UPDATE IN RADIOLOGY

Usefulness of ultrasonography in children with right iliac fossa pain

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Abstract Acute pain in the right iliac fossa (RIF) is common in children. It can arise from a wide variety of gastrointestinal and genitourinary processes that make up the differential diagnosis with acute appendicitis (AA). In this article, we describe the most representative findings of these processes on ultrasonography (US). We emphasize the characteristics that enable these processes to be differentiated from AA.
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Utilidad de la ecografía en niños con dolor en la fosa iliaca derecha

Resumen El dolor agudo en la fosa iliaca derecha es un cuadro frecuente en la infancia. Su origen puede ser secundario a un amplio abanico de procesos gastrointestinales y genitourinarios que constituyen el diagnóstico diferencial de la appendicitis aguda. En el presente artículo se describen los hallazgos ecográficos más representativos de tales procesos, insistiendo en las características que permiten diferenciarlos de la appendicitis aguda.
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Introduction

Acute pain in the RIF is common in pediatric patients. Although AA and intestinal intussusception are the typical causes, RIF pain can also be caused by multiple gastrointestinal and genitourinary disorders that should be considered in the differential diagnosis of AA.

US represents the ideal diagnostic modality in children with abdominal pain. Its excellent anatomic resolution in the pediatric population has helped reduce the negative
appendectomy rate. Technological advances in US allow examination of the layers of the intestinal wall and surrounding mesentery with high spatial resolution. This provides new clinical applications such as the assessment of acute inflammatory activity, response to treatment and complications of Crohn’s disease, US evaluation of acute recurrent appendicitis, follow-up of intestinal involvement in Schönlein–Henoch purpura (SHP), preoperative assessment of the viability in cases of ovarian torsion, or support for the decision of performing a biopsy in celiac disease.

The objective of this study is to describe the US findings and the key diagnostic findings of those conditions that may present with acute RIF pain in children, with an emphasis on AA, since this is the most common disease in children requiring surgery and the most common source of diagnostic errors.

**Technique**

The graded compression technique described by Puylaert in 1986 is based on the fact that gradual compression on the anterior abdominal wall eliminates bowel gas and intraluminal fluid from the bowel loops, reduces the distance between transducer and appendix, and displaces bowel loops out of the RIF. This compression allows visualization of iliac vessels and psoas muscle, since the appendix is anterior to these structures (Fig. 1A). In addition to be ineffective and painful, fast compression may result in rupture of an appendix at risk for perforation.

The exam is performed in the longitudinal and transverse planes. The ascending colon appears as a nonperistaltic structure containing fluid and gas. Inferiorly, the terminal ileum, compressible and peristaltic, can be identified. The cecal base, where the appendix arises, is 2–3 cm below the terminal ileum. While the base of the appendix is at a fairly constant location, its end may move freely, and its location is therefore very variable; however, this does not translate into a statistically significant difference in the rate of appendicitis.

The topography of the superior mesenteric vessels and their relationship with the aorta and inferior vena cava should be systematically identified.

**Normal right ilioc fossa**

The digestive tract comprises four concentric layers that can be differentiated histologically. The layers from deep to superficial are the mucosa—consisting of an epithelium with underlying lamina propria and the muscularis mucosa—, the submucosa, the muscularis propria and the adventitia. US shows a penta-stratified pattern where the first (superficial mucosa), third (submucosa) and fifth (adventitia) layers are hyperechogenic, and the second (muscularis mucosa) and fourth (muscularis propria) layers are hypoechoic (Fig. 1B).

In adults, the thickness in any segment of the digestive tract is ≤3 mm. In children, it ranges between 1.5 and 3 mm in the terminal ileum and 2–3 mm in the colon, depending on the age. Valvulae conniventes are <2 mm in width and 2–5 mm in length, being more numerous in the jejunum (two or three per cm) than in the ileum (two per cm). Given its intestinal origin, the appendix exhibits similar characteristics to the digestive tract, therefore, its maximum diameter should not exceed 6 mm in the transverse plane and its wall should not exceed 3 mm. Nonetheless, histologically normal appendixes > 6 mm can also be found in cases of accumulation of secretions in the lumen, hyperplasia or fecal impaction.

