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A practical guide for the management of acute abdominal pain with fever in patients with autosomal dominant polycystic kidney disease

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Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the development of numerous renal cysts leading to kidney enlargement and chronic kidney disease (CKD) [1]. Extrarenal manifestations, including polycystic liver disease (PLD) and connective tissue defects, are frequently observed in ADPKD. Acute cyst complications such as haemorrhage (CyH) and infection (CyI) represent rare but severe conditions of ADPKD [2, 3]. The distinction between cystic versus non-cystic abdominal complications is problematic [3]. We propose a practical guide for the diagnostic and therapeutic management of 'acute abdominal pain with fever' in patients with ADPKD.

An episode of febrile acute abdominal pain is a clinical challenge. The primary task of the physician consists of rapidly distinguishing patients who can be safely observed from patients who require hospitalization and specialist referral (Figure 1). The quickSOFA score has been developed to screen for patients at risk of developing sepsis and includes elevated respiratory rate $\geq$22 breathes per minute, altered mental status [Glasgow Coma Scale (GCS) score $<$15] and systolic blood pressure $\leq$100 mmHg. Patients with abnormal vital signs should be immediately hospitalized and intravenous (i.v.) access established.

Febrile acute abdominal pain most often derives from the digestive system but may also arise from the urinary tract or extra-abdominal diseases. The location of the pain by quadrant narrows the differential diagnosis, along with pain radiation. In ADPKD, the differential diagnosis includes both cystic and non-cystic causes of inflammation, that is such as diverticulitis and obstruction of the urinary and biliary tracts (Figure 1). Indeed, the incidence of urolithiasis is increased in ADPKD. Stone passage is painful and requires urgent management in the case of concomitant infection or ureteral obstruction. Its diagnosis is hindered by the distorted anatomy of the polycystic kidneys and the frequent intraparenchymal calcifications. Computed tomography (CT) of the abdomen is the most sensitive imaging technique for the detection and distinction of stones versus calcifications. The medical treatment of urolithiasis in ADPKD is similar to that in the general population. Obstruction and/or infection of the biliary tract are also common in ADPKD-associated PLD [4, 5]. Acute cholangitis can be suspected in the case of systemic inflammation, cholestasis and bile duct lesions (from imaging findings) [6]. Gallstones, prior cholecystectomy, duodenal diverticulosis, type 2 diabetes mellitus, recent retrograde cholangiopancreatography and kidney transplantation constitute risk factors for acute cholangitis [5]. The 2018 Tokyo guidelines help to personalize the therapeutic strategy, including the need for early biliary drainage [6].

Focusing on cyst-induced abdominal pain, CyH and CyI may take place in both renal and hepatic parenchyma (Figure 1). CyH occurs spontaneously or following contact sports or blunt trauma. Kidney and liver function usually remains stable. Renal CyH is not necessarily associated with haematuria. However, isolated CyH is a common cause of gross haematuria. Blood or urine cultures are essentially sterile. CT typically shows a spontaneous intracystic density $>$50 HU [7]. Isolated CyH is usually managed conservatively with bed rest, hydration and pain killers. Anecdotal cases of arterial embolization, (partial) nephrectomy or use of tranexamic acid have been reported for ongoing bleeding with haemodynamic instability. There is no need/indication for antibiotics. In contrast, CyI may cause abscess formation and life-threatening sepsis. CyI is 'definite' when the cyst contents (after drainage) show neutrophils or bacteria. Cyst aspiration should be encouraged when feasible, although it is not always apparent which cyst is responsible. CyI is 'probable' when four criteria are concomitantly met: fever $\geq$38°C, loin or liver tenderness, C-reactive protein plasma levels $>$70 mg/L and no CT evidence for CyH [2, 7] (Figure 1). Blood or urine cultures are mandatory to suggest the source of infection and tailor the antibiotics. Note that they remain sterile in ~50% of CyI cases [2, 7]. *Escherichia coli* represents the most frequent bacterium in CyI, with a prevalence of ~75%. Anaerobic bacteria account for ~15%. Fungi have also been detected. The conventional methods, namely ultrasonography and CT, show poor diagnostic yield in CyI, even after administration of i.v. iodinated contrast [2, 7]. The infusion of

