

Problem-solving combined with ultrasonography: a strategy for internists to improve case management and reduce diagnostic errors

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ABSTRACT

The rate of errors in the diagnostic process is reported in the literature to be between 10% and 15%. Most of these errors are various forms of cognitive errors, which can be reduced by using a problem-solving approach. Here we present two cases showing how a problem-solving approach integrated with ultrasound information, often available to internists using point-of-care instruments, and clinical feed-back can help to reach the correct diagnosis and aid the management of complex cases of internal medicine.

Introduction

The rate of errors in the diagnostic process is reported in the literature to be between 10% and 15%, with the rate being highest in specialties in which patients are diagnostically undifferentiated, such as emergency medicine, general practice and internal medicine.¹ While defects or deficiencies in organizational boundaries, care processes and operators are the bases of error in the care of patients, errors in the diagnostic process can arise from various forms of cognitive errors, such as:²⁻⁴ i) context errors, in which the physician inappropriately limits consideration to only one set of diagnostic possibilities, in lieu of others; ii) availability errors, in which the physician chooses the most likely diagnosis over conditions that are rarer, or chooses conditions that he or she is most familiar with;

and iii) premature closure, such that once a plausible condition is identified, other possibilities are not fully considered – the physician just stops thinking.

Clinical problem-solving is based on hypotheses and deduction but also on a probabilistic approach. It is a sequential deductive process, because it involves the acquisition of data by searching and screening, interpretation of data, hypothesis generation and evaluation. During the course of clinical problem-solving physicians formulate hypotheses and analyze data to test the hypotheses. The approach is, however, also probabilistic because it is based on associations between clinical variables (such as frequency or prevalence) and provides a measure of likelihood that a hypothesis is correct.⁵

Most errors arise when only an intuitive approach is used; in contrast, conclusions drawn from an analytic assessment are generally reliable. Analytic failures can occur, but these are usually due to other factors such as cognitive overload, fatigue or emotional perturbations.¹

In 2004, the American Institute of Ultrasound in Medicine concluded that the concept that ultrasound could be the stethoscope of the future had in fact already become reality and a recent review published in the *New England Journal of Medicine* highlighted the numerous applications of point-of-care ultrasonography in medicine (Table 1).⁶ Indeed, appropriate use of ultrasonography can reduce medical errors, provide a *real-time* diagnosis, replace or complement more complex imaging methods and, sometimes, reduce the need to consult radiologists for particularly demanding investigations. It should, however, be emphasized that the indiscriminate use of ultrasonography can lead to unnecessary interventions in the case of false positive findings and inappropriate interventions in the case of false negative ones.

The following two cases are focused on the usefulness of *problem-solving*, combined with *internist ultrasonography* to facilitate the diagnostic process, reducing diagnostic error.

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Case #1. Jaundice with a long unrecognized etiology

Description of the case

A 60-year old woman was referred to us with severe jaundice, anorexia, and fever, associated with microcytic anemia (hemoglobin 8.1 g/dL, mean corpuscular volume 81 fL), neutrophilic leukocytosis (white blood cell count 28,900/mm³, neutrophils 25,020/mm³), biological inflammatory syndrome [C-reactive protein (CRP) 178 mg/L, erythrocyte sedimentation rate 120 mg/L], abnormal liver function tests [aspartate aminotransferase (AST), 157 U/L, alanine aminotransferase (ALT) 71 U/L, total bilirubin 173 mg/dL, direct bilirubin 9.3 mg/dL, gammaglutamyltransferase (GGT) 107 U/L, alkaline phosphatase (ALP) 364 U/L] and abnormal coagulation tests (prothrombin time 1.56 s). The patient had taken antibiotic therapy (ceftriaxone 1 g i.m.) for a week at home, without benefit.

On physical examination the patient had jaundice of the skin and mucosa, normal hemodynamic parameters (blood pressure 110/70 mmHg, heart rate 100 beats/min, SaO₂ 90%), and a body temperature of 38°C.

