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Nosocomial legionellosis and invasive aspergillosis in a child with T-lymphoblastic leukemia

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ABSTRACT

Invasive aspergillosis of the lungs and the central nervous system and Legionella pneumophilia serotype 1 infection of the lungs were diagnosed in a 22-month old child during inpatient induction treatment for T-lymphoblastic leukemia. Environmental investigations i.e. samples from the hospital water system did not reveal any Legionella. The patient may have been exposed to waterborne pathogens despite terminal water filtration due to a technical device to release residual tap water from the hose after showering. A sodium chloride nose spray was found to be contaminated with the *A. fumigatus* isolate of the patient.

1. Introduction

Intensive induction chemotherapy for acute lymphoblastic leukemia increases the risk of infection, including rare opportunistic pathogens such as *Aspergillus fumigatus* or *Legionella pneumophila.* A well-known risk factor for both infections is the suppression of cellular immunity (in case of invasive Aspergillosis prolonged quantitative and qualitative impairments of granulocytes). We report the clinical course of a pediatric cancer patient, who developed nosocomial pulmonary Legionellosis and invasive Aspergillosis after a prolonged period of severe leukopenia and lymphopenia while receiving high-dose dexamethasone during induction treatment of acute T-lymphoblastic leukemia. In addition, this article describes and discussed the hospital hygiene investigation and infection control intervention triggered by this case.

1.1. Microbiological methods

Legionella spp. in water samples were detected according to the protocol DIN EN ISO 11731-2. Briefly, 250 ml was taken from the shower, the water pipe or the patient care products (only 50 ml). 100 ml of water or 50 ml of patient care products were filtered using a 0.2 μm membrane filter (PALL medical, Dreieich Germany). Filters were incubated on GVPC agar (Becton, Dickenson and Company, Heidelberg, Germany). Moreover, 1 ml was pipetted directly onto GVPC agar. Both samples were incubated for 10 days at 36 ± 2 °C. Plates were read on day 3, 5 and 7. Bacteria were isolated and subcultivated on BCYE agar without cysteine (Becton & Dickenson, Heidelberg, Germany). Colonies were identified employing mass spectrometry by MALDI-TOF® (BRUCKER, Germany).

Clinical samples were directly plated onto a GVPC agar and handled in the same way as water samples. The detection of *Legionella pneumophila* serotype 1 antigen was performed in fresh urine sample with an immunofluorescence-based assay using lateral-flow technology (Sofia™ Legionella FIA, Quiedel, San Diego, USA).

To detect molds or yeast patient material was inoculated on Sabouraud Glucose Agar with Gentamicin and Chloramphenicol (Oxoid, Germany) for 14 days at 35 ± 2 °C. Plates were read twice a week. MALDI-TOF was used for identification.

Aspergillus galactomannan Antigen Index was determined in Serum (Lehrnbecher et al., 2016), bronchoalveolar fluid (Maertens et al., 2009) and in cerebrospinal fluid (Soeffker et al., 2013) using an Aspergillus Antigen Elisa (Platelia™, bio-rad, Marnes-La-Coquette). An index above 0.5 was interpreted as possible sign for invasive Aspergillosis.

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The German national reference laboratory for legionella compared the legionella isolate found in specimen derived from the patients and the legionella isolate found in the water pipe using monoclonal antibodies. The German national reference laboratory for aspergillus compared the aspergillus isolates found in the child and in the nose spray using sequencing of the beta-tubulin gene.

1.2. Medical history and clinical course

A 22 months-old male toddler was admitted to our pediatric oncology center after a one-week history of fever and lymphadenitis. On admission, he showed no clinical signs of lower respiratory tract infection. On admission, the patient showed pallor, enlarged palpable lymph nodes and no signs of bleeding despite thrombocytopenia. The leukocyte count was elevated at 35.5×10^9/L. Microscopic examination of a peripheral blood smear showed 81% blasts (L1-morphology). A chest radiograph depicted a mediastinal mass (mediastinal tumor) but no signs of interstitial or alveolar infection. Bone marrow aspiration confirmed the diagnosis of acute T-lymphoblastic leukemia. Referring to the AIEOP-BFM-ALL 2009 protocol of the German Society of Pediatric Oncology and Hematology treatment for T-ALL in children comprises a prednisone pre-phase followed by dexamethasone (10 mg/m^2 BSA for 21 days), then tapering, combined with vincristine, daunorubicin, pegylated asparaginase and intrathecal methotrexate. Fig. 1 shows the time course of leukocytes and neutrophils during induction treatment, which started of day 3 of his first hospitalization.

