

## REVIEW ARTICLE

# The utility of abdominal ultrasonography in the diagnosis of fungal infections in children: a narrative review

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abdomen, child, fungemia, mycoses, ultrasonography

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**Abstract**

In paediatric patients, ultrasonography is one of the preferred medical imaging modalities due to the lack of ionising radiation. Abdominal ultrasonography can be a useful tool in diagnosing cases of fungal infections but may introduce some risks for further infection in vulnerable patients or cause anxiety and discomfort. The aim of this narrative review is to analyse the utility of abdominal ultrasonography in diagnosing fungal infections in children in terms of its positive hit rates and utility in typical use. Text words and indexed terms related to 'fungal infection and ultrasonography' and 'children' were searched on MEDLINE, EMBASE, Cochrane Library and Scopus. Paediatric oncology patients, neonates and generally immunocompromised children were found to be at-risk groups with increasing susceptibility to risk factors for contracting fungal infections. Abdominal ultrasonography was found to aid in the diagnosis of fungal infection in many cases, but not all patients with the identified risk factors were diagnosed with fungal infections and not all patients diagnosed with fungal infections had identified risk factors. Ultrasonography was found to be overutilised and the current decision process in requesting abdominal ultrasonography in diagnosing fungal infection should be revised. Further study into an effective criterion in requesting abdominal ultrasonography is suggested to reduce the overutilisation of ultrasonography, thus reducing risk of infection and discomfort while also saving time and money.

**Introduction**

Fever is often the first sign of infection in children and can trigger a clinical workup to determine a source in order to facilitate appropriate management. Diagnostic testing can help inform whether the responsible pathogen is bacterial, viral, fungal or a possibly combination. Immunocompromised children are particularly susceptible to infection and are also at increased risk of morbidity and mortality compared to the broader patient population.<sup>1,2</sup> Medical imaging examinations are potential tools in the algorithm used to determine a source of infection in febrile children along with clinical examinations, history taking and pathology testing.<sup>3</sup> A variety of medical imaging modalities can be utilised in the search for infection including general radiography; computed tomography (CT); positron emission

tomography (PET); magnetic resonance imaging (MRI); and ultrasonography. The two latter modalities are often preferred in children due to their lack of ionising radiation.<sup>4–6</sup> Each, however, has some limitations, MRI availability and examination length can be an issue, and there can be challenges using ultrasound imaging to evaluate lung and bony pathology. This review sought to benchmark the diagnostic accuracy of abdominal ultrasound imaging in detecting fungal infections in children and to determine current recommendations on the use of imaging in this clinical scenario.

**Methods**

MEDLINE, EMBASE, Cochrane Library and Scopus were searched for articles published between 2000 and December 2019. Clinical trials were searched to identify

unpublished studies. Grey literature was searched using Google Scholar. A range of text and index terms related to ‘fungal infection’, ‘ultrasonography’ and ‘children’ were used. A detailed search strategy and search term alternatives for each database are available in Table 1. The inclusion criteria accepted children who had a suspected fungal infection of the abdomen. For the majority of articles, this was 18 years and under except for the article by Adeyiga et al.<sup>7</sup> who discussed CT scans of two individuals aged 20 and 23 years. This article was used but these individuals over the age of 18 years were not included. The article by Festekjian et al.<sup>8</sup> also included individuals up to the age range of 22 years. Individuals over the age of 18 years could not be eliminated since the article did not isolate the results of these patients. However, out of 155 children, the median age was 2.3 years with an interquartile range of 10 months to 8.3 years. Thus, we justify including all individuals from this article due to the extremely small portion of individuals aged above 18 years and the significance this article provides to our review. The reference lists of studies meeting the inclusion criteria were searched to identify additional relevant studies. Abstracts in languages other than English were excluded. Three reviewers independently screened the abstract of the articles for studies related to abdominal ultrasound imaging in diagnosing fungal infection in children. The open-source program Abstrackr (Brown University, Providence, RI, USA) was used to screen the abstracts of articles.<sup>9</sup> A list of the screened studies was compiled and summarised in a table. The studies were read and analysed to formulate views and produce results regarding the research question.

## Results

### Main patient groups identified

Three main patient groups were identified in articles relating to the use of ultrasound imaging in diagnosing abdominal fungal infections in children. These included oncology patients (Table 2), neonates (Table 3) and generic cases (Table 4). The results are presented in relation to the patient groups identified.

### Oncology

Paediatric oncology patients are a recurring theme in the literature reporting abdominal fungal infections and appear to be one of the most commonly reported groups. Establishing common risk factors pertaining to abdominal fungal infections in this group is important to inform the

