Case Studies: Pediatric Fungal Infections

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Case 1

- This male patient at the age of 3 years was diagnosed with chronic renal insufficiency and he received continuous ambulatory peritoneal dialysis (CAPD) since the age of 4 years.

- When he was 5 years old, he underwent a cadaveric kidney transplant and was placed on triple immunosuppressive therapy (prednisolone, azathioprine, cyclosporin). After 2 years, due to chronic rejection, he was restarted on CAPD.
CAPD

- CAPD is a kidney dialysis procedure that removes wastes, chemicals, and extra water from your body. This type of dialysis uses the lining of your abdomen to filter your blood. The peritoneal membrane acts as an artificial kidney.

- CAPD requires no machine and can be done in any clean, well-lit place. With CAPD, your blood is always being cleaned. Before your first treatment, a surgeon places a catheter into your abdomen.....the site heals and the catheter stays.
Continuous Peritoneal Ambulatory Dialysis (CAPD)
Hemodialysis

- Hemodialysis uses a man-made membrane (dialyzer) that functions as an artificial kidney to clean your blood. The dialyzer is a canister connected to a hemodialysis machine.

- During treatment, your blood travels through tubes into the dialyzer, which filters out wastes, extra salt, and extra water. Then the cleaned blood flows back into your body. The hemodialysis machine monitors blood flow and removes wastes from the dialyzer.
Hemodialysis
Hemodialysis

- Hemodialysis can take 6-8 hrs and cannot be done at home.
- It is far more expensive than CAPD.
Case 1

- The patient is now 15 yrs old, he presented to the clinic with intermittent abdominal pain and a fever to 38.5°C (101.3°F) but his dialysate drainage was clear and there were no clinical signs of exit-site infection but, on PE, he did have peritoneal fluid in his abdomen.
- The WBC count of the dialysate was $4 \times 10^6$/mm$^3$ and it was submitted for bacterial and fungal cultures.
Case 1

• On admission, his peripheral WBC count was $7.1 \times 10^9/\text{mm}^3$ (67% neutrophils, 10% eosinophils, 8% monocytes and 15% lymphocytes).

• C-reactive protein (CRP) was 211 mg/L (normal = 8 mg/L) and increased to 497 mg/L one week after admission.

• Peritoneal fluid was removed and also submitted for bacterial and fungal cultures. The fluid WBC count was $> 10^9/\text{mm}^3$. 
Case 1

- Two days later, mold was growing from both the dialysate and peritoneal fluid cultures and he was started on amphotericin B. Unfortunately, after 7 days his fevers persisted and his CRP remained high so the amphotericin B was discontinued and he was started on oral voriconazole.
- His fevers subsided after 22 days and his CRP dropped to 74 mg/L. He was discharged to be followed weekly in clinic while still on oral voriconazole.
- Because week #1 dialysate cultures were still positive, oral terbinafine was added for combination therapy. A week later his CRP level was 3.3 mg/L and dialysate fluid cultures were negative and they remained negative. Combination therapy was used for 3 months and by then he was undergoing regular hemodialysis and in a stable condition.
Microscopic Exam
Purpureocillium lilacinum
(Paecilomyces lilacinus)
**Purpureocillium lilacinum**

- Formerly *Paecilomyces*
- Rapidly growing mold
- Initially white, becoming lilac
- *Penicillium*-like conidiophores with short chains of conidia
- Phialides are more tapered and elongated than *Penicillium*
- Likely to be Amphotericin B resistant
- Usually susceptible to Voriconazole
- Testing of individual isolates is highly recommended
Fungal Peritonitis (FP)

- Fungal peritonitis is a serious complication in children on continuous ambulatory peritoneal dialysis (CAPD) accounting for 15% of infections. The most common cause of the disease is *Candida*, predominately *C. albicans*, *C. parapsilosis*, and, more recently, *C. glabrata*.