She had a history of neurological complications from previous meningitis and psychiatric manifestations. She had had multiple admissions to other medical wards for recurrent cholangitis, associated with intrahepatic cholestasis (no documentation of this was available, except for a few discharge letters). One month previously she had been diagnosed with bile duct cancer and a plastic biliary stent had been placed by endoscopic retrograde cholangiopancreatography (ERCP).

Abdominal computed tomography (CT) had been performed on that occasion, which showed solid tissue of the proximal common bile duct, below the confluence of the bile, with dilatation of the intrahepatic bile duct. Pericaval, peripancreatic, inter-aortocaval and hepatic hilar lymph nodes were enlarged. CT scan of the chest showed bilateral pulmonary nodules, compatible with metastases (maximum diameter of 1 cm). ERCP showed lithiasis of the common bile duct (1.5

cm) and stenosis (2 cm) of the common hepatic duct with dilatation of the intrahepatic bile duct.

The patient was not treated with chemotherapy (gemcitabine), in consideration of her psychiatric manifestations.

Formulation of the clinical problem

The clinical problem was jaundice, anorexia, and fever, associated with microcytic anemia, biological inflammatory syndrome, alterations of liver and coagulation tests in a patient with a biliary stent for cancer of the bile duct.

This clinical problem raises two questions: i) What are: the possible causes of extrahepatic cholestasis in adults? and ii) What are the potential complications in patients with cholangiocarcinoma and palliative stenting?

The possible causes of extrahepatic cholestasis in adults are i) lithiasis of the common bile duct; ii) neoplasms (cholangiocarcinoma, carcinoma of the ampulla); iii) pancreatic diseases (neoplasm of pancreatic head, chronic pancreatitis, pancreatic pseudocyst of the head); iv) stenosis of the common bile duct and congenital malformations (cysts, Caroli's disease); and v) extrahepatic cholestasis without pathological significance in the post-cholecystectomy setting and in elderly subjects.⁷

The potential complications in patients with cholangiocarcinoma and palliative stenting are: i) recurrent sepsis; ii) biliary obstruction and occlusion of the stent; iii) progression of the malignancy; and iv) acute cholecystitis.

Formulation of the diagnostic hypotheses

In the light of the clinical problem and its possible causes, we formulated three diagnostic hypotheses: i) a new episode of cholangitis associated with obstruction of the biliary stent; ii) a new episode of cholangitis secondary to displacement of the biliary stent; and iii) a super-infection of prosthetic material with secondary sepsis.

Table 1. Applications of point-of-care ultrasonography in some medical specialties.

Specialty	Ultrasound applications
Cardiology	Echocardiography, intracardiac assessment
Critical care medicine	Procedural guidance, pulmonary assessment, focused echocardiography
Emergency medicine	FAST, focused emergency assessment, procedural guidance
Endocrinology	Assessment of thyroid and parathyroid glands, procedural guidance
Nephrology	Vascular access for dialysis
Neurology	Transcranial Doppler, peripheral nerve evaluation
Pulmonary medicine	Transthoracic pulmonary assessment, endobronchial assessment, procedural guidance
Rheumatology	Monitoring of synovitis, procedural guidance
Urology	Renal, bladder and prostate assessment, procedural assessment

Modified from Moore and Copel, 2011.⁶

Abdominal ultrasonography

In order to obtain more information we performed an ultrasound of the abdomen (Figure 1).

This showed that the liver contained multiple echo-free lesions secondary to dilatation of the intrahepatic bile duct, dilatation of the bile duct with a block near the outlet in the papilla. There were no stones in the gallbladder.

We reviewed the case and asked ourselves two further questions: i) What is the meaning of the ultrasound evidence of cysts communicating with the intrahepatic bile duct? and ii) Had we studied the history sufficiently, before the diagnosis of cholangiocarcinoma, of the intrahepatic cholestasis and recurrent cholangitis in the absence of gallbladder lithiasis?

Considering the possible etiologies of multiple cysts in the liver, two groups can be distinguished. Those in which the cystic lesions communicate with the bile duct and those in which they do not.⁸

Cystic lesions that do not communicate with the bile duct include hepatorenal polycystosis, liver polycystosis and biliary hamartomas.