The normal appendix is oval-shaped in the transverse plane and easily compressible. Conversely, in appendicitis, the appendix walls are inflamed, rigid and noncompressible. Its lumen may contain air or fluid, or be collapsed with adhesion of the mucosal layers, giving rise to a central echogenic line.

Lastly, the mesentery appears slightly echogenic.

**Acute appendicitis**

AA is the most common condition requiring surgery in children and the one leading to more diagnostic errors. Traditionally, AA has been described to occur when fecal matter or appendicoliths obstruct the appendiceal lumen, which is usually followed by infection. However, we know now that AA is not always secondary to obstruction and that several causes may lead to AA: lymphoid follicular hyperplasia obstructing the cecal–appendiceal junction, inflamed follicles in infectious processes, foreign bodies, or trauma. These factors lead to inflammation and an increase in intraluminal pressure. As a result, the appendix enlarges and induces inflammatory changes in the surrounding tissues, such as the pericecal fat and peritoneum. Ultimately, ischemia occurs and the inflamed appendix, eventually, perforates.

Sensitivity and specificity of sonography for the diagnosis of AA vary greatly between studies (up to 100 and 98%, respectively). The appendiceal diameter is considered the most relevant morphologic criteria (sensitivity > 98%) and, traditionally, the threshold diameter > 6 mm has been used for diagnosis of appendicitis. On transverse images, the appendix appears fixed, round and noncompressible. Hyperechogenicity of the pericecal fat is common. This fat may increase in volume and surround the appendix, which represents the inflamed omentum that migrates to the appendiceal area in case perforation occurs (Fig. 2A). Free fluid and mesenteric lymph nodes are frequent but unspecified. In up to 30% of cases, appendicoliths are seen in the appendiceal lumen.

Doppler signal varies depending on the stage of the disease. Although it might increase in the acute phase (Fig. 2B), it may diminish in case of appendiceal perforation. Therefore, Doppler examination alone cannot reliably distinguish between normal and abnormal appendix. Perforation can be suspected in the presence of an irregular contour of the appendix, fluid or collections, and dilated bowel loops with thickened walls (Fig. 1E). After perforation occurs, the appendix is usually decompressed and it is visible only in 30–60% of cases.

Acute pain, gas and severe obesity may complicate visualization of the appendix. Therefore, the nonvisualization of the appendix does not allow us to rule out AA despite the fact that the first studies considered the nonvisualization on US
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Figure 1  (A) US image of the normal right iliac fossa showing the psoas muscle and iliac vessels. (B) Axial US of the appendix shows the correlation between the normal pentastratified pattern and the corresponding histological layers. Hyperechogenic layers correspond to the superficial mucosa (m), submucosa (sb) and adventitia (a), while hypoechoic layers correspond to the mucosa and (mm) and muscularis propria (mc).

Recurrent acute appendicitis

In 10% of patients with AA, the symptoms and signs subside spontaneously 12–48 after the onset but they reappear later on.10 This phenomenon, known as "spontaneously resolving appendicitis", is thought to be due to the relief of obstruction. In these cases, US follow-up images show a gradual decrease in the appendiceal diameter.10 US follow-up in patients with AA, performed 6–36 h after the initial examination, represents a useful diagnostic tool that complements clinical follow-up and helps reduce the number of CT studies done on children.

Recurrence rate relates to the presence or absence of enlarged mesenteric lymph nodes. A study carried out by Cobben et al. on 60 patients showed that the subgroup of male patients with no enlarged mesenteric lymph nodes had a recurrence rate of 60%, which seems a clear indication for surgery. Conversely, the presence of enlarged mesenteric lymph nodes was associated to a lower recurrence rate.14

Figure 2  Appendicitis: (A) Transversal US image shows inflamed appendix with enlarged diameter and wall thickening, and hyperechogenicity of periappendiceal fat. (B) Longitudinal color Doppler US image shows inflamed appendix with hyperemic wall.
The term used to name this entity is also controversial. Some authors use the term "appendiceal disease" in patients with long-standing symptoms; however, to date this entity has not been satisfactorily described.

Cystic fibrosis

Patients with cystic fibrosis (CF) usually show markedly distended appendices secondary to the presence of inspissated secretions with associated pain. These cases are not to be confused with AA since in CF the appendix is distended but not inflamed. Additionally, there is no wall thickening and the concentric layer structure is intact, with no inflammation of the mesenteric fat (Fig. 2E). It has been postulated as a possible protective role of these secretions against AA considering the lower rate of occurrence in patients with CF (1–2%) compared with the normal population (7–8%). Nonetheless, the rate of perforations and abscess formation is higher, probably due to a delay in diagnosis because symptoms are often masked by the use of antibiotics.