- Recently, filamentous fungi such as *Aspergillus*, *Paecilomyces*, *Purpureocillium*, *Penicillium*, and *Zygomycetes* have emerged as causes of FP in these patients and are associated with high morbidity and mortality (30%).
Fungal Peritonitis (FP)

- The strongest risk factors for FP in CAPD patients are prolonged use of antibiotics and previous bacterial peritonitis. According to retrospective studies, 50% – 80% of patients with FP received broad-spectrum antibiotics in the preceding 3 months.

- Antibiotics, by killing the bowel flora, promote fungal colonization of the intestinal or genitourinary tract, molds then invade across the mucosal barrier to the peritoneal cavity.
Case 2

- BG was born with a birth weight of 574 grams at 25 weeks gestational age. At the time of her birth she was in severe respiratory distress, was treated with ventilation and surfactant and given a 7 day course of ampicillin and gentamicin.

- On the second week of life she received a 7 day course of vancomycin and cefotaxime for presumed nosocomial sepsis even though all blood cultures were negative at that time.
• Because her feeding tolerance was poor, she was placed on prolonged intravenous lipid hyperalimentation.

• On day 18 of life, a central line catheter tip grew *Candida albicans*. An ultrasound of her kidneys was then performed and it showed multiple lesions consistent with a renal *Candida* infection even though multiple urine and blood cultures taken at the same time were negative.
• An extended course of amphotericin B was initiated and on day 26, neonatologists noted an abscess behind her left ear. The abscess was drained and then grew an organism that initiated an infection control investigation. [I was asked to serve as an outside consultant to this process]
Abscess Gram Stain
Malassezia species (14)

- M. caprae
- M. cuniculi
- M. dermatis
- M. equina
- M. furfur*
- M. globosa*
- M. japonica*
- M. nana
- M. obtusa
- M. pachydermatis
- M. restricta*
- M. slooffiae
- M. sympodialis*
- M. yamatoensis*

* = can be normal on human skin
Malassezia species

- *Malassezia* is a genus naturally found on the skin surfaces of many animals, including humans. In humans, they become part of the skin flora during infancy.
- 6 species can be normal flora on the skin of humans but they can also cause dermatologic infections.
- All but one species require lipids or fats to grow, only *M. pachydermatis* can grow without lipid supplement, but this species grows faster and better in the presence of lipid — its growth is enhanced.
• After seeing the typical morphology on Gram stain of the abscess material, the microbiology lab at this hospital plated the abscess material on a Cornmeal with Tween 80 agar plate as well as a routine SAB plate.

• Cornmeal with Tween 80 contains polysorbate 80 which is a source of lipid— you can use a medium such as this, or add olive oil to a medium such as SAB to encourage the growth of *Malassezia*. 
• Two days later, a bipolar budding yeast was growing on both the plain SAB as well as the Cornmeal Tween 80 plate – which presumptively identified this organism as *M. pachydermatis*.

• The identification was reported to neonatology as well as to Infection Control.
Additional Information (from IC)

• Because of complications related to her diabetes, this infant’s mother had been hospitalized in the ICU since the baby was born.

• No family members had visited this infant – she had been seen and cared for exclusively by HCWs.
• What do you know about *Malassezia pachydermatis*?

• Knowing the history obtained via Infection Control, now what?
• *M. pachydermatis* is not normal flora in humans. It is normal skin flora in dogs and is known for causing both upper respiratory and ear infections in dogs.

• Infection Control obtained hand cultures on all of the physicians, nurses, and others who took care of this infant as well as skin cultures from the other babies in the nursery.
Culture Results

• One of the nurses had a hand culture positive for *M. pachydermatis*.