Hepatorenal polycystosis (PKD1 or PKD2) is one of the most common hereditary diseases. It is a monogenic, autosomal dominant condition with an incidence of 1:1-2000. Liver cysts are more numerous and voluminous in women and in older age renal involvement prevails. Ultrasonography is used in the diagnosis of complications, of which the most frequent are intracystic hemorrhage, infection and post-traumatic rupture.

Liver polycystosis is rare. It has been described in about 50 families. Its manifestations and complications are similar to those of hepatorenal polycystosis.

Biliary hamartomas (Von Meyenburg complexes) are embryogenic abnormalities. They may be associated with polycystic kidney disease, Caroli's disease, and congenital hepatic fibrosis. Rarely, they may undergo neoplastic transformation. Ultrasound findings are from two to multiple hypoechoic, hyperechoic or heterogeneous lesions. The diagnosis is made by nuclear magnetic resonance (NMR) imaging.

Cystic lesions that are in contact with the bile duct include Caroli's disease and syndrome, and peribiliary cysts.

Cystic dilations may be found in contact with the wall of the main extrahepatic bile duct and periportal veins (diameter from 1 to 2 cm), predominantly on the left. They are described in severe liver disease (cirrhosis, portal hypertension) and may be associated with polycystic liver/kidney, infection, metastases, complications after transplantation, and localized compression of the bile duct. The hypothesized pathogenesis include congenital, ischemic and mechanical mechanisms. The diagnosis is made by NMR imaging.

The other question we asked when reviewing the case was, independently of the diagnosis of cholangiocarcinoma, what are the causes of recurrent cholangitis in the absence of gallbladder lithiasis? The possibilities include primary sclerosing cholangitis, Caroli's disease and recurrent pyogenic cholangitis.

Additional diagnostic hypotheses in the light of the information acquired

Applying a cognitive approach to problem-solving and integrating the information from ultrasound studies we had two elements: i) the detection of multiple cystic dilations communicating with the intrahepatic bile duct and ii) a history of recurrent cholangitis without gallbladder lithiasis in a patient with cholangiocarcinoma. These elements led us to suspect Caroli's disease complicated by cholangiocarcinoma, with current stenosis of the palliative stent and secondary cholangitis.

Verification of the hypothesis

Blood cultures were negative. We did not perform cholangio-NMR considering the psychiatric manifestations, but did carry out ERCP which revealed the intrahepatic bile duct with dilated cysts, in confirmation of the suspected Caroli's disease, and stenosis of the common bile duct.

Management and clinical evolution

Broad-spectrum antibiotics (piperacillin-tazobactam) were given. The stenosis of the common bile duct was relieved and a new metal stent was placed. This was well tolerated, the patient became afebrile and her laboratory parameters improved (total bilirubin 4.71 mg/dL, direct bilirubin 2.48 mg/dL).

The patient was discharged with medium-dose steroid therapy, ursodeoxycholic acid (10 mg/kg) and the indication for abdominal ultrasound evaluation in first-degree relatives.

Two months later she had a new episode of cholangitis due to partial obstruction of the stent, with a partial response to antibiotic therapy. Seven months after the first hospitalization she was admitted again because of another episode of cholangitis, for which she was given antibiotics (full-dose piperacillin-tazobactam), hydrated and treated with steroids (prednisone 40 mg). Despite this management, the cholangitis evolved into sepsis and the patient died.

Focus on Caroli's disease

Caroli's disease is a rare congenital condition (incidence 1:1,000,000 with males and females equally



Figure 1. Abdominal ultrasound of case #1.

affected), characterized by fusiform or saccular dilata-tions of larger diameter intrahepatic bile ducts. The pathogenesis is unknown, but it is often an autosomal recessive trait, especially if associated with polycystic kidney disease.

The differential diagnoses include primary scleros-ing cholangitis, polycystic liver disease (hepatic and renal cysts), recurrent pyogenic cholangitis (this is dif-ficult to differentiate but there is sepsis and dilatation of extrahepatic as well as intrahepatic bile ducts with unusual saccular dilatations), and choledochal cysts (also hereditary, but cysts involve only the extrahep-atic bile duct).