Appendiceal mucocele

Appendiceal mucocele is characterized by distension of the appendix secondary to intraluminal accumulation of mucus. To date, four pathological processes leading to appendiceal mucocele have been described: obstruction at the cecal appendiceal junction; mucosal hyperplasia; mucinous cystadenoma and mucinous cystadenocarcinoma. US shows a distended appendix with no wall thickening and no regional inflammatory signs, with abundant echogenic content in the interior and the "onion skin" structure, a sign considered to be characteristic of mucoid material that allows differential diagnosis with appendiceal abscesses (Fig. 3).

Lymphoid hyperplasia related to viral infections

Follicular lymphoid hyperplasia is a histopathologic finding based on the enlargement of the lymphoid follicles in the lamina propria of the appendiceal mucosa, without infiltration of polymorphonuclear leukocytes. It is common in childhood, and according to some authors, it may be the cause of acute RIF pain in children. It also relates to intestinal intussusception.

Only on rare occasions does US allow for the diagnosis of this condition. In such cases, US findings include dilated appendix and thickening of the appendiceal mucosa and ileocecal valve, secondary to the presence of hypoechogenic nodules. Mesenteric lymph nodes are a constant. Cecum, mesenteric echogenicity and mobility of the distal ileum are normal.

Mesenteric lymphadenitis

Mesenteric lymphadenitis (ML) is a controversial entity, and we frequently resort to this diagnosis in patients in whom normal appendices have been removed. The term is used to refer to enlargement of some mesenteric lymph nodes, without or with ileitis. However, some papers describe the presence of enlarged (>10 mm in the short axis) mesenteric nodes in asymptomatic children. Increased color Doppler signal in the mesenteric vessels and minimal amount of free fluid may be seen (Fig. 3E). The nonvisualization of the inflamed appendix is more indicative of ML than AA.

Acute gastroenteritis

Acute gastroenteritis (AGE) is the most common inflammatory disease in children. It usually has a viral origin and the ileocolic region is the most frequently affected. The classic presentation of AGE does not require imaging studies. US shows dilated, hyperperistaltic fluid-filled small bowel loops with thin walls, where it is not uncommon to see transient intussusception (Fig. 4E).

Infectious ileitis or iliocecitis

Some bacteria—such as Salmonella, Campylobacter jejuni, Yersinia and, more rarely, Mycobacterium tuberculosis—have a strong affinity for the lymphoid tissue of the terminal ileum and give rise to enteritis whose symptoms may simulate those of AA. US findings include intestinal wall thickening and hypogenicity—usually with intact wall layers—, transmural or mucosal hypervascularity and enlargement of mesenteric lymph nodes. In contrast to AA, the mesentery is normal and the thickened bowel loops do not form a conglomerate around the appendix.

Tuberculous ileitis is rare in developed countries. It appears as asymmetrical, non-stratified thickening of the
Ileoceleal wall21-25 (Fig. 4A and B). Its clinical course is similar to that of chronic diseases with US findings similar to those of Crohn’s disease, but always with considerable involvement of the cecum.9 The microorganism induces an inflammatory process that eventually leads to ulcer formation with subsequent healing, as well as extensive infiltration of peritoneum, omentum and mesentry associated with centrally hypodense lymph nodes.24-26 There are no pathognomonic findings. Biopsy during colonoscopy and culture of lesions is the diagnostic technique of choice, while negative histologic results do not preclude tuberculosis.26

Crohn’s disease

In 25% of cases, Crohn’s disease (CD) begins in childhood, with involvement of the ileocecal region in 55% of patients.8 Acute abdominal symptoms simulating AA are not unusual. CD causes transmural inflammation that extends to the surrounding mesentery. On US this translates into circumferential wall thickening that may be segmental or multifocal, and finally, loss of wall stratification.8-10,27,28 The wall appears hypoechoic with an echogenic central line that represents the superficial mucosa (Fig. 5A and B). The mesentery is hyperechogenic and there is no motion of bowel loops with transducer pressure.10 Enlarged lymph nodes are found in approximately 15% of CD patients.29