• When the nurse was later interviewed, she admitted to having two dogs at home and that both the dogs had ear infections for which they were being treated.
Case 2

- BG died of multi-system organ failure on day 88 of life. Because of the investigative work done by Infection Control, two additional infants in the nursery were found to be colonized with the same organism.
Malassezia pachydermatis

- normal skin flora in lower animals, particularly dogs
- microscopically has typical broad-based polar bud with colarette
- mature in 4-5 days
- grows best at 35°C, poorly at 25°C
- shows enhanced growth in the presence of lipids (fatty acids) but lipids are not required for growth
Malassezia pachydermatis

- can be misidentified as *Candida lipolytica* in a number of yeast identification systems [API 20C] because it’s glucose, glycerol, and sorbitol positive and negative for most other biochemical test, but a microscopic exam should differentiate between them……SO…. every time you have an identification of *C. lipolytica*, perform a microscopic exam.
Other Important Yeast

- *Candida auris* is a newly identified emerging cause of serious and fatal infections. It was first described in Japan in 2009 from a patient with ear discharge.
- It has been identified in episodes of candidemia in South Korea, India, South Africa, Kuwait, and now the U.S. In addition to being highly pathogenic, this organism is multi-drug resistant to antifungal agents which is nearly unheard of for *Candida* spp.
Other Important Yeast

- Biochemical methods of identification will **incorrectly** classify this as another species of *Candida, C. haemulonii*. API Yeast ID cannot identify this organism and MALDI-TOF MS and Vitek 2 will identify this organism as *C. haemulonii*.

- The CDC has recommended that patients with *C. auris* infection be placed on both Standard AND Contact precautions and CDC would like to receive all isolates of *Candida auris* OR *C. haemulonii* identified in clinical labs.
Case 3

- A 26-week, 675 g, male infant was born by Cesarean section to a 32-yr old mother with a history of systemic lupus erythematosus, renal failure, & severe hypertension.....high risk pregnancy.
- Mom was on prednisone, minoxidil, labetalol, phenytoin, and aspirin therapy. Apgar scores were 5 and 8 at 1 and 5 minutes, respectively and the baby was transferred to our NICU immediately.
Case 3

- On day 8 of life, a 3 x 2 cm necrotic lesion was noted on the left leg over the tibia. On the same day, he also had borderline low blood pressures and hypoglycemia.
- His blood cultures sent on the same day were negative, but a repeat set on day 10 of life grew *Staphylococcus aureus* within 24 hours, and a mold after 3 days. Cultures on urine and cerebrospinal fluid were sterile.
Case 3

- Surface cultures from the leg lesion also grew a mold. A skin biopsy done from this site on day 12 of life showed presence of fungal hyphae on microscopy.
Case 3
Case 3

- The baby also developed an effusion in the left knee joint on day of life 15, which was aspirated, and also grew the same mold.
- Local surgical debridement was done on day 20. He was treated with Vancomycin for 14 days, and Amphotericin B for a total of 21 days (20 mg/kg).
- The isolate was susceptible to Amphotericin B, but resistant to Itraconazole, Fluconazole, and 5-flucytosine.
- Repeat cultures remained negative and the baby recovered with no further complications.
Fungal Isolate - on IMA
Fungal Isolate- on PFA
Curvularia spp.

- *Curvularia* are ubiquitous fungi found naturally in soil and in stagnant or fresh water. *Curvularia* are associated most often with allergic fungal sinusitis, but can cause disseminated infection in immunocompromised patients.

- In premature infants, *Curvularia* infection has been described as an invasive fungal dermatitis from a primary skin focus and immaturity of the skin barrier.
Curvularia spp.

- This patient had multiple risk factors for nosocomial infection and fungal disease, including extreme prematurity, central catheters, endotracheal intubation, total parenteral nutrition, antibiotic therapy, and steroid administration.
- This case also shows the need to consider cutaneous fungal infections in the differential diagnosis in critically sick neonates with necrotic skin lesions, even when an alternative diagnosis such as bacteremia can explain the systemic signs of illness.
Treatment of *Curvularia*

- In systemic fungal infections in neonates, Amphotericin B has been the gold standard of therapy.
- Fungal susceptibilities can be difficult to standardize but the sensitivity profile of the *Curvularia* isolate in our case is a cause for concern……..this isolate was resistant to azoles and 5-flucytosine.
Fungal Dermatitis in Neonates

• *Curvularia* and *Rhizopus* are the two major molds causing serious neonatal skin infections. In addition, *Curvularia* is now causing pneumonia in premature babies.