**Table 1.** Search strategies for each database used to find articles

Database	Search Strategy
MEDLINE (PubMed)	<i>Free Text</i> (child OR children OR pediatric OR paediatric) AND (ultrason* OR sonogr* OR ultrasound) AND (fung* OR mold OR mould) AND infect* AND abdo* <i>MeSH</i> ("ultrasonography"[MeSH Terms] OR medical sonography[MeSH Terms] OR sonography, medical [MeSH Terms]) AND ("fungemia"[MeSH Terms] OR mold[MeSH Terms] OR mycoses[MeSH Terms]) AND children[MeSH Terms]
EMBASE	<i>Free Text</i> (child* AND (ultrason* OR sonogr* OR ultrasound) AND fung* AND infect* AND abdo*) <i>Emtree</i> 'echography'/mj AND 'child'/mj AND 'mycosis'/mj
Cochrane Library	#1 MeSH descriptor: [Child] this term only #2 MeSH descriptor: [Mycoses] explode all trees #3 MeSH descriptor: [Ultrasonography] explode all trees #4 MeSH descriptor: [Abdomen] explode all trees
Scopus	((child OR children OR pediatric OR paediatric) AND (ultrason* OR sonogr* OR ultrasound) AND (fung* OR mold OR mould OR mycoses) AND infect* AND abdo*)

process of selective screening using imaging studies, specifically abdominal ultrasound imaging.

General risk factors for fungal infections in oncology patients include neutropenia (prolonged or febrile), use of broad-spectrum antibiotics, chemotherapy, catheter use and steroid therapy.<sup>7,10–20</sup> However, these risk factors rarely occur in isolation, which is not surprising given the nature of typical cancer-related induction therapy. For example, treatment for oncology patients typically involves both chemotherapy preceded by steroid therapy which leads to immunosuppression and neutropenia.<sup>7,11,13–17,20</sup> Thus, an index of suspicion for fungal infection should be built up in paediatric oncology patients dependent on these risk factors. For example, a patient with prolonged episodes of febrile neutropenia following chemotherapy while taking broad-spectrum antibiotics and central line catheter should warrant a high index of suspicion for fungal infection. On the other hand, a patient following chemotherapy who is also taking broad-spectrum antibiotics but without prolonged neutropenia may not warrant as high of an index of suspicion for fungal infection. Such a distinction in suspicion could assist in the decision whether to screen the patient for signs of fungal infection using imaging studies.

**Table 2.** Summary of literature concerning oncology patients

Article	Population	Risk factors	Imaging studies	Imaging Results	Organs or area affected	Confirmed Fungal pathogens	Level of evidence
Cohn et. al., 2016 <sup>8</sup>	50 children with invasive mould infection Group A (diagnosed before screening protocol) aged 1.2–17.5 years. Group B (diagnosed after) aged 0.9 – 17.5 years.	ALL, acute myeloid leukaemia (AML)	Group A: All had abdominal imaging (13 computed tomography (CT), 6 US). Group B: All had abdominal imaging (5 CT, 26 US).	Group A: 4 of 19 had intra-abdominal infection. Group B: 1 of 31 has intra-abdominal infection. Other sites: chest, nasal endoscopy.	Group A: 3 visceral infection, 1 bowel infection Group B: 1 visceral	<i>Rhizopus sp.</i> (1), <i>Aspergillus sp.</i> (2), <i>Fusarium sp.</i> (1), <i>Exserohilum sp.</i> (1)	Retrospective case study
Donker et. al., 2012 <sup>9</sup>	4 children (2–4 years old) with	haematological malignancies	ALL (3), T-cell non-Hodgkin lymphoma (1). Induction therapy: corticosteroids and chemotherapy. Develop subsequent neutropenic fever, receiving broad-spectrum antibiotics and empirical antifungals	All scans were abdominal. One patient solely US, two CT and US, one positron emission tomography (PET) and CT	2 of 3 abdominal US were negative for fungal infection	Liver (4), Spleen (3), Kidneys (2), Gall bladder (1)	<i>Candida albicans</i>
Lin et. al., 2003 <sup>12</sup>	Retrospective case study 5 children (4–18 years old) with acute leukaemia who developed hepatosplenic	microabscesses	ALL (2), AML (1), first relapse ALL (2). Chemotherapy, broad-spectrum antibiotics and empiric antifungals.	Abdominal US, CT and magnetic resonance imaging (MRI).	Abnormalities		
	demonstrated by all imaging studies (lesions). Hepatosplenic	microabscesses found in 2 patients by abdominal US after 7 and 14 days fever free.	Liver (5), Spleen (2), Kidney (1)	<i>Candida albicans</i> (1), <i>Candida tropicalis</i> (1)	Retrospective case study		
Decembrino et. al., 2016 <sup>13</sup>	6-year-old neutropenic boy	AML, chemotherapy, neutropenia, prophylactic antibiotics	Abdominal US	US showed fluid filled, distended appendix and inflammation. Suspected appendicitis.	Appendix	<i>Aspergillus carneus</i>	Retrospective case study

(Continued)