CD is associated with intestinal neovascularization. In contrast with what happens in areas of fibrotic scarring, in active disease there is mesenteric hyperemia and “comb sign”, indicative of increased blood flow in the vasa recta (Fig. 5B). This finding may help differentiate CD from infectious or eosinophilic ileitis or ileitis associated with SHP, where vascular proliferation is less conspicuous. Vessel density, assessed by Doppler US in affected bowel loops, correlates with disease activity and is used as a non-invasive technique for monitoring the course of the disease and the response to treatment.8,28,30 Vessel density is classified as low, moderate and high if there are 0-2, 3-5, or more than 5 Doppler signals per cm,2 respectively.30

Appendiceal involvement appears in 23% of patients with CD, manifesting as appendiceal hyperemia similar to that of AA. However, thickening > 5 mm and hyperemia of the terminal ileum support the diagnosis of CD. US findings in cecum and appendix are similar in both entities and therefore cannot be used for differentiation.28

Schönlein-Henoch purpura

SHP is a small-vessel vasculitis that may affect the intestinal tract. In some patients (10-30%), the intestinal involvement may precede skin lesions, simulating AA. The episodes of paroxysmal pain are secondary to edema in the subserosa and submucosa and hemorrhagic infiltration.8,31

Characteristic US findings include diffuse, circumferential thickening of the bowel wall, with focal intramural hematomas that appear as hyperechogenic areas, giving an irregular appearance to the thickened wall.2,8,31 Associated mesenteric adenopathy and free fluid are common. The duodenum and jejunum are the initially involved sites but, with recurrent episodes, the disease extends to the ileum.

Celiac disease

Up to 25% of children with celiac disease initially present with acute abdomen. US may help make an
There are characteristic intestinal findings that may be seen in the presence of underlying celiac disease. 

Intestinal intussusception is a common complication and may be involved. For this reason, the term "neutropenic enterocolitis" seems more appropriate. Histologic examination reveals bowel wall necrosis and hemorrhage, without inflammatory or tumoral infiltration. Imaging features include asymmetrical thickening of the cecal wall (>3 mm) that is usually hyperechogenic and heterogeneous with areas of different echogenicity secondary to necrosis or hemorrhage, and redundant mucosa (Fig. 6). In most cases, Doppler US shows hypervascularity and surrounding inflammatory changes, as well as free fluid.36-38

In same patients, in addition to the findings compatible with typhlitis, there might also be thickening of the appendix, possibly due to the same causative factors of typhlitis, and surgery may therefore not be indicated. This, combined with the fact that pediatric patients are not good candidates for surgery, makes the surgical management of these children, who present with appendiceal thickening and RIF pain, controversial.39

**Intussusception**

Intussusception involves invagination of a segment of intestine into the lumen of an immediately distal segment. Intussusception is usually idiopathic, associated with lymphoid hyperplasia, secondary to viral infections. Approximately 90% of patients with intussusception are younger than two years.3 Findings on abdominal radiograph may be

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**Figure 5** Crohn’s disease. (A) Color Doppler US shows marked wall thickening of the terminal ileum mainly due to a hyperechogenic submucosa, a finding characteristic of Crohn’s disease, and mural hypervascularity. (B) Presence of multiple enlarged lymph nodes of inflammatory appearance (*) and mesenteric hyperechogenicity and hypervascularity.
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Figure 7  Axial US image of an ileocolic intussusception shows three layers of loops and the mesentery. The outer layer is the receptor loop or intussusciens, which contains the central entering limb of the intussusceptum (i), located at the center of the intussusception next to the mesentery (M) dragging some lymph nodes (*). The receptor loop also contains the everted returning limb of the intussusceptum, which is thicker, constituting the outer hypoechoic ring of the doughnut (arrows).

non-specific and the use of conventional enema to make the diagnosis is no longer justified. US is the test of choice because it provides a diagnostic accuracy of 97–100%, allows for the detection of the causes and predictive factors of irreducibility, and can be used for follow-up and assessment of response to treatment.