• Babies who are at higher risk for *Curvularia* skin infections are those who are:
  - Premature
  - Kept in high humidity isolettes – 60%
  - and who have minor skin traumas -- the wound infections occur at the trauma sites.

• There is nothing characteristic of the skin lesions from *Curvularia* -- neonatologists have to be taught to always be suspicious and culture skin lesions, no matter how small.
Fungal Dermatitis in Neonates

- Invasive fungal dermatitis is a disease of the smallest, most immature neonates and is associated with vaginal birth, steroid administration, and hyperglycemia. **IT’S ON THE RISE!**

- It is presumed that the skin serves as a portal of entry for colonizing fungal species and may lead to disseminated infection.
Case 4

- The patient is a 12 hr old girl from Saudi Arabia who has been treated for ALL at a children’s hospital in Texas.
- She relapsed 3 times and was given a stem cell transplant. After developing grade 3 graft vs. host disease (GVHD), her parents demanded that she be transferred to our hospital (which required approval of the State Department).
Case 4

• On arrival, physical exam showed her vital signs were all stable, she was NOT febrile, she had a cushionoid appearance, and crackles were present at both lung bases.

• Stage 3 GVHD looks like a total body serious burn.

• Two days after admission she was taken to the O.R. where they brushed off the sluffing layers of skin and she was put on ceftazidime, methylprednisolone, & IL-2.

• 3 days after the procedure she developed a raised red lesion on her shoulder with a necrotic black center.
Case 4 - GVHD Skin Appearance
Case 4

• Infectious diseases was consulted and proposed the following differential diagnosis:
  • *Staphylococcus*
  • *Streptococcus*
  • Gram negative rods, especially *Pseudomonas*
  • *Mucor*
  • *Aspergillus*

• A skin biopsy was ordered as well as head and body CTs. The patient was placed on voriconazole.
Case 4

• Before the biopsy is performed, a nurse on the floor asks an ID physician if they “know anything about the skin cream the family is rubbing onto the patient’s skin every day?” …..she suggests they talk to the grandmother who appears to have many jars of the balm.

• Since the lab is asked if we will culture the balm, I accompany ID as they visit the grandmother. She claims the balm is made of honey, beeswax, tree bark, and ‘special spices’.
Biopsy Results
Mold: Macroscopic

- Rapid growth, mature in 3 days
- Wooly to cottony surface OR velvety surface
- Initially white, then yellow/olive green to brown front; cream to brown reverse
Conidiophore Structure

Aspergillum
Conidiophore structure
Patient Mold: Microscopic

- Conidial heads radiate and columnar
- Uniseriate and biseriate
- Rough-walled stipe
- Smooth- to rough-walled conidia
- Mature vesicles bear conidia past the 50% point.
Aspergillus flavus
Case 4- Treatment

• Voriconazole has now become the drug of choice for invasive aspergillosis. This is due to the increased efficacy and significantly less toxicity compared to amphotericin B.
• Caspofungin is a newer antifungal agent that is effective against invasive aspergillosis but more pediatric studies are needed prior to its widespread use.
• Currently caspofungin has been approved for use as salvage therapy for invasive aspergillosis that does not respond to existing antifungals.
Contaminated Spices

- Since 2013, spices from Saudi Arabia, Egypt, Pakistan, Lebanon, and India have been found to be “grossly contaminated” with bacteria and fungi.

- The most prominent fungi have been *Aspergillus* (80% *A. flavus*), *Penicillium*, and *Rhizopus*.

- To this date, there continue to be FDA warnings about purchasing spices from these countries.
Spice contamination a cause for concern