Patients begin to develop symptoms of Caroli's disease between 5-20 years old, or sometimes even later (80% of events occur in patients <30 years old). Following the onset of the first symptoms there is a sharp deterioration in the patient's quality of life, with the development of intrahepatic stones, intrahepatic abscesses, sepsis, which causes recurrent fever, jaun-dice, constant pain in the right upper quadrant of the abdomen, and acute cholangitis (64%). Potential com-plications include abscess, intra- and extra-hepatic cholelithiasis, cholangiocarcinoma (2.5-16%), chol-an-gitis, liver cirrhosis and, rarely, amyloidosis.

The diagnosis is made on the basis of laboratory tests showing cholestasis, neutrophilic leukocytosis, vitamin K malabsorption and a reduction in hepatic synthetic function; demonstration of the continuity of the cystic lesions with the biliary tract by abdominal ultrasound, CT of the abdomen, ERCP (the gold stan-dard), percutaneous transhepatic cholangiography or cholangio-NMR; and liver histology showing local-ized and non-obstructive dilatation of the bile ducts, intraluminal protrusions of the ductal walls and intra-ductal vascular tracts (arterial and venous portals).

An associated condition is Caroli's syndrome or congenital hepatic fibrosis. Whereas Caroli's disease involves the major tracts of bile ducts, the syndrome affects all parts of the intrahepatic ducts, small and large. Caroli's syndrome is frequently associated with polycystic kidney disease and can be inherited in an autosomal dominant or autosomal recessive manner; other associations are sponge kidney and tubular ec-tasia (Cacchi-Ricci's disease).

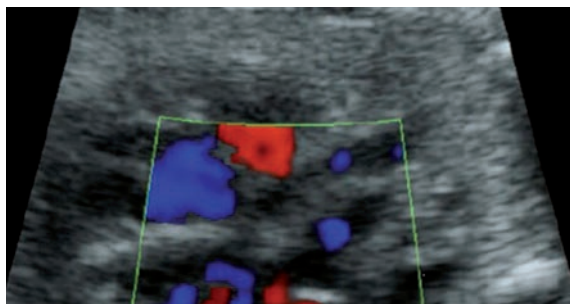


Figure 2. Abdominal ultrasound of case #2 showing left intrahepatic cholestasis.

The hypothesized pathogenesis of Caroli's disease is that biliary stasis enables carcinogenic substances contained in the bile to provoke chronic inflammation and dysplasia of biliary epithelium.

The treatment depends on the extent of the anom-alies. Localized forms can be managed with resection, lobectomy or hemi-hepatectomy, which often gives full and permanent benefit. Widespread forms are treated conservatively, with appropriate antibiotic therapy for cholangitis, ursodeoxycholic acid for intrahepatic lithi-asis, endoscopic therapy (sphincterotomy for clearance of intrahepatic stones), internal bypass, and liver trans-plantation (although the prognosis is poor if there is concomitant liver fibrosis and cholangitis and is not rec-ommended in the case of cholangiocarcinoma).

First-degree relatives should undergo abdominal ultrasound screening.

Case #2. Abdominal pain, vomiting and fever

Description of the case

A 44-year old man came to our observation be-cause of abdominal pain, vomiting and fever. He had a history of ulcerative colitis in clinical remission, which had been diagnosed a few years previously. In the preceding 5 years he had been seen occasionally in outpatient clinics and been admitted to hospital with a diagnosis of jaundice secondary to biliary lithiasis, which was managed with cholecystectomy and ther-a-peutic ERCP. However, the persistence of cholestasis without jaundice led to the performance of a liver biopsy (non-diagnostic) about 1 year previously. The patient was not taking any medications on a chronic basis, except for non-steroidal anti-inflammatory drugs for occasional episodes of migraine.

Physical examination was normal, except for ab-dominal tenderness.

The laboratory findings were as follows: neutrophil leukocytosis (white blood cell count 15,000/mm³, neu-trophils 12,000/mm³), biological inflammatory syn-drome (CRP 91-27 mg/L), altered liver tests (ALT 371-65 U/L, ALP 485-280 U/L).