Due to febrile neutropenia, the patient was treated with cefuroxime and later with piperacillin-tazobactam until day 6 of induction (day 8 of hospitalization); fever timely resolved under this treatment. His leukocyte count remained $<1.0 \times 10^9$/L until day 27 of induction. The patient received *P. jirovecii* prophylaxis (cotrimoxazole 30 mg/kg/d once a week) but no antifungal prophylaxis. Fluconazol was administered from day 13 to day 19 of induction treatment for oral candidiasis and clinical suspicion of candida laryngitis (hoarseness, voiceless crying) and later from day 27–33 of induction treatment empirically during febrile neutropenia. A laryngoscopy assessment on day 36 of induction treatment revealed only a mild inflammation; a pharyngeal swab yielded positive rt-PCR results for coronavirus NL63 and parainfluenza virus Type 3. The patient was discharged after 39 days of hospitalization in good clinical condition without fever or other relevant signs of infection after a bone marrow examination had shown first remission of the underlying T-ALL.

One day later, the patient was readmitted to the hospital with tachypnea, high fever, tachycardia, cough, low blood pressure and reduced oxygen saturation. Chest-radiograph revealed diffuse, fine-nodular pulmonary transparency-reduction with a marked opacification of the right lower lobe. The neutrophil count was 0.3×10^9/L. Broad spectrum antimicrobial treatment with meropenem, gentamicin and teicoplanin was started immediately for treatment of pneumonia and suspected sepsis. Bronchoalveolar lavage (BAL) was performed on the following day showing mucosal inflammation and pus predominantly in the right lower airways. Microbiologic investigations of the BAL fluid revealed two main pathogens: *Legionella pneumophila* serotype 1 and *Aspergillus fumigatus*. *Legionella pneumophila* serotype 1 antigen was detected in a fresh urine sample. Serum Aspergillus Antigen Elisa showed an elevated index (Table 1).

The attending physicians modified anti-infective treatment to target both pathogens with

- levofloxacin (20 mg/kg and day in 2 single doses IV for 21 days followed by azithromycin 10 mg/kg per day for 5 days, then 10 mg/kg/day two times a week for 6 weeks);
- Liposomal amphotericin B (4 mg/kg/day).

Table 1
Platelia® Aspergillus-Antigen index[b] (elevated values in bold letters).

Day of treatment[a]	Serum	Bronchoalveolar lavage	Cerebrospinal fluid
38	0.71		
42		0.42	
48	1.37		
51		0.29	
75	**0.61**		
76			**1.16**
110	0.36		

[a] Referring to the start of induction chemotherapy.
[b] An index >0.5 is elevated and increases the probability of invasive Aspergillosis.

This treatment regimen did not result in adverse effects except hypokalemia necessitating parenteral potassium supplementation. The patient recovered clinically after a second BAL (still positive in culture for *Legionella pneumophila*) but CT assessment of his thorax confirmed severe pneumonia of the right lower and middle lobe (Fig. 2).

One month after readmission during systemic antifungal treatment (at this time liposomal Amphotericin B 2.5 mg/kg per day), a left sided hemiparesis became apparent, which prompted a cerebral MRI assessment. The MRI revealed at least 4 intracerebral abscesses and signs of increased intracranial pressure (Fig. 3). The abscesses were managed by neurosurgery with postoperative external ventricular drains. Aspergillus Antigen Elisa was elevated in cerebrospinal fluid (CSF) obtained during surgery (Table 1). In a biopsy of the CNS abscess wall *A. fumigatus* was identified; however, no *A. fumigatus* grew in culture from tissue or CSF. Since recent guidelines have recommended voriconazole as first choice antifungal in CNS aspergillosis, antifungal treatment was switched to voriconazole (IV; 2×9 mg/kg on day one, followed by 2×8 mg/kg daily). On day 5 of voriconazole treatment, the patient developed acute pancreatitis with vomiting and severe abdominal pain. In addition, no therapeutic voriconazole levels could be detected in the patient's plasma or CSF. Since a liposomal preparation potentially aggravates pancreatitis, we administered caspofungin (50 mg/m^2 BSA/day) instead of voriconazole, until the elevated pancreas enzymes returned to normal and the impaired clinical condition of the patient improved again. Because therapeutic efficacy of caspofungin in invasive CNS aspergillosis is uncertain, antifungal treatment was continued with high dose of liposomal amphotericin B (8 mg/kg/days as a 3-h infusion for 28 days followed by 5 mg/kg/day as a 2-h infusion for 28 days, then 2.5 mg/kg/d 2 times a week as secondary prophylaxis). A subduroperitonal shunt had to be implanted to manage hydrocephalus malresorptivus and subdural hygroma, after neither MRI reexamination nor microbiological assessment of the CSF revealed residual fungal or bacterial CNS disease. The hemiparesis of the patient slowly improved and the attending pediatric oncologists decided to continue chemotherapy with a modified, less intensive regimen. The subduro-peritoneal Shunt was removed after two control MRI examinations. Sixteen months after this eventful induction therapy the patient is still in first remission of his T-ALL receiving maintenance treatment as an outpatient. Clinically he has no pulmonary symptoms and his hemiparesis resolved completely. His psychocognitive performance is according to his age.

