

Review Article: Point-of-Care Ultrasound Assessment of Tropical Infectious Diseases—A Review of Applications and Perspectives

Sabine B elard,* Francesca Tamarozzi, Amaya L. Bustinduy, Claudia Wallrauch, Martin P. Grobusch, Walter Kuhn, Enrico Brunetti, Elizabeth Joekes, and Tom Heller

Center of Tropical Medicine and Travel Medicine, Department of Infectious Diseases, Division of Internal Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; Department of Pediatric Pneumology and Immunology, Charit  Universit tsmedizin Berlin, Berlin, Germany; Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, World Health Organization Collaborating Centre for Clinical Management of Cystic Echinococcosis, University of Pavia, Pavia, Italy; Paediatric Infectious Diseases Research Group, Institute for Infection and Immunity, St. George's University of London, London, United Kingdom; Department of Medicine, Klinikum Muenchen-Perlach, Munich, Germany; Center for Operational Medicine, Medical College Georgia, Georgia Regents University, Augusta, Georgia; Division of Infectious and Tropical Diseases, University of Pavia/IRCCS San Matteo Hospital Foundation, Pavia, Italy; Department of Radiology, The Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, United Kingdom

Abstract. The development of good quality and affordable ultrasound machines has led to the establishment and implementation of numerous point-of-care ultrasound (POCUS) protocols in various medical disciplines. POCUS for major infectious diseases endemic in tropical regions has received less attention, despite its likely even more pronounced benefit for populations with limited access to imaging infrastructure. Focused assessment with sonography for HIV-associated TB (FASH) and echinococcosis (FASE) are the only two POCUS protocols for tropical infectious diseases, which have been formally investigated and which have been implemented in routine patient care today. This review collates the available evidence for FASH and FASE, and discusses sonographic experiences reported for urinary and intestinal schistosomiasis, lymphatic filariasis, viral hemorrhagic fevers, amebic liver abscess, and visceral leishmaniasis. Potential POCUS protocols are suggested and technical as well as training aspects in the context of resource-limited settings are reviewed. Using the focused approach for tropical infectious diseases will make ultrasound diagnosis available to patients who would otherwise have very limited or no access to medical imaging.

INTRODUCTION

Ultrasound (US) has been used to aid diagnosis and to guide therapy in a large number of tropical infectious diseases for a long time.¹ During the past two decades, technological advances have improved image quality and significantly reduced the size and price of US equipment. As a result, US has been established as a point-of-care test in clinical decision making and for procedural guidance in various medical specialties.² Point-of-care ultrasound (POCUS) is one of the few novel diagnostic tools to which the criticism of inflationary use of the term point-of-care does not apply.³ Emergency medicine (EM) physicians have pioneered and greatly advanced the point-of-care application of US. Today, the “focused assessment with sonography for trauma” (FAST) protocol is not only well recognized as a standardized diagnostic test in emergency departments, but also constitutes an integral part of diagnostic algorithms and EM training.^{4–7} The fundamental difference between POCUS and conventional US examination is that POCUS is performed by the treating physician who aims to answer simple, usually binary questions relevant to immediate patient management (e.g., “Is there a pleural effusion, yes or no?”). POCUS is not a comprehensive US assessment.⁸ Diagnoses for which POCUS is suitable should fulfill two criteria: 1) diagnosis must be relevant to consecutive treatment decision making and 2) diagnosis must be easily and accurately recognizable by physicians applying US without the necessity for extended US training. Whereas patients’ benefit from POCUS in affluent settings is mainly a reduced time to diagnosis and further management,

POCUS in resource-constrained settings provides the additional benefit that it is frequently the only diagnostic imaging modality available.^{9,10}

This review first describes the development and application of “focused assessment with sonography for human immunodeficiency virus (HIV)–associated tuberculosis (TB)” (FASH),^{11–16} which is the most widely studied and implemented application of POCUS in infectious diseases to date. Subsequently, other infectious diseases, endemic in tropical or resource-limited settings and accounting for significant morbidity and mortality in affected populations and for which POCUS has been investigated or for which POCUS may be a potential diagnostic tool, are reviewed and discussed. In view of the required focused approach of POCUS, it is important not only to define diagnostic criteria and test accuracy for each disease, but also to identify the target population in which the diseases of interest are highly prevalent and for whom POCUS will therefore be valid and most beneficial (e.g., HIV/TB coinfection in South Africa, echinococcosis in rural Argentina, or the Kenyan Turkana region). Finally, technical and teaching considerations are discussed.

FOCUSED ASSESSMENT WITH SONOGRAPHY FOR HIV/TB

TB is one of the most frequent opportunistic infections in HIV patients living in tropical countries and constitutes an immense problem in sub-Saharan Africa and beyond.¹⁷ Extrapulmonary TB (EPTB) is seen more frequently in immunocompromised patients and is more difficult to diagnose than pulmonary TB. Disseminated TB is a major cause of death in patients with HIV.¹⁸ Clinical symptoms are fever, weight loss, and night sweats, possibly with cough, shortness of breath, or other focal symptoms; frequently, cardinal signs and symptoms are less clearly evident in HIV coinfecting individuals.

*Address correspondence to Sabine B elard, Department of Pediatric Pneumology and Immunology, Charit  Universit tsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany. E-mail: sabine.belard@charite.de

TABLE 1
Summary of reported experiences of POCUS assessment of tropical infectious diseases

