbonate administration by constant infusion was administered. Ampicillin-sulbactam, clarithromycin and oseltamivir were started as empiric antibacterial and antiviral coverage. After 12 hours, a significant increase was observed in the infiltrates on the chest radiograph (Fig. 1). The patient was diagnosed with acute respiratory distress syndrome. We applied lung-protective mechanical ventilator strategies to our patient for acute respiratory distress syndrome. These included gentler ventilation using lower tidal volumes, limiting the inspiratory and plateau pressures, and in that process, achieving permissible levels of hypercapnia.[5]

Blood, urine and respiratory tract samples taken at admission and were sent to our hospital microbiology laboratory for examination. Because extensive virologic examination cannot be performed in our laboratory, we also sent respiratory tract samples to the Virology Reference Central Laboratory, Public Health Agency of Turkey. Nasopharyngeal and throat swabs were sent to the laboratory in virus transport medium (Virocult, Medical Wire & Equipment, Corsham, UK); bronchoalveolar lavage and transtracheal aspirate samples were sent in a sterile cap. In the virology laboratory, RNA extraction were performed using Qiagen EZ1Virus Mini Kit v2.0 (Qiagen, Hilden, Germany) according to manufacturer's instructions. Then multiplex real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test performed with Fast Track Diagnostics/Respiratory Pathogens 21 (Fast-track Diagnostics, Luxemburg) kit that detects respiratory pathogens. HCoV-NL63 was detected in all samples that were sent to Virology Reference Central Laboratory.

Despite supportive treatment, the patient had a second cardiac arrest in the 26th hour of hospitalization. Cardiopulmonary resuscitation was performed for 30 minutes, but was unsuccessful.

DISCUSSION

The human coronavirus NL63 was discovered in 2004 by Dutch virologists.[2] HCoV-NL63 mostly causes mild upper respiratory infectious symptoms. However, it can lead to severe LRTIs. We present a fatal LRTI associated with HCoV-NL63 in a 7-month-old malnourished infant.

Because most nutrients in the diet are essential for maintaining the function of immune cells, malnutrition is the main cause of immunodeficiency worldwide. Several studies have reported that in malnourished patients, common immune defects include an imbalance in the ratio of CD4/CD8+ T cells, low expression levels of CD69 on lymphocytes, biased T helper cell responses and reduced antibody responses.[6,7] We believe that malnutrition altered the patient's immune response and led to severe disease. The thymus was not present in radiographs. We could not perform basic immune work-up including lymphocyte subsets and serum immunoglobulin value because of insufficient time and poor clinical condition.

RT-PCR, enzyme-linked immunosorbent assays and real-time PCR are diagnostic tests for respiratory tract viruses.[8–10] We performed the real-time RT-PCR assays for detecting respiratory tract viruses, and HCoV-NL63 detected in all samples.

Our patient initially presented with upper respiratory prodrome, which progressed to pneumonia and respiratory failure. Initial blood tests and radiologic evaluation were compatible with a acute respiratory virus illness. Based on clinical features and the detection of HCoV-NL63 in respiratory tract samples taken on admission and the absence of any bacterial or fungal agents, the respiratory disease in our patient was considered HCoV-NL63-associated LRTI. In

conclusion, HCoV-NL63 may be fatal in children with immunodeficiency conditions such as malnutrition.

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REFERENCES

1. World Health Organization. *Programme for the Control of Acute Respiratory Infections: Fifth Programme Report 1990–1991*. Geneva: World Health Organization; 1992.
2. van der Hoek L, Pyrc K, Jebbink MF, et al. Identification of a new human coronavirus. *Nat Med*. 2004;10:368–373.
3. Bastien N, Anderson K, Hart L, et al. Human coronavirus NL63 infection in Canada. *J Infect Dis*. 2005;191:503–506.
4. Oosterhof L, Christensen CB, Sengeløv H. Fatal lower respiratory tract disease with human corona virus NL63 in an adult haematopoietic cell transplant recipient. *Bone Marrow Transplant*. 2010;45:1115–1116.
5. Jahagirdar A, Prayag S. Low tidal volume ventilation in acute respiratory distress syndrome. *Indian J Crit Care Med*. 2005;9:189–194.
6. Nájera O, González C, Toledo G, et al. CD45RA and CD45RO isoforms in infected malnourished and infected well-nourished children. *Clin Exp Immunol*. 2001;126:461–465.
7. Rodríguez L, González C, Flores L, et al. Assessment by flow cytometry of cytokine production in malnourished children. *Clin Diagn Lab Immunol*. 2005;12:502–507.
8. Liolios L, Jenney A, Spelman D, et al. Comparison of a multiplex reverse transcription-PCR-enzyme hybridization assay with conventional viral culture and immunofluorescence techniques for the detection of seven viral respiratory pathogens. *J Clin Microbiol*. 2001;39:2779–2783.
9. Dijkman R, Jebbink MF, El Idrissi NB, et al. Human coronavirus NL63 and 229E seroconversion in children. *J Clin Microbiol*. 2008;46:2368–2373.
10. Gaunt ER, Hardie A, Claas EC, et al. Epidemiology and clinical presentations of the four human coronaviruses 229E, HKU1, NL63, and OC43 detected over 3 years using a novel multiplex real-time PCR method. *J Clin Microbiol*. 2010;48:2940–2947.