1.3. Hospital hygiene/Infection control investigations

During the incubation period of the Legionellosis the patient was hospitalized for a total of 39 days; he left the hospital only twice for less than 2 h during induction treatment but remained on the

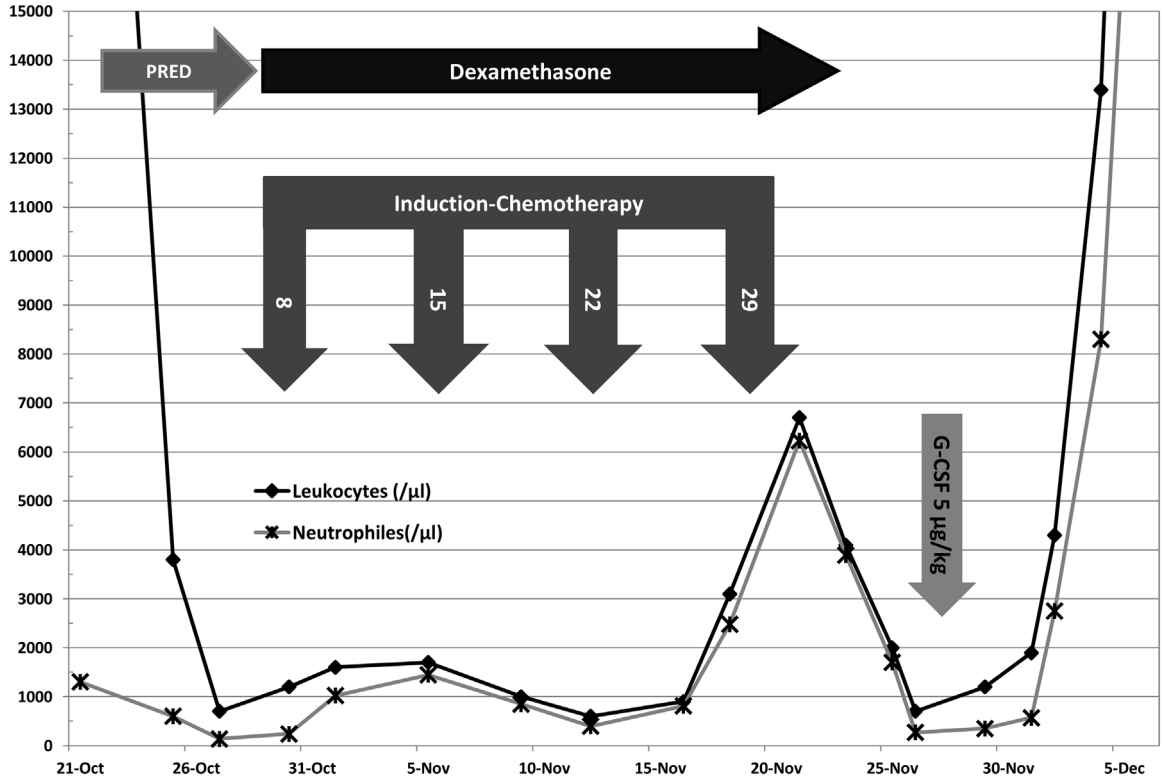

Fig. 1. Treatment schedule and time course of leukocyte counts.