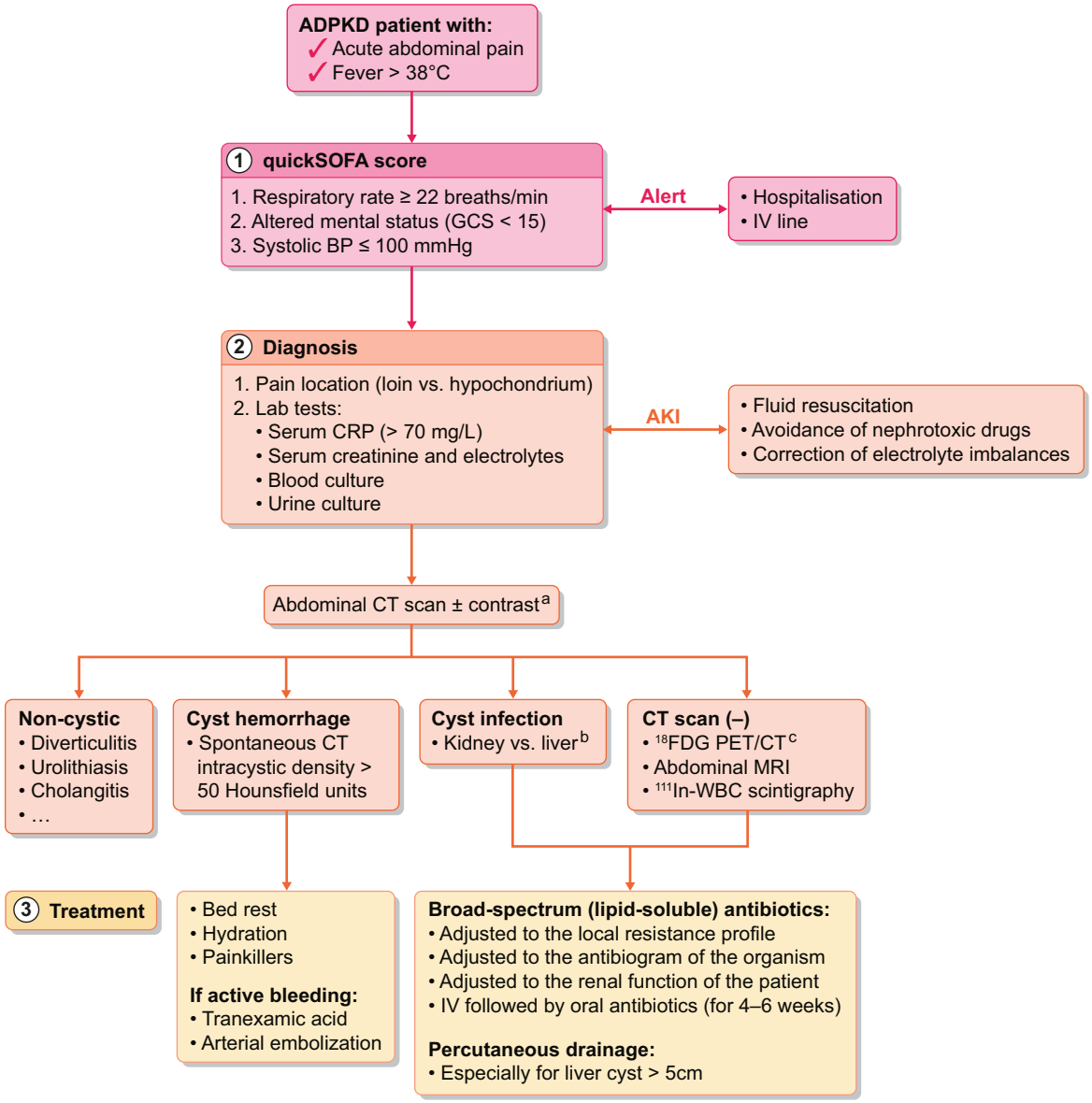

FIGURE 1: Diagnostic algorithm for the management of patients with ADPKD presenting with acute abdominal pain and fever.
AKI, acute kidney injury; BP, blood pressure; eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging. [a]The infusion of radiocontrast should only be performed if appropriate. [b]In the case of suspected cyst infection, the determination of the infected site, that is, the liver or kidney or both, is essential. [c]The choice of the imaging procedure depends on the expertise and technical resources of each clinical center.

radiocontrast in patients with advanced CKD should only be performed if the attending physician deems it appropriate.

Magnetic resonance imaging shows high intracystic signal intensity on diffusion-weighted images and wall thickening in the case of CyI [8]. However, its specificity is poor (∼66%) in severe organomegaly (which is frequent in ADPKD). 18-Fluoro-deoxy-glucose (^{18}F-FDG) positron-emission CT has proved useful in the diagnostic algorithm of CyI, especially when cyst uptake of ^{18}F-FDG is greater than the physiological accumulation of ^{18}F-FDG in the liver [9, 10]. 111-indium white blood cell (WBC) scintigraphy may represent an alternative to localize the infected cyst, although it requires radiolabeling of the patient's WBCs before reinfusion and sequential imaging (with poor spatial resolution and high interobserver variability).

In the case of abdominal sepsis, the rapid i.v. administration of fluid and broad-spectrum antibiotics is crucial. The predictors of complicated CyI include leucocytosis, atypical pathogens, early infection after transplantation and hepatomegaly. Lipid-soluble antibiotics, like fluoroquinolones, show good penetration into cysts and have bactericidal activity against Gram-negative pathogens [2]. However, resistance to fluoroquinolones is increasing worldwide. Repeated antibiotic courses and drainage procedures favour the emergence of nosocomial strains resistant to β-lactams. These water-soluble antibiotics, including carbapenems, show poor penetration into infected cysts. Based on the sparse literature, one may propose that the initial antibiotics should include drugs of low toxicity and high volume of distribution, such as quinolones or

sulfamethoxazole/trimethoprim, to be continued for 4–6 weeks. Initial dual therapy seems superior to monotherapy [2]. Drug dosage should be adapted to CKD. Second-line antibiotics include cefotaxime or vancomycin. In the absence of improvement post- antibiotics, percutaneous puncture of the infected cyst should be performed for cyst decompression and bacteriologic documentation. Large (diameter $\geq$5 cm) cysts may particularly benefit from early drainage, namely in the liver [2]. Emergent surgical intervention with open or laparoscopic cyst drainage, drain placement, partial or total nephrectomy or liver cyst resection of partial hepatectomy may be required. Failure of clinical improvement with antibiotics should also raise the suspicion of a fungal infection. Recurrent renal CyI in patients evaluated for kidney transplantation may justify pretransplant nephrectomy. Liver transplantation could be considered in patients with recurrent liver CyI or acute cholangitis.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest with regards to the present manuscript.

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