Abdominal ultrasonography revealed left intrahep-atic cholestasis (Figure 2).

Formulation of the clinical problem

The clinical problem was jaundice and fever in a pa-tient with persistent intrahepatic cholestasis and a pre-vious diagnosis of chronic inflammatory bowel disease.

This clinical problem raises at least three ques-tions: i) What is cholestasis without jaundice? ii) What are the causes of intrahepatic cholestasis in adults? and iii) What medications cause cholestasis?

Cholestasis without jaundice is often diagnosed following the incidental discovery of asymptomatic elevations of ALP and GGT. An increase in bilirubin levels is a late event. An isolated increase of GGT is not specific to cholestasis and this enzyme is often in-duced by alcohol or drugs. An isolated increase of ALP can be observed in rare diseases (*e.g.*, progres-

sive familial intrahepatic cholestasis I and II, deficiency of bile acid synthesis), bone diseases (*e.g.* Paget's disease) and pregnancy. The cut-off values of the laboratory parameters are the subject of debate: ALP > 1.5 and GGT > 3 times the upper limit of normal have been proposed.

Intrahepatic cholestasis can be divided into hepatocellular and cholangiocellular forms. The causes of these two forms of intrahepatic cholestasis in adulthood are shown in Table 2.⁹

Medications that can cause cholestasis are listed in Table 3.

Table 2. Causes of intrahepatic cholestasis in adulthood.

Hepatocellular cholestasis	Cholangiocellular cholestasis
Sepsis, endotoxemia-induced cholestasis	Primary biliary cirrhosis (AMA+/AMA-)
Cholestatic variety of viral hepatitis	Primary sclerosing cholangitis
Alcoholic or non-alcoholic steatohepatitis	Overlap syndromes of primary biliary cirrhosis and primary sclerosing cholangitis with autoimmune hepatitis
Drug or parenteral nutrition-induced cholestasis	IgG4-associated cholangitis
Genetic disorders (<i>e.g.</i> ACB4 deficiency, intrahepatic cholestasis of pregnancy, erythropoietic protoporphyria, benign recurrent intrahepatic cholestasis, progressive familial intrahepatic cholestasis)	Idiopathic adulthood ductopenia
Malignant infiltrating disorders (<i>e.g.</i> hematologic disease, metastatic cancer)	Ductal plate malformations: biliary hamartoma, Caroli's syndrome
Benign infiltrating disorders (<i>e.g.</i> amyloidosis, sarcoidosis hepatitis and other granulomatoses, storage diseases)	Cystic fibrosis
Paraneoplastic syndromes (<i>e.g.</i> Hodgkin's disease, renal carcinoma)	Drug-induced cholangiopathy
Ductal plate malformations (<i>e.g.</i> congenital hepatic fibrosis)	Graft-versus-host disease
Nodular regenerative hyperplasia	Secondary sclerosing cholangitis (due to various forms of cholangiolithiasis, ischemic cholangiopathies: hereditary hemorrhagic teleangiectasia, polyarteritis nodosa and other forms of vasculitis), infectious cholangitis related to AIDS and other forms of immunodepression, etc.)
Vascular disorders (<i>e.g.</i> Budd-Chiari syndrome, veno-occlusive disease, congestive hepatopathy)	
Cirrhosis (any cause)	

Modified from European Association for the Study of the Liver, 2009.⁹

Table 3. Medications that can cause intrahepatic cholestasis.

Hepatocellular cholestasis	Ductular/ductal cholestasis
Sex hormones	Allopurinol
Carbamazepine	Amoxicillin-clavulanic acid
Chlorpromazine	Azathioprine
Amoxicillin-clavulanic acid	Barbiturates
Trimethoprim-sulfamethoxazole	Captopril
Erythromycin, clarithromycin	Carbamazepine
Nitrofurantoin	Chlorpropamide
Chlorpropamide	Clindamycin
Azathioprine	Phenytoin
Cyclosporine	Sulpiride
Propafenone	Trimethoprim-Sulfamethoxazole
Nifedipine	Medicinal herbs
Medicinal herbs	
NSAIDs, nimesulide	

NSAIDs, non-steroidal anti-inflammatory drugs.