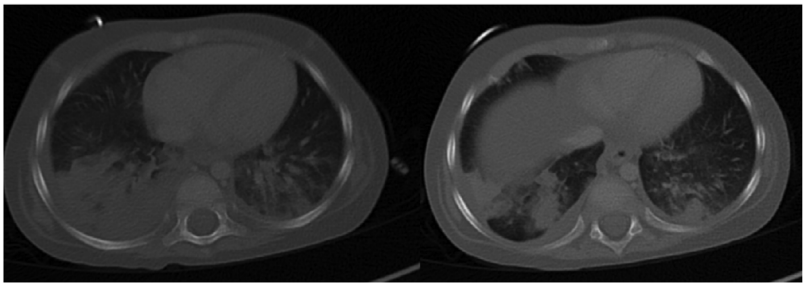

Fig. 2. Chest CT-scan on day 38 of induction treatment.

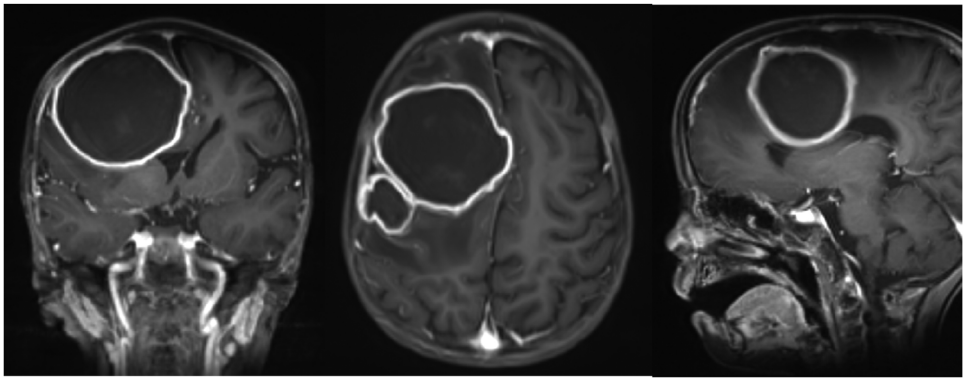

Fig. 3. Cranial MRI Scan on day 80 of induction treatment.

campus of the University Hospital. Immediately after the confirmation of this case of Legionnaires' disease, the result was notified to the hospital hygiene and infection control department. To prevent an outbreak involving other immunocompromised patients of the pediatric oncology unit, environmental investigations have to be initiated to identify or exclude an environmental source of the infection (Cunha et al., 2016)

The room air in the department of pediatric oncology is filtrated (H13) and all water outlets in patient rooms (including shower tops) are equipped with terminal 0.2 µm filters (disposable

tap filters; Aquasafe filter AQ31F1S, PALL Corporation; Dreieich, Germany). In addition the water is supplemented with chlorine dioxid (0.2–0.3 mg/l). Six months before the patient was admitted, *Legionella* spp. had been detected in the hospital warm water supply system. Twice a year the hospital water system is examined for the presence of *Legionella* spp. After the diagnosis of nosocomial Legionellosis, 20 samples from water pipes of all rooms the child possibly had used were reevaluated with standard methods but no growth of *Legionella* spp. was detected. However, the isolate of the last positive detection (6 months previously; 6 colony forming units in 100 ml, detected in a water outlet of a bathroom in a different part of the same building) had been stored and was available for comparison with the patient' isolate (typing performed by the National Reference Center for Legionellosis, Dresden, Germany). The patient harbored a *L. pneumophila* serogroup 1 type Allentown/France whereas the previous isolate from the water pipe was serogroup 1 too but belonged to a different type (Bellingham).

Even with terminal 0.2 μm filters in use on the pediatric oncology ward, the environmental investigation revealed that the patient might have had contact with unfiltered water. The hoses of all showers on the ward were connected to a device, which released residual water after each use to the shower basin to avoid abundant bacterial growth in a "standing water column". These devices had been put into place before the unit decided to use terminal water filtration to protect the patients from waterborne pathogens. The patient repeatedly sat on a towel on the floor of the bathroom while his mother was taking a shower (Fig. 4). The hose emptying devices were removed; in addition to the release of unfiltered water, they may have had a negative impact on the integrity of the water filter membrane due to desiccation. Swabs were taken from the shower basin and the floor of the bathroom, which yielded growth of coagulase-negative staphylococci and *Pseudomonas* spp. (not *P. aeruginosa*). No *Legionella* spp. could be cultivated. All cooling systems (Mercante and Winchell, 2015), were shut down at the time the Legionellosis was detected in the child. Nevertheless, cooling systems were re-tested in 2016 but no *Legionella* spp. was found.