Disease (protocol)	Population	Clinical symptoms	US findings	Suggested action	Evidence	Reference
TB (FASH)	Africa (particularly southern Africa), Asia, and South America with high HIV/TB coinfection prevalence	Fever Weight loss Cough Abdominal symptoms (diarrhea, pain, and abdominal distension), shortness of breath Hypotension	Enlarged hypoechoic lymph nodes Micro-abscesses in spleen and/or liver Pleural effusion Pericardial effusion Ascites	Do sputum smear exam Start empirical TB treatment Test for HIV if not done previously and treat accordingly	Well described and widely used in South Africa	11–15,127
Echinococcosis (FASE)	Sheep farming populations, South America, Middle East, eastern Europe, The Mediterranean, Central Asia, China, east Africa	Symptoms depend on cyst's size, number, and organ affected Jaundice Right upper quadrant pain Most cases have few or no symptoms	Appearance depends on cyst stage (WHO-IWGE) CE1: anechoic with double wall CE2: honeycomb appearance, adjacent anechoic daughter vesicles contained in the "mother" cyst's wall CE3a: anechoic with "lily sign" (detached endocyst) CE3b: daughter vesicles within a solid matrix of the "mother" cyst CE4: inhomogeneous content with visible hypoechoic folded endocyst ("ball of wool" sign) CE5: same as CE4 with calcified wall Hypoechoic, but not anechoic, round homogenous liver lesion: possible amebic abscess Differentials: a) Lesion containing gas, irregular shape: possible pyogenic abscess b) Central calcification: possible Brucella abscess c) Noninfectious lesion, e.g., necrotic tumor	Stage-specific treatment of liver CE (WHO-IWGE)	FASE implemented in Argentina	33–36,40,43
Amebic liver abscess	Worldwide in tropical countries	Fever Right upper quadrant abdominal pain	CE5: same as CE4 with calcified wall Hypoechoic, but not anechoic, round homogenous liver lesion: possible amebic abscess Differentials: a) Lesion containing gas, irregular shape: possible pyogenic abscess b) Central calcification: possible Brucella abscess c) Noninfectious lesion, e.g., necrotic tumor	Start antibiotic e.g., metronidazole treatment Amebic serology In imminent rupture, US-guided aspiration <i>Brucella</i> serology	Individual descriptive studies only	46,48,49
Intestinal schistosomiasis	People in contact with fresh water in Africa, southeast Asia, and Brazil	Abdominal pain Intestinal bleeding Malabsorption Hepatosplenomegaly Fever Eosinophilia Malnutrition, anemia	Increasingly wide echogenic fibrosis around portal tracts (pattern D–F) "Tortoise back" pattern in Asia Dilated portal and splenic vein and collateral vessels Enlarged caudate lobe Splenomegaly Ascites	Refer for endoscopy for patterns E + F Refer also if pattern D and signs of portal hypertension Treat medically and advise against exposure for other cases	WHO guidelines available for population screening	59,64–70

(continued)

TABLE 1
Continued

Disease (protocol)	Population	Clinical symptoms	US findings	Suggested action	Evidence	Reference
Urogenital schistosomiasis	People in contact with fresh water in Egypt and sub-Saharan Africa	Hematuria Urinary tract symptoms Fever Eosinophilia Malnutrition, anemia Dyspareunia Infertility	Irregular, thickened bladder wall (in fully distended bladder) Upper urinary tract dilation Bladder polyps and masses	Medical treatment Possibly referral for cystoscopy in case of persistence	WHO guidelines available for population screening	58,60
VHFs (e.g., Dengue, CCHF, Ebola)	Widely prevalent throughout the tropics	Fever Muscle pain Headache Rash Petechia	Effusions (pericardial, pleural) and ascites as signs of plasma leakage Gall bladder wall thickening Subcapsular hepatic fluid Volume status assessment (IVC, left ventricle, and pulmonary edema)	Intensified surveillance for patients with negative prognostic signs Changes in fluid replacement therapy in shock Consider vast differential diagnoses	Individual descriptive studies only	84-87,89,90,93
Lymphatic filariasis	Sub-Saharan Africa, southeast Asia, and endemic areas of Central and South America	Hydrocele Lower limb lymphedema	Dilation of inguinal lymphatic vessels Filarial dance sign Echo-free or hyperechoic hydrocele Thickened scrotal skin Hepatosplenomegaly Lymph node enlargement Nodular splenic lesions (diagnostic accuracy of these findings is currently unclear for diagnosis of visceral leishmaniasis)	Scrotal surgery for hydrocele, complex hydrocele Conservative treatment with doxycycline and deferred surgery for echo-free hydrocele Unclear	Individual descriptive studies only	71,73
Visceral leishmaniasis	Indian subcontinent, Sudan	Fever Abdominal pain Pancytopenia			Individual descriptive studies only	79,80

CCHF = Crimean-Congo hemorrhagic fever; CE = cystic echinococcosis; FASE = focused assessment with sonography for echinococcosis; FASH = focused assessment with sonography for HIV-associated TB; HIV = human immunodeficiency virus; IVC = inferior vena cava; POCUS = point-of-care ultrasound; TB = tuberculosis; US = ultrasound; VHF = viral hemorrhagic fever; VL = visceral leishmaniasis; WHO-IWGE = World Health Organization Informal Working Group on Echinococcosis.

The diagnosis of EPTB in HIV-infected patients is challenging but vital to patient management. The majority of EPTB patients in resource-poor settings are diagnosed on the basis of clinical case definitions (e.g., World Health Organization [WHO]¹⁹) and only in a minority of cases is microbiological confirmation feasible. The value of US for diagnosing EPTB has long been recognized. The sonographic features suggestive of EPTB, in populations with a high prevalence of HIV/TB coinfection, are as follows:

1. Pleural effusion, particularly when unilateral. In a study from sub-Saharan Africa, unilateral pleural effusion was caused by TB in over 90% of cases and was highly associated with HIV infection.²⁰
2. Pericardial effusion is consistently reported to be due to TB and to be associated with HIV coinfection in the majority of cases in Africa.²¹ Pericardial fluid can easily be identified by POCUS,²² as well as its hemodynamic significance and potential need for pericardiocentesis.²³
3. Although not included in current WHO guidelines, enlarged abdominal lymph nodes and splenic microabscesses have been repeatedly reported as characteristic findings of abdominal TB in HIV-infected patients (Figure 1A).²⁴ Lymph nodes affected by TB present as hypoechoic round structures and are considered pathological when larger than 1.5–2 cm. Abdominal tuberculous lymphadenopathy is frequently located in the upper abdomen, for example, in the liver hilum, around the celiac axis and in the para-aortic area. In some cases, lymphadenopathy can also be found in the mesentery of the caecum (especially in cases of cecal involvement of TB) and in the splenic hilum. Splenic microabscesses are visible as multiple hypoechoic lesions between 0.5 and 1 cm, in an often enlarged spleen (Figure 1B). Presence of ascites can also be a sign of peritoneal TB, especially, if further features suggestive of abdominal TB are demonstrated.