Approximately 90% of intussusceptions are ileocolic. The diagnostic image of intussusception is located at the receptor bowel loop, which would explain why the lesion is not detected in the RIF, but in the subhepatic region (Fig. 5E). The ‘doughnut’ sign refers to the transverse section of the intussusception that shows a thick hypoechoic ring and an echogenic center. The target sign consists of concentric hypo- and hyperechogenic rings, whose number varies depending on the extension of the edema (Fig. 7). The pseudokidney sign refers to the kidney-like appearance of the loop inside the receptor loop, in the longitudinal section (Fig. 5E), usually exceeding 5 cm in length. The main prognostic indicators for irreducibility and ischemia on US include presence of liquid trapped inside the intussusception, absence of flow on Doppler US, enlarged lymph nodes, thickening of the outer ring of the doughnut and presence of gas in the intussusceptum.

**Meckel diverticulum**

Meckel diverticulum, related to a persistent omphalomesenteric duct, occurs on the antimesenteric border of the ileum. Meckel diverticulum is a true diverticulum composed of all layers of the intestinal wall. It should be suspected in children with inflammatory signs of RIF in whom a normal appendix and a lesion connected to the terminal ileum with similar appearance to that of AA are visualized.

**Right-sided diverticulitis**

Right-sided diverticulitis is an unusual inflammatory condition that can mimic AA. It should be considered in young patients with RIF pain and normal appendix. Right-side diverticula are true diverticula, composed of all intestinal layers, and are usually congenital and solitary. US findings of right-sided diverticulitis include direct visualization of the diverticulum in the right wall of the colon, focal thickening of the colonic wall at the diverticulum site and inflammation of the adjacent fat. This condition is usually self-limited and does not require surgery.

**Enteric duplication cysts**

Enteric duplication cysts are congenital abnormalities that result in duplication of a normal bowel loop. They normally occur on the mesenteric border of the bowel, usually on the ileum. The walls are composed of all intestinal layers and most lesions do not communicate with the lumen of the digestive tract. They may contain ectopic gastric mucosa or lymphoid tissue. US examination shows a well-defined, fluid-filled mass with tubular or spherical shape and an echogenic inner mucosal layer (Fig. 8). In some cases, the content is heterogeneous as a result of hemorrhage or thick material in the interior.
Burkitt lymphoma

Burkitt lymphoma is the most common intraabdominal tumor in children aged 5–12. It usually occurs in the terminal ileum and US demonstrates bowel wall thickening with transmural involvement with loss of stratification and markedly hypochoicogenic. Ascites and enlarged mesenteric lymph nodes are frequent.

Epiploic appendagitis

Epiploic appendagitis (EA) is an unusual cause of acute abdomen in children. It is a benign and self-limited condition occurring secondary to torsion or spontaneous venous thrombosis of the draining veins of the epiploic appendages. As a result, ischemic necrosis of the fatty tissue with associated peritoneal irritation occurs. US images show a noncompressible hyperechoic ovoid mass usually 1.5–5 cm in diameter that is surrounded by a thin hypochoicogenic rim and is adherent to the colon (Fig. 6E). Color Doppler US shows absence of central blood flow, unlike the increase in blood flow normally detected in appendicitis.

Omental infarction

Omental infarction is a rare cause of abdominal pain in children. It may be primary or secondary to omental torsion, trauma, vasculitis or hypercoagulability. US findings show an ovoid noncompressible hyperechoic mass in the right flank immediately beneath the rectus abdominis. This mass is larger than that in AE, not connected to the colon and without halo. Both AE and omental infarctions are self-limited processes that usually do not require surgery.

Lymphangioma

Lymphangiomas are benign cystic tumors, usually multiloculated that arise from the endothelium of lymphatic vessels and are filled with serous or chylous fluid. Mesenteric lymphangiomas are rare and usually discovered incidentally.

Acute abdominal symptoms may occur as a result of rupture, torsion, infection or hemorrhage (Fig. 7E).

Ovarian torsion

Ovarian torsion is the most frequent alternative diagnosis to AA in girls with RIF pain. It is usually unilateral and with right-sided preference. Although it may result from excessive mobility of the ovary, it may be associated with ovarian tumors or cysts (in girls, benign teratomas).