In addition to the water outlets different patient care products were analyzed but similarly revealed no *Legionella* spp. However, in a 0.9% sodium chloride nose spray used by the patient *Aspergillus fumigatus* was found. The two *Aspergillus fumigatus* isolates (of the patient and the nose spray) were identical confirmed by the National Reference Laboratory in Jena, Germany (partial sequencing of the ß-tubulin gene; *Aspergillus fumigatus* var. *ellipticus*).

2. Discussion

Our patient developed his infection after a prolonged period of severe leukopenia and lymphopenia (Fig. 1) while receiving high-dose dexamethasone during induction treatment of T-ALL. In contrast to the standard ALL treatment with prednisolone, the dexamethasone-based induction in children with T-ALL (PGR) is associated with an increased risk of adverse events (Teuffel et al., 2011). We did not perform a bronchoalveolar lavage on admission, since the patient showed no sign of respiratory infection and this procedure would have been associated with a high risk of life-threatening complications in a toddler with a large mediastinal tumor. In this regard, the patient might have been colonized with *Aspergillus fumigatus* before entering the clinic. The fever of the patient (on admission) responded well to cefuroxim and piperacillin-tazobactam, two antimicrobial agents without activity against *Legionella* spp. (Pedro-Botet and Yu, 2009).

Legionellosis is an extremely rare complication of cancer treatment in childhood (Gutzeit et al., 1987). In the AIOP BFM ALL 2009 population, comprising prospectively documented data from at about 5000 patients until Feb. 2016, no other case of Legionellosis has been reported (pers. communication with Dr. J. Alten, AIEOP-BFM ALL 2009 Study Coordination Center, Kiel, Germany). De Castillo et al. (del Castillo et al., 2016) observed a series of 40 patients during 15 years and stated, that *Legionella* spp. should be considered in the differential diagnosis of nodular lung lesions in immunocompromised patients, especially those with hematologic malignancies. They depicted CT scans of a 17 year old male with pulmonary Legionellosis showing a right middle lobe nodule with central cavitation and a *surround ground glass halo* which is considered to indicate invasive fungal infection in severely immunocompromised patients (Patterson et al., 2016).

In our case the environmental investigation focused on water outlets since Legionnaires' disease is primarily acquired by the inhalation of contaminated aerosols or by microaspiration of contaminated water (Cunha et al., 2016; Mercante and Winchell, 2015). In 2010, the German Commission of Hospital Hygiene and Infection Prevention has recommended the use of terminal tap water filtration to prevent exposure in immunocompromised hospitalized patients if other methods cannot ensure that the water is free of opportunistic pathogens (Kommission für Krankenhaushygiene und Infektionsprävention beim Robert Koch-Institut, 2010). All water taps in our pediatric oncology unit have been equipped with terminal water filters. However, the already existing water hose emptying devices may have exposed the patient to the pathogen, while he was sitting on the bathroom floor on a towel after his mother took a shower (Fig. 4). This possible environmental source could not be confirmed, since no sample yielded the growth of *Legionella* spp. In this regard, we could not determine the origin of our patient's infection, despite that he had been hospitalized continuously for 39 days before the onset of symptoms (the regular incubation period of legionellosis is 2–10 days).

There is no standard treatment defined for pulmonary Legionellosis in pediatric cancer patients receiving intensive chemotherapy (Pedro-Botet and Yu, 2009). The treatment regimen relied on retrospective cohort studies, which suggested levofloxacin and/or azithromycin as the first line treatment in pulmonary Legionellosis (Garcia-Vidal et al., 2017; Nagel et al., 2014). We decided to combine these two agents (after informed consent of the parents) and to administer azithromycin over a prolonged duration after the second BAL (after 7 days of IV levofloxacin) still revealed growth of *Legionella pneumophila*. In addition, our treatment schedule concerned the urgent need for continuation of anticancer chemotherapy. Radiologic follow-up investigations (including CT scans) are difficult to interpret in terms of cure, in particular in a patient with concomitant invasive Aspergillosis of the lung.

Antifungal treatment with liposomal amphotericin B was started with 3 mg/kg/day and continued with 4–5 mg/kg/days for 3 weeks. Then, liposomal amphotericin B maintenance treatment was administered with 2.5 mg/kg/day. Obviously, this daily dose was not capable to prevent (or treat) central nervous system Aspergillosis in our patient. The fourth ECIL-Guideline published in 2014 (Groll et al., 2014) recommends liposomal amphotericin B at a dose of 3 mg/kg/day, and states, that higher doses may be considered.