The feasibility and success of training clinicians to accurately detect abdominal lymphadenopathy and splenic microabscesses through short courses, using a curriculum developed in South Africa, has been demonstrated.²⁵ It has also been documented extensively in EM that pleural,²⁶ pericardial,²⁷ and ascitic⁴ fluid can be detected by POCUS with high sensitivity and specificity. There is no reason to doubt the similar value of POCUS for the detection of effusions and ascites secondary to infectious diseases. As a logical consequence, a

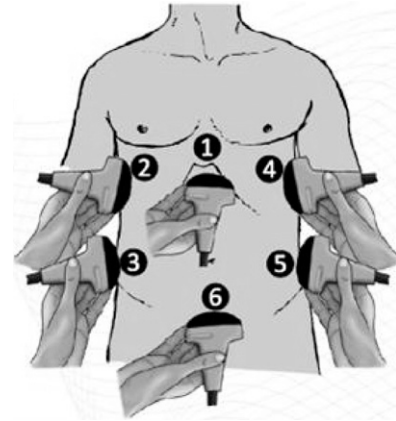


FIGURE 2. Ultrasound (US) probe positions used in focused assessment with sonography for human immunodeficiency virus–associated tuberculosis (FASH) protocol. (1) Epigastric/subxiphoidal transverse view, (2) longitudinal pleural view right, (3) longitudinal right flank/upper quadrant view, (4) longitudinal pleural view left, (5) longitudinal left flank/upper quadrant view, and (6) transverse pelvic view (adapted from Heller et al. 2012¹¹).

single POCUS protocol for EPTB (FASH) has been compiled using the US views of FAST and US views for detection of abdominal lymphadenopathy and splenic microabscesses¹¹ (Figure 2). Because of the high prevalence of HIV/TB coinfection, FASH has become one of the most frequently used POCUS modules in South Africa.¹⁵ Further studies showed that in approximately 25% of patients with a FASH examination suggesting EPTB, the patient's chest X-ray was not suggestive of TB, indicating a significant proportion of patients in whom the diagnosis will be missed if only chest X-ray is performed as part of their diagnostic TB work-up.¹³ The use of FASH in pediatric patients is currently under investigation, but preliminary data indicate that FASH is also applicable in the pediatric population.¹⁶ An evaluation of FASH as a tool to monitor response to treatment in HIV-infected patients with EPTB showed that the persistence of positive findings, after a treatment period of 3 months, is an indicator of treatment complications such as mycobacterial resistance, poor compliance, or immune reconstitution inflammatory syndrome.¹⁴ It needs to be emphasized that a definitive diagnosis of the etiology underlying FASH findings is not possible by US only; however, in a high-prevalence setting, commencing TB treatment based on clinical and sonographic findings and observing the patient's clinical and sonographic response is justified.²⁸

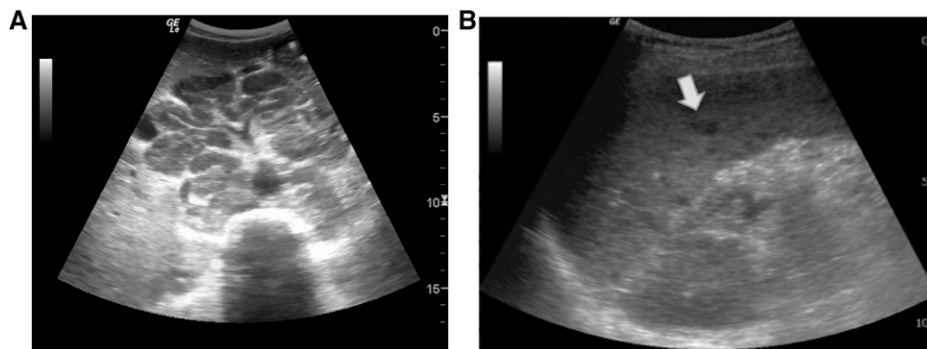


FIGURE 1. (A) Epigastric transverse view: enlarged round hypoechoic tuberculous lymph nodes behind the liver in the area of the celiac trunk. (B) Left longitudinal flank view: enlarged spleen with small hypoechoic lesions (arrow) due to tuberculous microabscesses.

FOCUSED ASSESSMENT WITH SONOGRAPHY FOR ECHINOCOCCOSIS

Cystic echinococcosis (CE) is highly prevalent in sheep farming areas, especially in central Asia, China, South America, the Mediterranean, eastern Europe, and considerable parts of Africa.^{29,30} In humans, CE cysts develop predominantly in the liver (60–70%) and lungs (20–30%). On average, 60–75% of infected patients with hepatic CE are asymptomatic.³¹ When present, symptoms may be local (most commonly right upper quadrant pain) or systemic (fever, jaundice, or allergic manifestations), due to mass effect, communication with hollow structures, superinfection, or loss of integrity of the cyst's wall. Based on individual case reports, it has been hypothesized that HIV may affect the course of CE and lead to unusual and potentially more severe clinical disease.³²

US is the technique of choice for abdominal CE diagnosis, staging, and follow-up³³ and enables US-assisted percutaneous therapeutic procedures. The different types of cysts can be grouped according to the WHO-IWGE (Informal Working Group on Echinococcosis) classification, which is also the basis of the stage-specific approach to the clinical management of CE (Figure 3).^{34,35}

Sonographic features of CE cysts are as follows³⁵:

1. Double wall of the cyst, especially evident in fluid-filled CE1 cysts.
2. “Water lily sign” of CE3a cysts, which reflects the detached endocyst fluctuating in the cyst fluid content.
3. “Honeycomb appearance” of multivesiculated cysts (CE2 and CE3b), in which the impression of “septa” is formed

by the adjacent walls of daughter vesicles (CE2) or in which daughter vesicles have formed in pseudo-solid, hyperechoic, and nonhomogeneous cyst content (CE3b).

4. The “ball-of-wool” sign of CE4 cysts, characterized by the appearance of hypoechoic, degenerating cyst membranes folded inside pseudo-solid cyst content.
5. The wall calcification of cysts with pseudo-solid content (CE5).

Key in the differentiation between CE1 and simple cysts is the visualization of the double wall, which is absent in non-parasitic cysts. Serology and, if necessary, US-guided aspiration and microscopic analysis of the cyst content will further aid the diagnosis.