Formulation of the diagnostic hypotheses

In the light of the clinical problem and the information available, we formulated four diagnostic hypotheses: i) cholestasis secondary to viral hepatitis, ii) primary biliary cirrhosis; iii) primary sclerosing cholangitis; and iv) infiltrative liver disease.

Verification of the hypotheses

Tests for hepatotropic viruses (hepatitis B surface antigen and core antigen, hepatitis C virus) were negative.

There was no evidence of organ-specific immune disorders (ANA, AMA, ASMA, LKM: negative) and immunoglobulins were within normal limits.

Cholangio-NMR showed moderate dilatation of the left intrahepatic hemi-biliary system, which had the appearance of a rosary and seemed to contain material with low-signal intensity, a finding compatible with sclerosing cholangitis. The presence of intra-ductal calculi could only be suspected; the right intra-hepatic biliary ducts, common bile duct, cystic duct and main pancreatic duct all appeared normal.

We made a diagnosis of sclerosing cholangitis

Management and clinical evolution

The patient was treated with ursodeoxycholic acid (15 mg/kg), obtaining progressive normalization of the indices of cholestasis and improvement of symptoms. At discharge, outpatient follow-up was recommended.

The patient did not return for further checks. However, 9 months later he had a new episode of abdominal pain associated with vomiting, which did not benefit from treatment with proton pump inhibitors. He underwent endoscopy which was positive for antral gastritis and a hiatal hernia. Because of the development of jaundice in the following days, he went to the Emergency Department of another hospital, where he was working, and where it was proposed that he was admitted. The patient refused and returned to our Unit.

On admission, the laboratory tests showed:

cholestasis (total bilirubin 7.16 mg/dL, direct bilirubin 6.68 mg/dL, ALP 489 U/L, GGT 423 U/L), hepatonecrosis (ALT 412 U/L), and a biological inflammatory syndrome (CRP up to 113 mg/L). Physical examination revealed cutaneous jaundice, a soft abdomen with pain, normal bowel sounds and hemodynamic parameters within the norm. Blood cultures were performed (negative) and the patient was started on empirical antibiotic therapy with piperacillin/tazobactam, which produced a progressive clinical remission.

The diagnosis was cholangitis in a patient with an acute exacerbation of primary sclerosing cholangitis and associated ulcerative colitis in remission. The patient was scheduled for outpatient follow-up of primary sclerosing cholangitis and ulcerative colitis.

Focus on the internist ultrasound process in the case of detection of intrahepatic bile duct dilatation

Intrahepatic bile duct abnormalities are often discovered by chance or, sometimes, during investigations for abdominal colic, jaundice (if multisegmental), or cholestasis. Ultrasound is the first step to differentiate the etiology of dilated intrahepatic bile ducts. The search for a neoplastic lesion associated with dilatation differentiates two groups of pathologies: biliary disease not caused by a parenchymal tumor and biliary disease secondary to a lesion in the adjacent parenchyma.

In the case of no abnormalities of the liver parenchyma, various patterns may be seen: unifocal stenosis, multifocal stenosis and no stenosis.

Unifocal stenosis (Figure 3) may develop as the outcome of surgery or biliary trauma and cause bile duct dilatation, or be the initial manifestation of primary sclerosing cholangitis (peripheral/segmental).

Multifocal stenosis (Figure 4) is typical of primary sclerosing cholangitis and autoimmune cholangitis. In the former case there is alternation of strictures and dilatations, giving the appearance of a string of pearls, and

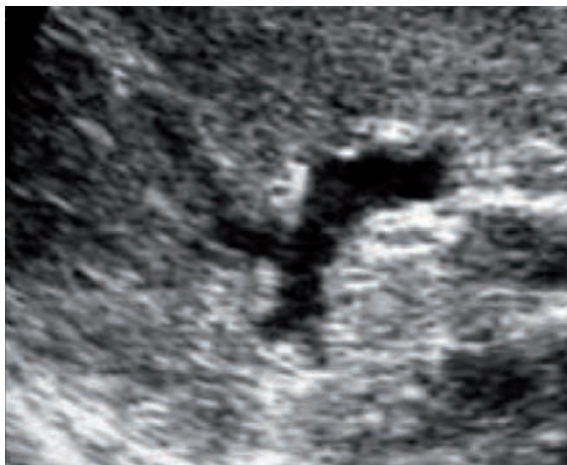


Figure 3. Abdominal ultrasound: unifocal stenosis.