TAUROLIDINE IN PEDIATRIC HOME PARENTERAL NUTRITION PATIENTS

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Abstract: To reduce the incidence of catheter-related bloodstream infections in home parenteral nutrition patients, the use of taurolidine was introduced in the Sophia Children's Hospital in 2011. This introduction led to a reduction in catheter-related bloodstream infections: 12.7/1000 catheter days before the use of taurolidine, compared with 4.3/1000 catheter days afterwards (n = 7) [relative risk = 0.36, 95% confidence interval: 0.20–0.65 (P = 0.018)].

Key Words: taurolidine, catheter, infection, parenteral nutrition, children

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Home parenteral nutrition (HPN) is started in our tertiary care children's hospital in around 5 to 10 pediatric patients each year, because of intestinal failure (IF) due to different causes such as necrotizing enterocolitis.[1] One of the main complications of parenteral nutrition (PN) is catheter-related bloodstream infection (CRBSI).[2]

The treatment of a CRBSI includes hospitalization and intravenous antibiotics. If clinical improvement is not seen, the ultimate measure may need to be the removal of the central venous catheter (CVC). Given the fact that PN treatment can be a lifesaving treatment in patients with IF, preservation of the catheter by preventing CRBSI is of major importance.[3]

Only one retrospective study has described the positive effect of taurolidine lock on the incidence of CRBSI on 19 pediatric HPN patients. This study reported a significant reduction (P = 0.002) in CRBSI from 8.6 CRBSI to 1.1 CRBSI per 1000 catheter days.[4]

Taurolidine appears to be an antimicrobial agent which mode of action seems to be different from other antimicrobial agents. Its methylol derivatives irreversibly bind to cell walls of bacteria and fungi, resulting in the prevention of microbial adherence.[5,6] Bacterial resistance to taurolidine has not been reported in literature.[7]

In an effort to reduce the incidence of CRBSI in our HPN patients, the use of taurolidine lock was introduced in the Sophia Children's Hospital in 2011. Because the causes of CRBSI are known to be multifactorial,[2] we assessed the effect of taurolidine lock on CRBSI in our population of HPN patients, and determined whether this intervention had the expected reduction in CRBSI.

In this retrospective study, we evaluated the effect of taurolidine on the incidence of CRBSI in our pediatric HPN patients.

MATERIALS AND METHODS

Patients with IF at Sophia Children's Hospital who required PN between the 1st of September 2008 and the 31st of December 2012 were included. Data were retrieved from the electronic patient records. The Medical Ethics Committee has waived the need for informed consent.

All patients were treated by the multidisciplinary IF team comprising a pediatric gastroenterologist, pediatric surgeon, dietician, microbiologist and nurse practitioner.

Taurolidine (Taurosept 2%, Geistlich Pharma, Wolhusen, Switzerland) was started as soon as PN was administered for less than 23.5 hours/d. Before introduction of taurolidine, a lock solution of heparin (100 U/mL) was used during periods when the HPN was not administered.

Data on CRBSI were collected by reviewing all blood cultures and patient records. A CRBSI was defined as positive CVC blood culture or a positive peripheral blood culture, and clinical infectious signs such as fever of 38°C or higher, and initiation of intravenous antibiotics. If a second positive CVC blood culture was found, it was defined as a new infection if it was caused by a different microorganism or if it was cultured at least 7 days after completion of the antibiotic treatment. Multiflora was defined as a mix of at least 2 microorganisms from at least 2 different classes of microorganisms.

For analysis, patients were divided into 3 groups.

Group 1: patients who started on PN treatment without taurolidine and subsequently started with taurolidine lock. In this crossover group, patients were used as their own control.

Group 2: patients who never received a taurolidine lock during their PN.