US screening for hepatic CE has been conducted in many endemic countries for years.^{36–40} For example, in Argentina, a yearly 2-day “focused assessment with sonography for echinococcosis” (FASE) training course has been implemented since 2000, where general practitioners working in rural endemic areas with no previous experience with US are trained in FASE. Four standard images are acquired, and according to results of scans and consultations with experts, patients are offered stage-specific clinical management.³⁶ Annual screening of large populations and regular long-term follow-up of diagnosed cases without costly travel by the patients to tertiary care facilities, as well as reduction in loss to follow-up, were achieved. The repeated annual training ensures sustainability, by compensating for the high turnover of general practitioners in rural areas.

In other endemic settings, the implementation of short protocols allowing the diagnosis and classification of CE

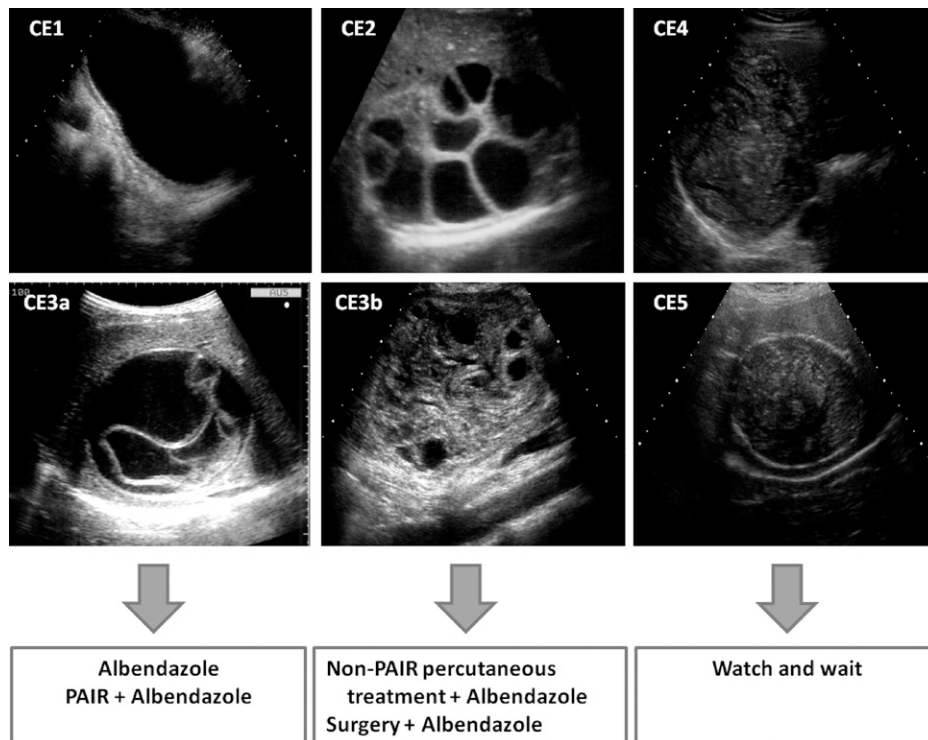


FIGURE 3. Suggested cystic echinococcosis (CE) stage-specific clinical management options according to World Health Organization Informal Working Group on Echinococcosis (WHO-IWGE) Expert consensus.³⁴ PAIR = puncture, aspiration, injection of a scolicalid agent, and re-aspiration. Non-PAIR percutaneous treatments include several percutaneous techniques using cutting instruments and large bore catheters to evacuate the entire cyst content.

cysts according to the WHO-IWGE criteria could provide the basis for early detection and clinical management of the infection. As cysts of different stages show very different responses to various management options,^{41–44} staging supported through remote advice by experts in treatment centers could be helpful.

OTHER INFECTIOUS DISEASES WITH POTENTIAL FOR POCUS APPLICATION

Amebic liver abscess. Amebiasis is one of the most common parasitic diseases worldwide and is prevalent in all tropical countries.⁴⁵ Amebic liver abscess is more common in adults than in children and more common in men than in women. Patients usually present with fever, possibly right upper quadrant pain and jaundice. The condition is well suited for a POCUS approach.⁴⁶

Sonographically, amebic liver abscess presents as a focal hepatic lesion, which is single in 60% of cases and is most commonly located in the posterior part of the right lobe (Figure 4A). The amebic abscess is usually hypoechoic compared with normal liver tissue, without an appreciable rim or capsule. In the center or at the periphery of the amebic abscess, hyperechoic areas may be seen. After anti-amebic treatment,⁴⁷ the lesion tends to become more hypoechoic and the margins become better defined.^{48,49} Serology can support the diagnosis when available; US-guided aspiration shows material of necrotic hepatocytes (“anchovy sauce”) typical in amebic abscesses. Diagnosis does usually not require aspiration. The clinical and sonographic picture, in conjunction with a history of possible exposure, is sufficient to start metronidazole treatment. Today, the indication for aspiration as diagnostic or therapeutic intervention is mainly limited to cases with an acute risk of rupture.⁵⁰

The main clinical and sonographic differential diagnosis of amebic liver abscess is pyogenic liver abscess (Figure 4B). These are more commonly reported outside the tropics, often in patients with risk factors, such as biliary tree infections, diverticulitis, and a history of abdominal intervention. Although occasionally difficult to identify in the early stages, because of similar echogenicity of the surrounding liver tissue, pyogenic lesions eventually become hypoechoic compared with liver and can be more variable in shape and often have irregular walls. Pyogenic liver abscesses are also more often multiple, involving both lobes of the liver, and some

show areas of marked echogenicity due to gas bubbles, which are not a feature of amebic abscesses unless superinfected. Treatment can be attempted with broad-spectrum antibiotics covering gram-negative and anaerobic bacteria.

A few further etiologic infectious differentials of abscess-like liver lesions need to be mentioned. If a central calcification is visible within the abscess, *Brucella* infection should be considered.⁵¹ *Fasciola* infection may present with hypoechoic lesions, especially subcapsular, and forming linear “tracks” through the liver.⁵² As with hepatic CE, other differential diagnoses of focal liver lesions, infectious and noninfectious, need to be considered.