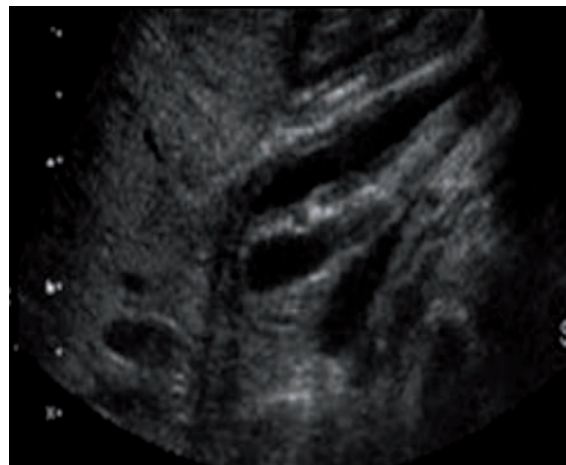


Figure 4. Abdominal ultrasound: multifocal stenosis.

often intrahepatic lithiasis. The gold standard diagnostic investigation is cholangio-NMR, which shows thickening of the bile duct. The median age of affected patients is 40 years and 60-70% of cases occur in subjects with inflammatory bowel disease (especially ulcerative colitis). Markers of autoimmunity are negative, except ANCA, which is positive in 65-72% of cases. In autoimmune cholangitis there is extended segmental stenosis, frequently to the common hepatic duct, with dilatations before and after the strictures. Patients with this condition tend to be elderly subjects with autoimmune pancreatitis. They are ANCA-negative, sometimes have raised levels of IgG and respond to steroid therapy.

Finally, dilated intrahepatic bile ducts in the presence of normal liver parenchyma and absence of intrahepatic stenosis may be due to intrahepatic lithiasis (Figure 5), stricture of the biliary tree-digestive tract anastomosis, low phospholipid associated cholelithiasis (LPAC) syndrome, adenomas/papillomatosis, Caroli's disease and parasitosis (roundworm). Intrahepatic lithiasis is more frequent in the left side of the liver, is rare in Europe, and may occur in isolation or associated with gallstones and intrahepatic bile duct lithiasis. Rare, multiple adenomas of the biliary tract, which may be secretory (with secondary jaundice, abdominal pain) or not (31%) degenerate into differentiated adenocarcinoma in 72% of cases, but resection is associated with a good prognosis.

The causes of unifocal or multifocal biliary dilatation associated with a mass (Figure 6) are usually biliary stricture due to malignancy, metastases, hepatocellular carcinoma infiltrating the bile ducts or cystic lesions. The malignant causes of biliary stricture include cholangiocarcinoma, intrahepatic cholangiocarcinoma and Klatskin's tumor. This tumor is poorly visualized on ultrasound if small, but is seen better in magnetic resonance imaging (contrast uptake after 3 min). It is associated with intrahepatic lithiasis, sclerosing cholangitis or congenital abnormalities, with chronic inflammation of the bile duct. Cystic lesions include hydatid cysts, hepatic cystadenoma and simple cysts (in the case of hemorrhage).

Recommendations for evaluating the adult patient with cholestasis

The recommendations of the European Association for the Study of the Liver regarding evaluation of adults with cholestasis are listed below. The evidence and recommendations are graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE system) (Table 4).⁹

- A detailed history and physical examination are essential (III/C1).
- Abdominal ultrasonography is the first-line non-invasive imaging procedure in order to differentiate intra from extrahepatic cholestasis (III/C1).
- Testing for serum antimitochondrial antibodies (AMA) is mandatory in adults with chronic intrahepatic cholestasis (III/C1).
- Magnetic resonance cholangiopancreatography

(MRCP) is the next step to consider in patients with unexplained cholestasis (III/C1).