**Table 2.** Continued.

Article	Population	Risk factors	Imaging studies	Imaging Results	Organs or area affected	Confirmed Fungal pathogens	Level of evidence
Tibúrcio et. al., 2015 <sup>14</sup>	6-year-old girl with neuroblastoma (disseminated)	Multimodal therapy (including chemotherapy), febrile neutropenia, broad-spectrum antibiotics. Abdominal pain, hepatosplenomegaly <i>Candida sp.</i>	Pre-emptive abdominal US PET/CT performed to differentiate between tumour and abscess. Retrospective case study	Histopathology exam indicated fungal infection. US showed splenic lesions, suspected tumour or abscess.	Spleen		
Celkan et. al., 2019 <sup>15</sup>	40 children with leukaemia (no age provided)	ALL, AML, chronic myeloid leukaemia (CML), prolonged fever, neutropenia, broad-spectrum antibiotics, central venous catheter, fungal infection at other sites (55% had co-infection: 18 lungs, 2 kidney-lungs, 1 brain, 1 oesophageal), chemotherapy	Abdominal ultrasound performed in all cases at median of 7 days after febrile neutropenic episode. 26 had CT and 6 had MRI (all findings consistent with US).	Ultrasound showed evidence of hepatosplenic fungal infection in 16, splenic infection in 11 and hepatic infection in 13.	Liver (29), Spleen (27)	<i>Candida Albicans</i> , <i>C. Parapsilosis</i> , <i>C. Norvegensis</i> , <i>C. Tropicalis</i> (2), <i>C. Crusei</i> (2)	Retrospective case study
Ranjani et. al., 2016 <sup>16</sup>	7-year-old girl with risk of pre-B ALL	Febrile neutropenia, broad-spectrum antibiotics, chemotherapy	Abdominal US	US showed heterogenous hypoechoic lesion at upper pole of right kidney. Appearance suggested infection or infarct. Fine-needle aspiration consistent with fungal infection	Kidney	<i>Mucor sp.</i>	Retrospective case study
Lashkari et. al., 2016 <sup>17</sup>	14-year-old girl with AML	Prolonged neutropenia sepsis, central venous access device	Abdominal US	US showed multiple microabscesses in liver and spleen	Liver and spleen. Co-infection with liver.	<i>Trichosporon Asahii</i>	Retrospective case study
Leucht et. al., 2013 <sup>18</sup>	117 children with AML, ALL or allogenic stem cell transplant (no age provided)	Prolonged fever, neutropenia, ALL, AML, stem cell transplant	Abdominal US, chest/sinus CT	145 (81%) abdominal US performed. Findings suspicious of fungal infection found in 7 (5%)	N/A	N/A	Retrospective case study

(Continued)

Table 2. Continued.

Article	Population	Risk factors	Imaging studies	Imaging Results	Organs or area affected	Confirmed Fungal pathogens	Level of evidence
Ebadi et. al., 2013 <sup>19</sup>	18-month-old boy with stage 3 neuroblastoma	Chemotherapy, immunosuppression, neutropenia	Abdominal US and CT	of abdominal US. Only 1 (0.7%) of US lead to invasive diagnostic procedure Initial US: Multiple hypoechoic foci in spleen Serial abdominal US: enlarged splenic lesions, complete hypoechoic pattern	Spleen, pancreas	<i>Mucor</i>	Retrospective case study
Yen et. al., 2011 <sup>10</sup>	15 paediatric patients with HSF (age 0.1–17.5 years)	Haemato-oncologic malignancies (11), aplastic anaemia (2), broad-spectrum antibiotics, fever, abdominal pain, hepatosplenomegaly	Chest X-ray, CT, US, MRI and gallium scan	Abdominal US detected HSF lesions in 10/15 (67%) compared to Abdominal CT which detected 15/15 (100%).	Liver (15), spleen (10), kidney (8). Other: Lung (2)	<i>Candida sp.</i> (10), <i>Aspergillus sp.</i>	Retrospective case study
Adeyiga et. al., 2012 <sup>11</sup>	Cases of fungal masses in children	Immunocompromised due to neutropenia after treatment of haematological malignancies, transplantation, acquired immunodeficiency syndrome and chronic granulomatous diseases	Abdominal US, CT, MRI	On abdominal US, hepatic fungal infection appears as microabscesses. Appearance depends on phase of infection and treatment	Liver	<i>Candida sp.</i>	Retrospective case study

Table Index: US = ultrasound, CT = computed tomography, PET = positron emission tomography, MRI = magnetic resonance imaging, ALL = acute lymphoblastic leukaemia, AML = acute myeloid leukaemia

Abdominal ultrasound imaging was used in all cases in the literature as a screening or diagnostic measure, with or without suspicion for fungal infection.<sup>7,10–20</sup> In most cases of abdominal fungal infection, ultrasound imaging was not the primary diagnostic measure.<sup>10,11,13–15,17</sup> Rather, blood culture, fine-needle aspiration, histopathological investigations or other imaging studies were the primary determining procedure in confirming a fungal infection.<sup>10,11,13–15,17</sup> However, ultrasound imaging has been demonstrated to be a good indicator for general pathology such as inflammation or infection and can aide in the diagnosis or suspicion of fungal infection as a pre-emptive screening measure.<sup>15,17,18,20</sup>

The most common imaging indicator of fungal infection seen in the literature was hepatosplenic lesions or microabscesses. Limitations in the specific diagnostic nature of ultrasound imaging are outlined in a reported case where pre-emptive abdominal ultrasound imaging revealed hypoechoic splenic lesions, which raised the suspicion for a tumour or candida induced abscess.<sup>15</sup> However, due to the small size of the lesions, ultrasound imaging was not able to distinguish if the pathology was related to tumour spread or infection.<sup>15</sup> Positron emission tomography was needed to differentiate the pathology and confirmed the case of candida induced abscess.<sup>15</sup> This case demonstrated that although