Apart from individual case descriptions,⁴⁶ no published data on the use of POCUS to diagnose amebic and other liver abscesses is available. POCUS protocols to screen the liver using 3–4 scan positions, including an intercostal and epigastric approach appear feasible, but will need validation in further studies. Upon finding a characteristic lesion, antibiotic treatment may be started. However, if a liver lesion does not show the typical, characteristic appearances of an abscess or CE cyst for example, and the binary approach of POCUS cannot be applied, the findings should be viewed with caution and treatment decision should be guided by clinical assessment. Referral for a formal US assessment or other imaging, where available, should also be considered.

Schistosomiasis. Schistosomiasis is a waterborne helminthic infection mainly affecting either the urogenital tract (*Schistosoma haematobium*) or the gastrointestinal tract (*Schistosoma mansoni*, *Schistosoma japonicum*). To a lesser extent, all can affect the lung causing pulmonary hypertension.⁵³ More than 250 million people are affected worldwide and there are more than 200,000 deaths per year attributable to schistosomiasis in sub-Saharan Africa.⁵⁴

Schistosomiasis-associated morbidity is due to inflammation and consecutive fibrosis around entrapped eggs in the tissues. This leads to progressive organ damage and failure.⁵³ It is important to note that morbidity persists even after eggs are no longer detectable in stool or urine. This highlights the importance of early antihelminthic therapy to prevent and reverse early fibrosis.⁵⁵

Urogenital schistosomiasis. Urogenital infection is seen mainly in sub-Saharan Africa, Egypt, and on the Arabian Peninsula. *Schistosoma haematobium* adult worms mature in the vesical plexus. The hallmark symptoms of urogenital schistosomiasis are dysuria and hematuria; earlier symptoms,

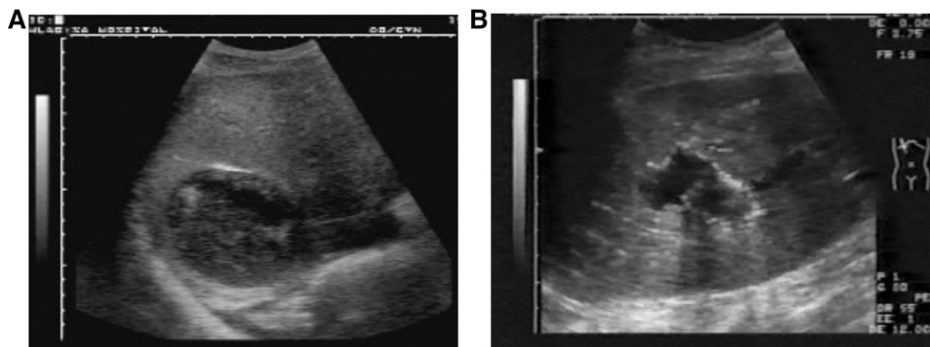


FIGURE 4. (A) Right longitudinal upper quadrant view: amebic liver abscess posteriorly in the right lobe of the liver, presenting as a round hypoechoic lesion with hyperechoic debris and without a clearly discernable wall. (B) Right longitudinal upper quadrant view: pyogenic liver abscess presenting as an irregularly shaped, hypo- to anechoic lesion, containing hyperechoic gas bubbles with posterior acoustic shadowing.

particularly in children, include fatigue and anemia.⁵⁶ The peak of morbidity is observed in children aged 7–14 years; however, infection occurs as early as infancy in endemic areas.⁵⁷ In longstanding infections, symptoms of urinary tract obstruction and kidney failure are seen, secondary to fibrosis of bladder and ureter. Squamous cell carcinoma of the bladder is a possible late complication.

Fibrotic changes of the urinary tract because of schistosomiasis can easily be identified by US,⁵⁸ and findings are described in WHO guidelines for identification and reporting of schistosomiasis.⁵⁹ Bladder wall thickening and intravesical masses are common observations; in advanced disease, upper urinary tract obstruction is characterized by dilatation of the renal pelvis (Figure 5).

US in urinary schistosomiasis has been reported to be an “simple-to-learn” examination.⁶⁰ In support of this assertion, the detection of urinary tract dilatation (e.g., as a consequence of urolithiasis) is commonly taught in POCUS courses in EM for the evaluation of flank pain. A POCUS protocol for urinary schistosomiasis using the lateral abdominal scans to visualize the kidneys, and a pelvic scan for the bladder could be developed and studied for clinical feasibility and value. As schistosomiasis has a highly focal geographical distribution, it is important to identify endemic areas and patient groups at risk. In former hyperendemic regions, where control programs have reduced the prevalence of infection, patients with low-intensity infection and sequelae may still be found. Diagnosis may be missed if it is only based on the detection of eggs in urine, as the egg excretion does not necessarily correlate with egg entrapment. Patients with urogenital schistosomiasis could therefore be identified by suggestive POCUS and then treated with praziquantel. Most bladder pathology regresses after treatment and can be monitored by US. Urinary tract dilatation frequently persists even in successfully treated patients.⁶¹ Non-resolving masses, especially in adult patients, should be investigated further by cystoscopy in view of the risk of bladder cancer.

Intestinal schistosomiasis. Although the highest prevalence of *S. mansoni* infection leading to intestinal and hepatosplenic disease is found in sub-Saharan Africa, cases are also encountered in the Caribbean and South America, mostly Brazil. *Schistosoma japonicum*, affecting similar organs, remains endemic in limited areas of China, the Philippines, and parts of Indonesia.⁶² As *S. mansoni* adult worms mature in the portal vein, schistosomiasis-associated morbidity develops as eggs



FIGURE 6. Epigastric transverse view: liver with bright hyper-echoic fibrosis surrounding the intrahepatic portal vessels, due to *Schistosoma mansoni*.

become entrapped in the tissues (bowel wall and periportal area) causing initial inflammation and subsequent fibrosis. Liver changes evolve from mild to severe periportal fibrotic changes with preservation of parenchyma until the final stages. Reactive splenic hyperplasia and portal hypertension ensue and dire downstream consequences include death from bleeding of esophageal varices.⁶³

The diagnostic sonographic liver features, such as echogenic rings or streaks around the portal venous branches and echogenic bands extending from the main portal vein to the liver surface, are well described; various fibrosis patterns are summarized in a WHO report (Figure 6).⁵⁹ In *S. japonicum* infections, the additional finding of a network of fibrosis may be seen, resulting in a so-called “tortoise back” appearance.⁵⁹ The WHO patterns are well established and widely used.⁶⁴

Focused US in intestinal schistosomiasis could be used for different purposes depending on the stage of the disease: 1) identifying early, potentially reversible fibrotic changes (WHO patterns B–D) in patients (mostly children) from endemic areas, who would benefit from medical treatment with antiparasitic drugs (praziquantel) and 2) identifying affected patients at imminent risk of bleeding (WHO patterns E and F), who might benefit from endoscopy.