- Endoscopic ultrasound (EUS) is an alternative to MRCP for evaluation of distal biliary tract obstruction (II2/B1).
- Diagnostic endoscopic retrograde cholangiopancreatography (ERCP) should be reserved for highly selected cases. If the need for a therapeutic maneuver is not anticipated, MRCP or EUS should be preferred to ERCP because of the morbidity and mortality related to ERCP (II2/A1).
- A liver biopsy should be considered in patients with otherwise unexplained intrahepatic cholestasis and negative AMA test (II/C1).

Genetic testing for *ABCB4*, when available, should be considered in patients with a negative AMA test and biopsy findings that might be compatible with primary biliary cirrhosis or primary sclerosing cholangitis.

Discussion

Both case descriptions show how analysis with problem-solving and feedback of the case are fundamental for reducing some cognitive errors (especially

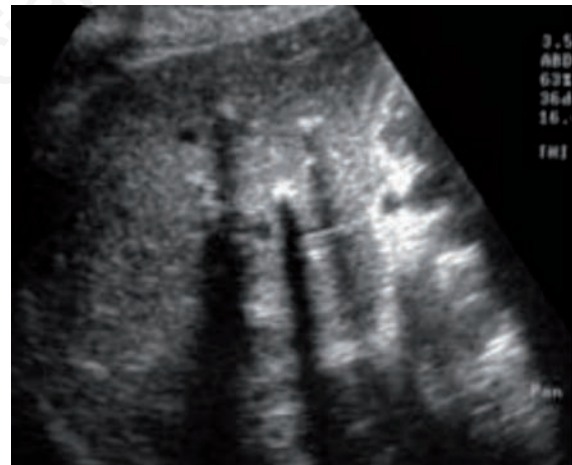


Figure 5. Abdominal ultrasound: intrahepatic lithiasis.



Figure 6. Abdominal ultrasound: unifocal/multifocal biliary dilatation associated with a mass.

Table 4. Categories and grading of evidence and strength of recommendations.

Categories of evidence		
Grade	Evidence	
I	Randomized controlled trials	
II-1	Controlled trials without randomization	
II-2	Cohort of case-control analytic studies	
II-3	Multiple time series, dramatic uncontrolled experiments	
III	Opinions of respected authorities, descriptive epidemiology	
Evidence grading		
Evidence	Notes	
High quality	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate, any change of estimate is uncertain	C
Recommendations		
Strong	Factors influencing the strength of recommendation included the quality of the evidence, presumed patient important outcomes, and cost	1
Weak	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption	2

Modified from European Association for the Study of the Liver, 2009.⁹

context and availability errors) and picking up overlooked elements (e.g. the association between inflammatory bowel disease - primary sclerosing cholangitis; intrahepatic cholestasis without lithiasis - recurrent cholangitis).

Abdominal ultrasound by internists, combined with problem-solving, should be considered part of the case management of patients with cholestasis, with the aim of achieving two main outcomes: accelerating the diagnosis and reducing costs.

With regards to accelerating the diagnosis, the reduction in the diagnostic latency should be associated with a secondary reduction of mortality and improved quality of life of the patients. Indeed, in both of the cases presented here, the lack of an initial analytical approach (reasoning process with problem-solving combined with abdominal ultrasound) resulted in a late diagnosis. In the first case this determined the patient's death. However, the combined approach has, at least, made it possible to screen first-degree relatives for Caroli's disease. In the second case the diagnosis enabled the correct treatment to be given and appropriate follow-up to be planned (essential for the screening of cholangiocarcinoma and intestinal neoplasia).

With regards to a reduction of costs, although this is probable, there is a lack of cost-efficacy and cost-benefit studies comparing ultrasound by internists and ultrasound by radiologists. In a search of PubMed we found only one cost-effectiveness study on the usefulness of contrast-enhanced ultrasonography in patients with hepatic lesions.¹⁰

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