**Table 3.** Summary of literature concerning neonates and immunocompromised children

Article	Population	Risk factors	Imaging studies	Imaging Results	Organs or area affected	Confirmed Fungal pathogens	Level of evidence
Noyola et al., 2001 <sup>23</sup>	106 infants with invasive candidiasis, 65 of which had abdominal US	Antibiotic therapy, central venous catheters	Abdominal US,	echocardiogram, ophthalmoscopy examination		Abdominal US: 5/65 infants had abnormalities attributed to candidiasis from imaging. Echogenic liver lesions, dilation of renal pelvis with increased echogenicity	Liver and kidneys. Other: Heart and eye
<i>Candida sp.: C. albicans (54), C. parapsilosis (26), C. glabrata (3), C. tropicalis (1), C. lusitanae (1), C. guilliermondii (1).</i>	Retrospective case study						
Markhouli et al., 2001 <sup>24</sup>	49 neonates with acquired fungal sepsis	Mechanical ventilation, umbilical venous catheter, broad-spectrum antibiotics	US of brain, heart and abdomen	Abdominal US: 42 neonates with renal US and 40 with liver US. Abnormalities found in 7.1% and 2.5% of patients respectively	Liver and kidneys.	Other: Heart	<i>C. albicans, C. parapsilosis, C. tropicalis, C. glabrata</i>
Retrospective case study							
Ray et al., 2018 <sup>25</sup>	Preterm infant with late-onset sepsis	Intravenous broad-spectrum antibiotics, respiratory support, high C-reactive protein	Cranial and abdominal US	Abdominal US revealed lesion in left kidney, characteristic of renal fungal ball	Kidney	N/A	Retrospective case study
Sie et al., 2006 <sup>26</sup>	Preterm neonate	Broad-spectrum antibiotics	Abdominal radiograph, abdominal CT, renal US	Renal US revealed dilation of left collecting system with echogenic material in calyces	Kidney	<i>Candida sp.</i>	Retrospective case study

Table index: US = ultrasound, CT = computed tomography

ultrasound imaging has limited ability as a primary diagnostic tool for fungal infections, pre-emptive screening can be useful to indicate general pathology, prompting further imaging leading to a diagnosis of fungal infection.

There are reported cases corroborating this sentiment, in which hypochoic lesions found in the liver, spleen or kidney are typically associated with fungal infection.<sup>17,18,20</sup> In one such case, the lesions were indicative of infection or infarct, however, fine-needle aspiration to the site was

required to confirm a fungal infection.<sup>17</sup> Other cases showing similar lesions include a reported case where abdominal ultrasound imaging revealed multiple microabscesses in the liver and spleen of a girl with acute myeloid leukaemia and blood culture confirmed fungal infection.<sup>21</sup> Lin (2003) reported a series of patients with hepatosplenic microabscesses and other abnormalities revealed by ultrasound imaging.<sup>13</sup> Cultures from catheters, blood and stool confirmed fungal infection.<sup>13</sup> Ebadi (2013) reported a case where abdominal ultrasound

**Table 4.** Summary of literature concerning generic cases

Article	Population	Risk factors	Imaging studies	Imaging Results	Organs or area affected	Confirmed Fungal pathogens	Level of evidence
El-Shabrawi et al., 2011 <sup>27</sup>	10-year-old boy with	basidiobolomycosis	Fever, abdominal pain/tenderness, blood eosinophilia	Abdominal CT and US	Both	imaging studies detected large caecal mass	GIT
Montravers et al., 2015 <sup>30</sup>	N/A	<i>Basidiobolus ranarum</i>	Retrospective case study				Clinical Practice Guidelines
Festekjian et al., 2009 <sup>28</sup>	155 children with candidemia	Prematurity, underlying					

immunocompromising disorder and longer than 2 days of candidemiaEchocardiogram, chest CT and abdominal US108/180 had abdominal US (60%)

Only 15/180 (8%) had invasive candidiasisLiver, spleen*Candida sp.*Retrospective case studyCheung et al., 2019<sup>31</sup>51 practitioners surveyed.

Episodes of fungemia from paediatric gastroenterology service observedN/AAbdominal US and echocardiogramsPre-intervention: 18 episodes of candidemia, abdominal US done in 100%, 0 positive findings

Post-intervention: 7 episodes of candidemia, abdominal US done in 43%, 0 positive findingsN/AN/ACase studySidhu et al., 2013<sup>29</sup>12-year-old boy with perinephric abscessFever, previous antibiotic therapyAbdominal US and CTAbdominal US revealed enlarged left kidney with hypoechoic lesion.