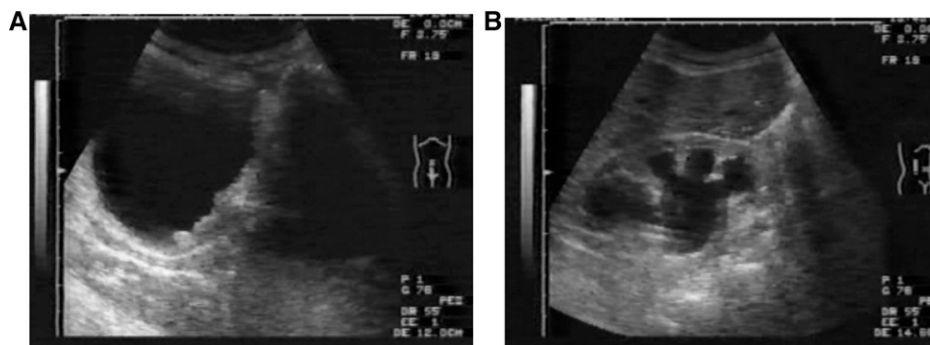


FIGURE 5. (A) Longitudinal pelvic view: thickened and irregular wall of the urinary bladder secondary to *Schistosoma haematobium* infection. (B) Right longitudinal flank view: dilatation of the renal collecting system, secondary to fibrosis and obstruction in *S. haematobium* infection.

WHO patterns B–D, representing patients with mild liver fibrosis, are not pathognomonic and can be difficult to differentiate from normal liver or other disease etiologies.⁶⁵ The interobserver agreement has been found to be low, especially for mild cases.⁶⁶ Without the US imaging experience needed to subcategorize these patients accurately, misdiagnosis of milder cases of intestinal schistosomiasis can easily occur. Patients with image pattern B and C rarely need endoscopy as their risk of bleeding is low. However, in endemic areas, those patients could benefit from early treatment that potentially slows down the development of ongoing disease, and reverses early fibrosis.

US can reliably visualize significant hepatic fibrosis (WHO patterns E and F), which is helpful in identifying patients with clinically advanced disease. These patients are at higher risk of variceal bleeding⁶⁷ and should undergo endoscopy if possible. The patient's risk for variceal bleeding increases when portal hypertension is present. Sonographic changes suggestive of portal hypertension are an increased diameter of the portal vein (normally < 12 mm in adults) or splenic vein (normally < 9 mm),⁶⁸ the presence of ascites, and the development of portosystemic collateral vessels.⁵⁹ The most commonly described collateral veins are the perigastric, the paraumbilical, and the splenorenal veins. Detection is increased by color Doppler, which also allows detection of hepatofugal circulation.⁶⁸ Enlargement of the caudate lobe compared with the right lobe is another finding, which is relatively easy to visualize by US, and reflects changes in portal blood supply in the cirrhotic liver. Caudate lobe enlargement has been described in patients with schistosomiasis.⁶⁹ Splenomegaly can also be a sign of portal hypertension, and in schistosomiasis, the spleen may show multiple nonspecific tiny echogenic foci (Gamma–Gandy bodies).⁷⁰ The size of the spleen is easy to assess; however, possible alternative diagnoses such as chronic splenomegaly in areas hyperendemic for malaria, visceral leishmaniasis (VL), or chronic HIV infection reduce its entity-specific diagnostic value in the absence of collaterals. When signs of portal hypertension are present, patients should undergo endoscopy whenever possible even if they only show milder forms of periportal fibrosis (pattern D).

For busy clinicians, the entire WHO protocol, including multiple measurements, might be too complicated and time consuming. A simplified POCUS protocol applying a few standardized liver views could be devised to identify patients

with hepatosplenic involvement in intestinal schistosomiasis and to identify in particular those patients at risk of variceal bleeding. The results would guide management decisions: antihelminthic treatment⁴⁷ and sonographic follow-up for mild cases and antihelminthic treatment and referral to a tertiary center with capacity to perform endoscopic sclerotherapy for severe cases.

Lymphatic filariasis. Lymphatic filariasis, predominantly caused by *Wuchereria bancrofti*, is a disfiguring and disabling disease affecting an estimated 120 million people throughout the tropics. The highest burden of pathology is born by infected men showing hydrocele; another sign is lower limb lymphedema.

US has proven particularly useful in detecting pathology in male patients. So far, it has mainly been used to detect moving worms in suprastesticular lymphatic vessels of infected men participating in clinical trials (the so-called “filarial dance sign”). Worm nest finding in women may also be possible, although less frequently documented.⁷¹ Large volume hydrocele in males, hyperechoic appearance of scrotal fluid, and presence of lymph scrotum (thickened scrotal skin > 0.45 cm, porous and wart like skin appearance, pain attacks, and leakage of lymph fluid) are associated with increased risk of testicular inflammation and necrosis (Figure 7).⁷² Recently, it has been reported that 56% of examined males in an endemic area in Ghana presented with hydroceles of variable degree and 9% showed echodense fluid,⁷³ suggesting a considerable proportion of patients to be at risk of testicular inflammation and necrosis; the relative frequency of different “filaricele” conditions is, however, unknown.

The use of POCUS approach beyond clinical trials for management of individual patients has received much less attention. Brief US protocols scanning the scrotum for abovementioned signs could be useful in allocating patients with hydrocele to high- or low-risk groups and to adapt the therapeutic approach. Medical treatment with doxycycline ameliorates lymphedema and hydrocele in infected patients (i.e., with detectable filarial circulating antigens).^{74,75} Interestingly, doxycycline treatment has also been found to ameliorate mild to moderate lymphedema in patients without active infection (i.e., filarial antigen negative),⁷⁶ but so far it is unknown if this treatment is also effective in early stages of hydrocele in patients without active infection. Surgical programs for hydrocele due to lymphatic filariasis have been



FIGURE 7. (A) Longitudinal scan of hemiscrotum showing anechoic fluid hydrocele. (B) Longitudinal scan of hemiscrotum showing low-intensity echoes in hydrocele fluid and thickened scrotal skin.

launched,⁷⁷ and it is crucial to identify patients at high risk of scrotal complications for referral to surgery. POCUS could play a decisive role in this identification.