US, CT and MRI show similar non-specific findings that vary depending on the duration of the torsion and the presence of an underlying mass (Fig. 9A–C). The most constant finding is an enlarged ovary that appears heterogeneous due to edema and hemorrhage. In 74% of cases, US examination demonstrates multiple small cysts in the periphery of the ovary. This finding alone is not indicative of torsion since it can also be seen in polycystic ovaries and even in normal ovaries in the fertile woman; but it can be indicative of torsion in the setting of pain with unilateral ovarian enlargement. The presence of fluid-blood level has been described as a pathognomonic sign of ovarian torsion. Other findings include thickened fallopian tube, fluid in the pouch of Douglas, ipsilateral deviation of the uterus and thickening of the coexisting mass wall, if present.

Sometimes, color Doppler US has a limited diagnostic utility. Although it may show absence of arterial flow, up to 60% of ovarian torsions show normal arterial waveforms because the symptoms of venous thrombosis appear before the arterial obstruction occurs. Additionally, the arterial flow persists because of the dual ovarian blood supply from the ovarian artery and the ovarian branches from the uterine artery. The most common finding is a decreased or absent venous flow. The main use of color Doppler is to the preoperative assessment of the viability of the ovary, associated with the presence of central venous flow, while absence of flow is associated with non-viability. The whirlpool sign is the identification of the twisted vascular pedicle at color Doppler US. This sign is not always visible, but its presence suggests that the ovary is still viable.
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Figure 10  Persistent urachus. Child with abdominal pain, fever and mictional syndrome. Echogenic tubular structure connected to the umbilicus (*) in contact with the bladder dome (v).

Hemorrhagic ovarian cyst

Ovarian cysts may cause pain due to hemorrhage or rupture.9 Classically they appear as avascular complex cystic lesions, with a thin reticular pattern, fluid-detritus levels and/or hyperechogenic areas in relation to coagulated blood (Fig. 8E).9 The absence of involvement of the adjacent fat helps differentiate it from an abscess. The presence of free peritoneal fluid is common.

Ovarian tumors

Most ovarian tumors in girls are benign and painless but, on occasions, they may cause pain due to compression of

Differential diagnosis of acute pain in the right iliac fossa in children

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Figure 11  Diagram depicting the anatomy of RIF and the possible disorders arising from its structures.
adjacent structures or increase in size. Cystic teratoma is the most common ovarian tumor. US shows a complex solid-cystic mass with echogenic or hypoechogenic component depending on the amount of fat, fluid or calcium (Fig. 9E).54,62 The rest of benign ovarian tumors are usually cystadenomas that usually present as large unilocular cystic lesions with thin septa that may show solid poles.

Acute pyelonephritis

In most cases of acute pyelonephritis, US findings are normal, but there might be focal or generalized renal enlargement, areas of hypo- or hyperechogenicity (Fig. 10E), loss of corticomedullary differentiation, thickening of the pelvic and/or ureteral urothelium, and/or perinephric inflammatory changes.9,63 Color Doppler US shows cortical hypoperfusion.64

Urachal anomalies

Urachal anomalies are caused by incomplete persistence of patency of the urachus. Urachal sinus refers to the persistence of the urachus at the umbilical end. At US, the persistent urachus and the urachal sinus are small-caliber tubular structures, which appear as a fluid-filled long tube or as an echogenic cord (Fig. 12). Diverticulum and cyst are fluid-filled masses, with or without communication with the bladder, respectively. Internal echoes result from infection.65

In addition to acute pyelonephritis and urachal anomalies, other urinary disorders such as ureterohydrourephrosis (Fig. 11E) and vesicoureteral reflux may also cause acute and intermittent abdominal pain.9 For this reason, the urinary system must also be assessed during US examination.

Conclusion

US is a useful technique for the evaluation of acute RIF pain in children. Multiple conditions may cause RIF pain (Fig. 11). The high spatial resolution of US in children, even better than that of CT, provides relevant information regarding these disorders and may help confirm or rule out AA, or establish an alternative diagnosis, without the need of invasive techniques.

Authorship

1. Responsible for the integrity of the study (original idea of the study): GAG.
2. Conception of the study: GAG, LRR.
3. Design of the study: LRR.
4. Acquisition of data: GAG, JBGH.
5. Analysis and interpretation of data: LRR, GAG, JBGH.
6. Statistical analysis: N/A.
7. Bibliographic search: LRR.
8. Drafting of the paper: LRR, STS.
9. Critical review with intellectually relevant contributions: GAG, JBGH and STS.
10. Approval of the final version: LRR, GAG, JBGH, STS.

Conflict of interest

The authors declare not having any conflict of interest.

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