Culture positive for fungiKidney*Fusarium chlamydosporum*Retrospective case studyTable index: US = ultrasound, CT = computed tomography, MRI = magnetic resonance imaging, HSF = hepatosplenic fungal infection

imaging initially showed multiple hypoechoic foci in the spleen.<sup>20</sup> Serial abdominal investigations later showed enlargement of splenic lesions with a marked hypoechoic pattern and fungal culture confirmed a fungal infection.<sup>20</sup>

Ultrasound imaging is good at revealing lesions in the liver, spleen and kidneys which are typical to fungal infection, and some reports from other sites.<sup>10,11,13–20</sup>

One unusual presentation reported a fungal infection involving the appendix.<sup>14</sup> The ultrasound scan showed a fluid filled, distended and inflamed appendix, consistent with the appearance of appendicitis.<sup>14</sup> Although appendicitis is not commonly fungal in nature, the risk factors of acute myeloid leukaemia, chemotherapy, neutropenia and prophylactic antibiotics along with the ultrasonography appearances led to a high suspicion of fungal infection.<sup>14</sup> Histopathological examination of the appendix later confirmed fungal infection.<sup>14</sup>

These cases demonstrate that abdominal ultrasound imaging played a role in several cases of proven fungal infection in children. Hepatosplenic lesions are not specific to fungal infection but should certainly raise suspicion in the oncology patient. In addition, the cases demonstrate the importance of evaluating relevant risk factors when interpreting imaging findings. These same risk factors may also be useful in determining a selective screening process in certain patient groups. What is not

clear is what specific risk factors or combination of risk factors warrants further investigation via imaging without overutilisation.

Most studies to date in the literature have included cohorts of patients which had multiple risk factors for fungal infection,<sup>7,11–17,19,20</sup> leading to the possibility of reporting bias which resulted in higher rates of detection by imaging. One study with the specific aim to study the utility of radiographic investigations in children with prolonged fever and neutropenia is a study of 117 neutropenic children receiving allogeneic stem cell transplant (SCT).<sup>22</sup> In this study, only 5% of ultrasound imaging studies found presentations suspicious of fungal infections, with 0.7% leading to invasive diagnostic procedures.<sup>19</sup> Only one patient met criteria for proven invasive fungal infection and one for probable infection. These children had prolonged fever and neutropenia<sup>19</sup> which are two of the biggest risk factors for fungal infections as previously outlined. This study did not mention the use of chemotherapy or broad-spectrum antibiotics. However, given the patients had leukaemia, it is likely they received such treatment. The study suggests that using the risk factors of prolonged fever and neutropenia to justify requesting abdominal ultrasonography for fungal infection is not selective enough may lead to the overutilisation of ultrasound

imaging. This could be improved by adding additional previously mentioned risk factors to the criteria, but further studies are needed to confirm this. Typical signs and symptoms should also be investigated to develop a more holistic criteria in developing suspicion for a fungal infection.

A study which investigated the application of a standardised screening protocol in diagnosing invasive fungal infections in children with haematologic malignancies introduces a different perspective to the matter.<sup>10</sup> The screening protocol included nasal endoscopy, non-contrast chest computed tomography and abdominal ultrasonography in all children with haematologic malignancies undergoing chemotherapy.<sup>10</sup> Although they found that introducing this screening protocol reduced mortality rates from fungal infection, only 1 out of 26 abdominal ultrasonography scans found evidence of intra-abdominal disease.<sup>10</sup> The majority of patients had fungal infection diagnosed by nasal endoscopy or chest computed tomography rather than abdominal ultrasound imaging.<sup>10</sup> While the standardised screening protocol reduced mortality rates, almost all of the abdominal ultrasound scans presented negative readings.<sup>10</sup> This reinforces the importance of establishing an effective and specific criterion for the request of abdominal ultrasound imaging. If the criterion is not specific enough, scans will be overutilised with little contribution to diagnostic utility. If the criterion is too specific, some cases of fungal infection will be missed, leading to higher mortality rates.

There is a key limitation in the diagnostic ability of ultrasonography in neutropenic patients which stems from the condition. It is difficult to visualise fungal lesions during the neutropenic phase since the inflammatory response is insufficient to form an infiltrate large enough to be detectable as a discrete lesion.<sup>11</sup> Often, ultrasonography can be falsely negative during these early neutropenic stages, since the lesions are too small.<sup>11</sup> Thus, an early diagnosis of fungal lesions would be extremely difficult as the clinical manifestation would not be evident in ultrasound scans before neutrophil counts return to normal.<sup>13</sup> One case reported serial abdominal ultrasound imaging conducted at 2-day intervals.<sup>20</sup> Initial scans only revealed hypoechoic foci in the spleen while subsequent scans showed the enlargement of splenic lesions and complete hypoechoic patterns. This demonstrates the usefulness of repeated scans in selected cases.

## Neonates

Neonates are another group commonly seen in the literature who are susceptible to abdominal fungal

infections. Understanding the risk factors of this group can also aid in developing specific criteria for requesting abdominal ultrasound imaging if there is suspicion of fungal infection. Common risk factors shared with oncology patients include the use of broad-spectrum antibiotics and indwelling catheters.<sup>23–26</sup> Other risk factors include the use of mechanical ventilation<sup>24,25</sup> and elevated C-reactive protein levels.<sup>25</sup> Preterm infants were also common among the literature.<sup>25,26</sup> Further studies into more specific risk factors and signs or symptoms of abdominal fungal infection in neonates may also be useful.