Visceral Leishmaniasis. Each year, an estimated 500,000 new patients suffer from VL caused by many different species of *Leishmania*; the disease burden is particularly high on the Indian subcontinent and in east Africa.⁷⁸ Patients present with fever, cough, abdominal pain, diarrhea, wasting, and pancytopenia. US consistently reveals hepatosplenomegaly, and, in a large proportion of cases, abdominal lymphadenopathy.^{79,80} In recent reports, nodular changes in the spleen have been reported, particularly in children⁸¹ but also in adults.⁸²

Whether these US findings, which could be incorporated into a POCUS protocol, could help with the diagnosis or follow-up of VL and/or with the differential diagnosis between TB and VL in coendemic areas, remains to be studied. The hardest-hit regions (southern Sudan; Bihar State, India) would be locations where such POCUS protocols could be of value and where studies of the validity of such POCUS protocols could be conducted.

Viral hemorrhagic fever. Viral hemorrhagic fevers (VHFs) are caused by a variety of viruses (*Arenaviridae*, *Filoviridae*, *Bunyaviridae*, *Flaviviridae*, and *Rhabdoviridae*). Worldwide, dengue virus is the most common VHF, but in specific geographic areas other viruses such as Crimean–Congo hemorrhagic fever (CCHF) virus may be also prevalent. Because of the large-scale outbreak in west Africa in 2014 and its high mortality rate,⁸³ the Ebola virus has recently gained much importance. Clinically, VHF infections present with fever, headache and muscle pain, rashes, and abdominal symptoms. On progression, hemorrhagic phenomena such as thrombocytopenia, bruises, and internal bleeding occur, which may be followed by shock and death.

Effusions detected by US (pleural, pericardial, and ascitic) have been described as signs of plasma leakage in children⁸⁴ and adults⁸⁵ with dengue infection. The presence of effusions correlated with progression to more severe forms of the disease (dengue hemorrhagic fever (DHF), dengue shock syndrome), and its negative predictive value was found to be very high.⁸⁵ Gallbladder wall thickening^{85,86} and subcapsular splenic and hepatic fluid collections⁸⁷ have also been reported as signs of plasma leakage. It has been suggested that during a dengue epidemic, the diagnosis of DHF should be considered when US demonstrates gallbladder wall thickening, ascites, splenomegaly, and pleural effusion in a febrile patient with thrombocytopenia.⁸⁸

Similarly, in a multivariate analysis in CCHF, gallbladder wall thickening, and intra-abdominal fluid collections were found to be significantly associated with disease severity.^{89,90} Validation of a standardized POCUS protocol to diagnose and predict severity of VHF in epidemic situations and to adapt monitoring and supportive treatment accordingly appears worthwhile.

Beside the potential predictive value for severity assessment in VHF, US can be used to determine hemodynamic parameters in patients with VHF. POCUS is well established in the care of critically ill patients for the assessment of the filling status of the inferior vena cava and the left ventricle.⁹¹ Intercostal scanning of the lung can show suggestive signs of interstitial pulmonary edema, and thus guide fluid administration.⁹² This is particularly helpful in patients with highly contagious VHF as other forms of physical examination such

as auscultation may be hindered by isolation measures and protective equipment. A preliminary report on the use of US in patients infected with Ebola virus supports these indications and suggests the use of focused POCUS done by infectious disease clinicians trained in isolation measures and in relevant POCUS protocols.⁹³ Small mobile US equipment should remain in the isolation unit to prevent spread of the infection.

MISCELLANEOUS INFECTIOUS DISEASES

The potential value of US in supporting diagnosis and management of a range of other infectious diseases in tropical areas and beyond appears huge and increasing. Varying experience with US for assessment of infectious diseases has been reported and some are mentioned in brief below. The suitability and value of POCUS protocols in these diseases remains to be studied. Diagnostic usefulness of US in infections caused by flukes other than *Schistosoma* spp. has been reported for fascioliasis-related hepatic and biliary disease,^{52,94,95} pulmonary and abdominal paragonimiasis,⁹⁶ and clonorchiasis.⁹⁷ Other helminthic infections for which US has been used include onchocerciasis,^{98–100} abdominal and ocular toxocariasis,^{101,102} and ascariasis and its complications such as bile duct invasion.^{103–105} Further parasitic diseases for which experimental US experience is available include Chagas disease,¹⁰⁶ myiasis,^{106,107} and even malaria.¹⁰⁸ The usefulness of POCUS in bacterial infectious diseases has recently been reviewed, describing differentiation between cellulitis and abscesses, diagnosis of septic arthritis, identifying underlying causes of sepsis, and pneumonia.¹⁰⁹ Further US applications have been reported for leprosy,^{110,111} rheumatic heart disease as sequelae of *Streptococcus pyogenes* infection,¹¹² mycetoma,¹⁰⁵ and opportunistic infections in patients living with HIV.^{113,114} With US getting closer to the point of care and into the hands of treating physicians, its use in infectious diseases may increase, and further POCUS indications may become established.

TECHNICAL AND TRAINING REQUIREMENTS

Technical. Technical requirements for POCUS equipment are relatively basic. Most commercially available machines can be used.

The size of the device plays an important role when mobile scanning is intended.

The availability of electricity and US gel needs to be considered in remote settings, and a voltage stabilizer may be required in a situation where voltage peaks put the machine at risk of damage.

In many places, only gray-scale (“black and white”) scanners will be available, which can perfectly serve the purpose. The additional availability of color Doppler on the scanner is helpful to identify blood flow. It will, for example, be helpful to find collaterals in abdominal schistosomiasis, but also be of value in identifying vessels in other anatomical regions. It does, however, significantly increase the cost of the equipment.

To facilitate web-based, remote review and support, an option to extract digital images and video clips onto an external storage device is highly desirable.