Our case adds further evidence to the argument, that cerebral MRT should be routinely performed in all pediatric cancer patients with invasive Aspergillosis of the lung (Broenen et al., 2014). CNS Aspergillosis in pediatric leukemia patients is a severe life threatening complication with high mortality despite neurosurgical and antifungal treatment (Broenen et al., 2014; Groll et al., 2013). According to the clinical judgement of the attending pediatric oncologists, the antifungal drug of first choice, voriconazole, caused acute pancreatitis in our patient. We cannot exclude, that the pancreatitis was an adverse event of PEG-asparaginase chemotherapy, but pancreatitis appeared during treatment with

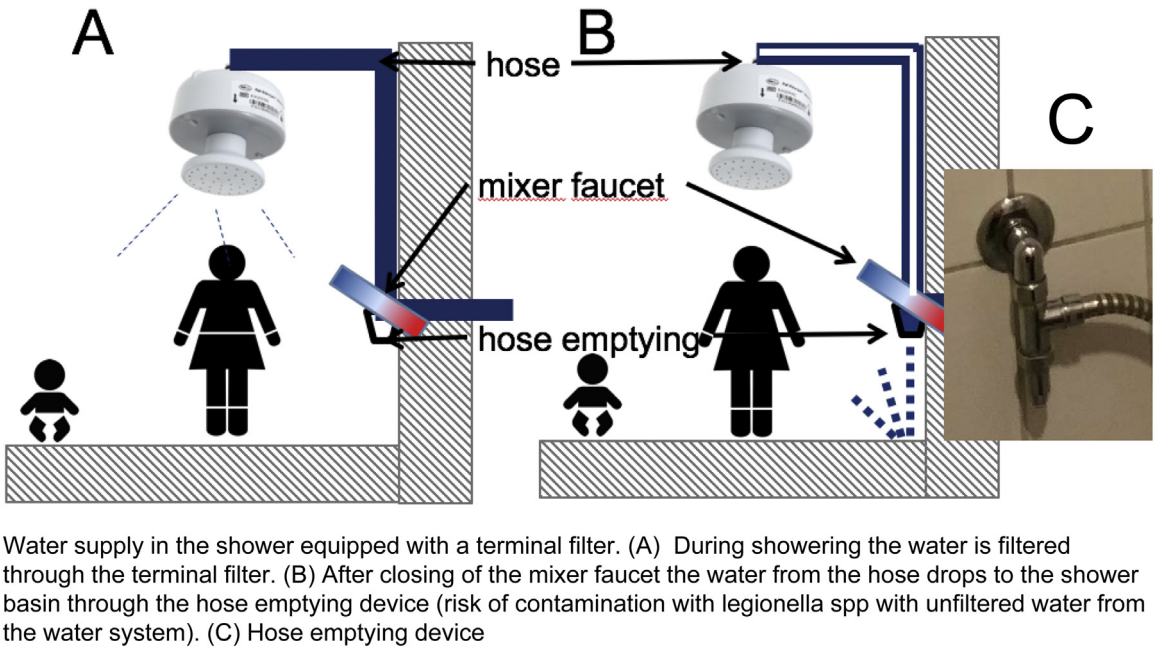

Fig. 4. Suspected mechanism of exposure.
Water supply in the shower equipped with a terminal filter. (A) During showering the water is filtered through the terminal filter. (B) After closing of the mixer faucet the water from the hose drops to the shower basin through the hose emptying device (risk of contamination with *Legionella* spp. with unfiltered water from the water system). (C) Hose emptying device.

voriconazole and disappeared after stopping voriconazole treatment. The recommended voriconazole dose in this age group did not result in sufficient plasma and CSF levels. The pharmacokinetics of voriconazole is highly variable in patients of this age group (Zembles et al., 2016). Fortunately, the combination of neurosurgical interventions, caspofungin and prolonged treatment with high dose liposomal amphotericin B led to disease control and eventually cure despite ongoing anticancer treatment.

3. Conclusions

Although extraordinary rare, Legionellosis has to be confirmed or excluded in pediatric leukemia patients with fever and pneumonia after prolonged leukopenia and high dose corticosteroid treatment. Technical devices to release residual water out of the hose after showering may cause patient's exposure to waterborne pathogens despite terminal water filtration. Nose spray may be contaminated with pathogens (such as *A. fumigatus*) and should be substituted by single use vials in severely immunocompromised patients.

Conflict of interest declaration

All authors state that they do not have a conflict of interest to declare concerning this article.

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