It should be noted that culture results negative for fungi does not always rule out fungal infection.<sup>25</sup> Instead, elevated C-reactive protein and thrombocytopenia are factors which should warrant some level of suspicion of fungal infection.<sup>25</sup>

Common manifestations of fungal infection occurred in the kidney and could be detected by abdominal ultrasound scans. Two cases reported dilated renal structures (renal pelvis and collecting system) and increased echogenicity or echogenic lesions in the kidneys which were suggestive of fungal infection.<sup>23,26</sup> Other appearances include rounded echogenic lesions in the kidney which was deemed characteristic of a renal fungal ball.<sup>23,25</sup> The liver was also affected in two cases which showed evidence of echogenic lesions such as a fungal ball.<sup>23,24</sup> Most of these cases confirmed the diagnosis of fungal infection using blood, urine or peritoneal fluid culture, with only one exception using C-reactive protein levels as mentioned before. Therefore, abdominal ultrasound imaging has some diagnostic utility in identifying signs of fungal infection in neonates.

The next factor to consider is the incidence of positive fungal infections detected by abdominal ultrasound imaging. In one case, only 5 of 65 infants with candidiasis had abnormalities in the ultrasound imaging appearance which could be attributed to candidiasis.<sup>23</sup> In another report, 42 neonates with fungal sepsis underwent renal ultrasonography while 40 underwent liver ultrasonography.<sup>24</sup> The imaging detected abnormalities in 7.1% and 2.5% of the neonates, respectively. Thus, the appearance of fungal infection obtained by abdominal ultrasound imaging is relatively low given the total number of scans. The risk factors outlined before could be used as a baseline for such a criterion, but further studies may be needed to develop an efficient and effective protocol.

## Generic cases

Some of the literature did not fall into a specific group but provide a more generic view of the use of ultrasound



imaging in diagnosing abdominal fungal infections which are outlined in Table 4. Risk factors identified throughout these articles include anaemia, use of broad-spectrum antibiotics or previous antibiotic use, prematurity and having an underlying immunocompromising disorder.<sup>8,27,28</sup> Common symptoms include fever and abdominal pain.<sup>27,28</sup> This emphasises the incidence of fungal infection in certain risk groups. Thus, for these groups, the risk of fungal infection should be kept in mind. A further suspicion of fungal infection can be generated by the increasing presentation of certain risk factors or symptoms. As suggested before, a specific criterion would need to be developed for each of these groups to maximise efficiency of requesting ultrasound imaging.

Imaging results and appearances of abdominal ultrasound imaging were consistent with the previously discussed literature. Appearances of fungal infection as microabscesses and lesions are present.<sup>28</sup> Other imaging appearances included a large caecal mass<sup>27</sup> and an enlarged kidney.<sup>28</sup> These appearances are not unique to fungal infections and could be the result of many causes. Typically, a culture is needed to determine the cause of the infection.

### Common fungal species identified

Across the literature summarised in Tables 2–4, *Candida species* were the most common confirmed fungal pathogen by far, followed by *Aspergillus species* and *Mucor species*. The most common *Candida species* was *C. albicans*, followed by *C. parapsilosis* and *C. tropicalis*. The most common organ affected was the liver, followed by the spleen and the kidneys.

### Discussion

Benchmarking the diagnostic accuracy of abdominal ultrasonography in detecting fungal infections in children is a challenge, and there are no current guidelines that recommend the routine use of abdominal ultrasound imaging in this setting even though it is widely utilised. More broadly published guidelines for the management of intra-abdominal infections state that ultrasound imaging can be used for the diagnosis of collections and effusions, the site of these collection and whether they are simple or complex.<sup>29</sup> However, ultrasound imaging remains non-specific in terms of the nature and source of the infection.<sup>29</sup> This is reserved for invasive procedures such as fine-needle aspiration. With this in mind, two studies have attempted to provide some additional insight into the utility of abdominal ultrasound imaging in children with fungal infection.<sup>8,30</sup>

The first reported that there was no significant difference in the number of diagnostic studies obtained between patients with and without invasive candidiasis.<sup>8</sup> It could be argued that either patients with invasive candidiasis are not getting enough imaging studies or that patients without invasive candidiasis are getting too many imaging studies. Both issues could be addressed with the introduction of a criterion to decide whether to request imaging studies, as discussed before.

The second study by Cheung and colleagues aimed to reduce overutilisation of echocardiograms and abdominal ultrasound studies in evaluating children with fungemia by educating practitioners and developing a clinical flow chart to help decide whether to request imaging studies.<sup>30</sup> An initial root cause analysis found that there were no written guidelines or clinical pathways to help decide whether to request imaging studies. Practitioners are also fearful of missing positive findings and have presumed expectations from colleagues. Thus, two countermeasures were proposed: practitioner education and the development of a clinical pathway. Prior to practitioner education, 51 practitioners were surveyed and 22% self-reported performing routine abdominal ultrasound studies. After the education, none of the practitioners planned to perform routine abdominal ultrasound studies. Prior to the intervention, 18 episodes of candidemia occurred in the paediatric gastroenterology service. Abdominal ultrasound imaging was conducted 100% of the time with no positive imaging findings. After the intervention, 7 episodes of candidemia occurred where abdominal ultrasound imaging was conducted 43% of the time, with no imaging positive findings either. Therefore, the researchers propose that abdominal ultrasound imaging in diagnosing paediatric fungemia is overutilised and can safely be decreased.<sup>30</sup>

The intervention implemented in this case matches the proposed criterion discussed before. Some form of clinical guideline should exist that helps practitioners in the decision on whether to request abdominal ultrasound studies. Criteria for the intervention in Cheung's study,<sup>30</sup> included being critically ill, having an underlying risk factor, concerning signs/symptoms and having persistent positive blood cultures or fever. Previously discussed literature provides some insight on the typical risk factors or signs and symptoms which should be included in the criteria.