The final choice of equipment will mainly depend on local availability and maintenance provision. Obviously, the available budget plays a substantial role, but cost of equipment has come down significantly in recent years, improving affordability.

Training. US is a highly operator-dependent tool, which can easily lead to misdiagnosis if implemented inappropriately and without adequate training. The WHO scientific Group on Clinical Diagnostic Imaging concluded that "... more important than the equipment is the availability of skills..."¹¹⁵ For comprehensive US use, the WHO recommends that physicians should undergo training over 3–6 months, including 300–500 examinations. However, these formal training programs, while ideal, are often too time consuming to achieve meaningful coverage in resource-limited settings. In the absence of formally trained sonographers or radiologists, US training should be aimed at health-care professionals, especially those working on the front line. In particular, this means general physicians and clinical officers in district hospitals and clinics who have little or no experience with imaging technology and who cannot afford to be away from their clinical duties for a long training course. Focused POCUS applications do not require as much training, and thus allow a degree of flexibility. If physicians could be trained in short courses, which will reduce their absence from clinical duties, while providing them with the most relevant US skills,¹⁰ this would widen access to this very useful diagnostic modality.

Short courses have been reported to be sufficient to teach POCUS modules.¹¹⁶ Regular, short US courses with a focus on infectious diseases are held in Pavia, Italy,¹¹⁷ in Lima, Peru,¹¹⁸ and previously in Liverpool, United Kingdom.¹¹⁹

However, the great advantage of courses held directly in low-resource settings is that they will allow local physicians to participate without excessive travel expenses or lengthy leave of absence. In addition, this allows for more rapid and relevant learning, as infection-specific pathologic findings are more prevalent in endemic areas. Short training courses have been reported from various sites in resource-limited settings.^{9,120–122} However, there has been neither widespread dissemination nor standardization of these training initiatives nor robust validation, particularly in terms of the operator's maintenance of adequate technical ability in the long term.

In addition, there is no literature available on how many exams are needed to achieve competency in US skills for clinicians in developing countries. However, in industrialized countries, figures of approximately 30–40 supervised examinations are consistently reported in the literature to master one particular POCUS protocol. For example, 40 exams are reportedly necessary to accurately detect intrauterine first trimester pregnancy and complications,¹²³ while only 30 may be needed to learn how to detect hydronephrosis.¹²⁴ As it has become apparent that some operators acquire skills more rapidly than others, there is an increasing move toward uniform, cross-specialty competency-based assessment, which may be of benefit when designing future courses.¹²⁵

As external trainers are often only available for short periods, other methods to ensure continuous support and quality assurance need to be considered. With increasing availability of internet access and faster connections in geographically remote settings, the application of telemedicine

solutions could be expanded to support practitioners in areas where direct supervision is scarce or absent. Recently, the feasibility of a tele-US system using Skype™ (Luxembourg, Luxembourg) and cheap, widely available, consumer electronics equipment, was successfully piloted for remote supervision of FASH exams in Lambaréné, Gabon.¹² Another, even easier, option is the extraction of digital images and video clips that can then be sent via secure telemedicine servers for review and second opinion.

A number of introductory texts covering the use of US in infectious diseases exist.^{126–128} All are specifically aimed at physicians with limited imaging experience working in resource-limited settings and are available free or at low cost.

Several associations such as the American College of Emergency Physicians¹²⁹ endorse the approach of focused US exams. A section of the International Federation for Emergency Medicine has recently developed a consensus document drawing on regional and national guideline standards and training requirements to summarize recommendations for an appropriate level of training that will allow for the provision of a safe and effective US service.¹³⁰ Analogous to these recommendations, the development of standardized training and practice guidelines for POCUS courses in the field of infectious diseases, based on previous experience and available training material, is a key priority in the field. Recommendations and standards, building on those existing for EM US, should be created. In our opinion, a modular approach consisting of theoretical and practical sessions would be feasible. Initially, protocols and questions, which are easier to master, such as FASH or the detection of urinary tract changes in schistosomiasis can be taught. Once the trainee gains experience in the technology of US, technically more demanding topics such as liver POCUS, echinococcal cyst morphology, and even the assessment of collateral vessels may be taught in further modules. A rigorous evaluation of these training methods is highly desired, but unfortunately not yet available. Modular training could facilitate the availability and accelerate the spread of POCUS.

CONCLUSIONS

US is a powerful diagnostic tool, which has become increasingly available and affordable. From the aforementioned considerations and our own clinical experience, we are of the opinion that POCUS is ideally suited to the diagnosis of several infectious conditions in resource-limited settings (Table 1). We believe that focused, high-quality training will be the key to the successful expansion of US applications. To facilitate this, standardized protocols and training curricula that enable health-care workers to answer dedicated, "focused" questions need to be developed and validated in the field. Using the focused approach will make US diagnosis available to patients who would otherwise have very limited or no access to medical imaging.

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Authors' addresses: Sabine Bélar, Department of Pediatric Pneumology and Immunology, Charité Universitätsmedizin Berlin, Berlin, Germany, E-mail: sabine.belard@charite.de. Francesca Tamarozzi, Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy, E-mail: f_tamarozzi@yahoo.com.

Amaya L. Bustinduy, Paediatric Infectious Diseases Research Group, Institute of Infection and Immunity, St. George's University of London, United Kingdom, E-mail: bustinj06@gmail.com. Claudia Wallrauch, Department of Medicine, Klinikum Muenchen-Perlach, Munich, Germany, E-mail: claudiawallrauch@web.de. Martin P. Grobusch and Tom Heller, Center of Tropical Medicine and Travel Medicine, Department of Infectious Diseases, Division of Internal Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, E-mails: m.p.grobusch@amc.uva.nl and echnatom@web.de. Walter Kuhn, Emergency Medicine, Medical College of Georgia, Georgia Regents University, Augusta, GA, E-mail: tkuhn@gru.edu. Enrico Brunetti, Division of Infectious and Tropical Diseases, University of Pavia/IRCCS San Matteo Hospital Foundation, Pavia, Italy, E-mail: enrico.brunetti@unipv.it. Elizabeth Joeekes, Department of Radiology, Liverpool School of Tropical Medicine, Liverpool, United Kingdom, E-mail: e.joeekes@liverpool.ac.uk.

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