### Conclusions

In the management of abdominal fungal infections in children, abdominal ultrasound studies provide important diagnostic information in many recorded cases. The literature identified specific risk groups who are more

susceptible to abdominal fungal infections which included oncology patients, neonates and generally immunocompromised patients. Specific risk factors for fungal infections within these groups along with general risk factors were also identified in the literature. Ultrasound imaging can identify the typical pathological appearances of fungal infection or hint at general pathology, aiding in the diagnostic process. However, as outlined in some studies, not all patients with the identified risk factors contracted a fungal infection and not all patients who contracted fungal infections matched all the identified risk factors. In addition, ultrasound imaging failed to provide any additional diagnostic information in a significant portion of patient with some identified risk factors. Therefore, the current level of suspicion of fungal infection warranted by the risk factors is questionable, where further studies are needed to identify a suitable criterion for requesting abdominal ultrasound studies for patients with suspected abdominal fungal infections.

Specific at-risk groups and risk factors should form a starting point in the development of a criterion to raise suspicion for fungal infections. An acceptable criterion could then aide practitioners in deciding whether abdominal ultrasonography is needed.

Oncology patients are the group at highest risk of abdominal fungal infection. For this group, we recommend pre-emptive screening with abdominal ultrasonography when a combination of risk factors including neutropenia, use of broad-spectrum antibiotics and use of chemotherapy are all present, along with symptoms of abdominal pain or fever. Additional risk factors which can raise suspicion of fungal infection include use of indwelling catheters and steroid therapy. Further prospective studies on risk factors and symptoms associated with abdominal fungal infection and positive abdominal ultrasound studies should be conducted to provide a greater quantitative understanding in establishing a criterion. Serial ultrasound scans should be considered for patients with prolonged symptoms and risk factors even with a negative initial result. This is especially true for neutropenic patients, since ultrasound scans can be falsely negative during early fungal infection and early neutropenic stages as previously discussed.

For neonates without other known disease states, a combination of general risk factors which should warrant pre-emptive screening with abdominal ultrasonography include use of broad-spectrum antibiotics, use of mechanical ventilation and use of indwelling catheters. Preterm infants warrant a higher index of suspicion of fungal infection. Thus, we recommend pre-emptive screening at least for preterm infants taking broad-spectrum

antibiotics. High C-reactive protein levels were associated with fungal infection in one case. However, other risk factors including use of broad-spectrum antibiotics and respiratory support were present. Thus, we cannot recommend abdominal sonography for patients solely with high C-reactive protein levels. Further prospective studies should be conducted to support and build upon our recommendations.

Not many generic cases without other underlying malignancies were reported in literature. Some risk factors present included antibiotic therapy, eosinophilia and an underlying immunocompromising disorder. Symptoms included abdominal pain and fever. Due to the lack of literature concerning generic cases, we cannot recommend any guidelines or criteria for the use of abdominal sonography. It is also extremely difficult to create guidelines for generic cases given the wide range of possible risk factors and symptoms, as well as a wide range of possible disease states these factors could be attributed to. Therefore, this is an area that needs further research.

The implementation and further development of such a criterion would aim to reduce the amount of unnecessary abdominal ultrasound studies in paediatric patients, thus saving time, money and discomfort for patients.

## References

1. Bartlett A, Cann M, Yeoh D, et al. Epidemiology of invasive fungal infections in immunocompromised children; an Australian national 10-year review. *Pediatr Blood Cancer* 2019; **66**: e27564.
2. Pana ZD, Roilides E, Warris A, Groll AH, Zaoutis T. Epidemiology of invasive fungal disease in children. *J Pediatric Infect Dis Soc* 2017; **6**(suppl1): S3–11.
3. Westra SJ, Karmazyn BK, Alazraki AL, et al. ACR appropriateness criteria fever without source or unknown origin—child. Imaging EP on P, editor. *J Am Coll Radiol* 2016; **13**: 922–930.
4. Pearce MS, Salotti JA, Little MP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet* 2012; **380**: 499–505.
5. Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, et al. Cancer risk in 680 000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. *Br Med J* 2013; **346**: f2360. <https://doi.org/10.1136/bmj.f2360>
6. Thukral B. Problems and preferences in pediatric imaging. *Indian J Radiol Imaging* 2015; **25**: 359–364.
7. Adeyiga AO, Lee EY, Eisenberg RL. Focal hepatic masses in pediatric patients. *Am J Roentgenol* 2012; **199**: W422–W440.

8. Festejkian A, Neely M. Incidence and predictors of invasive candidiasis associated with candidaemia in children. *Mycoses* 2011; **54**: 146–153.
9. Wallace BC, Small K, Brodley CE, Lau J, Trikalinos TA. Deploying an interactive machine learning system in an evidence-based practice center. ACM Press, New York, New York, USA 2012; pp. 819. In: Proceedings of the 2nd ACM SIGHIT symposium on International health informatics - IHI '12 [Internet]. <https://doi.org/10.1145/2110363.2110464>
10. Cohn SM, Pokala HR, Siegel JD, et al. Application of a standardized screening protocol for diagnosis of invasive mold infections in children with hematologic malignancies. *Support Care Cancer* 2016; **24**: 5025–5033.
11. Donker AE, Mavinkurve-Groothuis AMC, Van Die LE, Verweij PE, Hoogerbrugge PM, Warris A. Favorable outcome of chronic disseminated candidiasis in four pediatric patients with hematological malignancies. *Med Mycol* 2012; **50**: 315–319.
12. Yen T-Y, Huang LM, Lee P-I, Lu C-Y, Shao P-L, Chang L-Y. Clinical characteristics of hepatosplenic fungal infection in pediatric patients. *J Microbiol Immunol Infect* 2011; **44**: 296–302.
13. Lin P-C, Chang T-T, Jang R-C, Chiou S-S. Hepatosplenic microabscesses in pediatric leukemia: a report of five cases. *Kaohsiung J Med Sci* 2003; **19**: 368–374.
14. Decembrino N, Zecca M, Tortorano AM, et al. Acute isolated appendicitis due to *Aspergillus carneus* in a neutropenic child with acute myeloid leukemia. *New Microbiol* 2016; **39**: 65–69.
15. Tibúrcio FR, de Sá Rodrigues KE, Vasconcelos HMM, Miranda DM, Simões e Silva AC. Usefulness of positron emission tomography in the differentiation between tumor and infectious lesions in pediatric oncology: a case report. *BMC Pediatr* 2015; **15**: 108.
16. Celkan T, Kizilocak H, Evim M, et al. Hepatosplenic fungal infections in children with leukemia – risk factors and outcome: a multicentric study. *J Pediatr Hematol Oncol* 2019; **41**: 256–260.
17. Ranjani S, Mehdi I, Mallya P, Sreenath C, Palassery R. Mucor pyelonephritis in a child with acute lymphoblastic leukemia—a case report. *Pediatr Blood Cancer* 2016; **63**: S116–S117.
18. Lashkari H, Faheem M, Kumar R, Shenoy R. SIOP 2016 Scientific Programme+Index. *Pediatr Blood Cancer* 2016; **63**: S5–321.
19. Leucht S, Lo R, Thomas K, Punnett A, Alexander S. 2013 ASPHO abstracts. *Pediatr Blood Cancer* 2013; **60**(S2): S1–105.
20. Ebadi M, Alavi S, Ghojevand N, Kazemi Aghdam M, Yazdi MK, Zahiri A. Infantile splenorenopancreatic mucormycosis complicating neuroblastoma. *Pediatr Int* 2013; **55**: e152–e155.
21. Lashkari H, Faheem M, Kumar R, Shenoy R. Successful management of breakthrough disseminated trichosporon asahii infection in a child with acute myeloid leukaemia (AML). *Pediatr Blood Cancer* 2016; **63**: S190.
22. Leucht S, Lo R, Thomas K, Punnett A, Alexander S. Utility of radiographic investigations of children undergoing intensive myelosuppressive therapy with prolonged fever and neutropenia. *Pediatr Blood Cancer* 2013; **60**: S50.
23. Noyola DE, Fernandez M, Moylett EH, Baker CJ. Ophthalmologic, visceral, and cardiac involvement in neonates with Candidemia. *Clin Infect Dis* 2001; **32**: 1018–1023.
24. Makhoul IR, Kassis I, Smolkin T, Tamir A, Sujov P. Review of 49 neonates with acquired fungal sepsis: further characterization. *Pediatrics* 2001; **107**: 61–66.
25. Ray S, Shankar S. Renal ultrasound imaging in a preterm infant with a persistently elevated C reactive protein. *BMJ Case Rep* 2018. May 26, 2018:bcr-2018-225164.
26. Sie AHL, Patel N, Spenceley N. Neonatal urinary ascites in renal candidal infection. *J Paediatr Child Health* 2006; **42**: 387–388.
27. El-Shabrawi MHF, Kamal NM, Jouini R, Al-Harbi A, Voigt K, Al-Malki T. Gastrointestinal basidiobolomycosis: an emerging fungal infection causing bowel perforation in a child. *J Med Microbiol* 2011; **60**: 1395–1402.
28. Sidhu S, Chander J, Singh K. Perinephric abscess caused by *fusarium chlamydosporum* in an immunocompetent child: Case report and identification of the morphologically atypical fungal strain. *Indian J Pathol Microbiol* 2013; **56**: 312.
29. Montravers P, Dupont H, Leone M, et al. Guidelines for management of intra-abdominal infections. *Anaesth Crit Care Pain Med* 2015; **34**: 117–130.
30. Cheung D, Puertolas-Lopez M, Scott G, et al. Decreasing overutilization of echocardiograms and abdominal imaging in the evaluation of children with fungemia. *J Clin Outcomes Manag* 2019; **26**: 270–276.