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REVIEW

Ultrasound for the diagnosis of infectious diseases: Approach to the patient at point of care and at secondary level

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Summary Bedside ultrasound evaluation for infection can be performed promptly at the bedside, using simple equipment and without irradiation. Visualization of the foci often enables prompt antimicrobial therapy and even early ultrasound-guided procedure, facilitating earlier confirmation. These procedures are made safer using the real-time visual control that ultrasound provides. Future challenges for an infectious diseases specialist include gaining experience about the appropriate use of point-of-care ultrasound (POCUS). Ultrasonography training is required to ensure competent use of this technology.

Introduction

Ultrasonography is a simple, safe, and noninvasive tool that has been used by physicians (not only radiologist) for more than half a century to aid in diagnosis and guide procedures in day-to-day practice. Over the last decades, new technologies has improved the ultrasound equipment, being more sophisticated and less expensive, which has facilitated the spread of point-of-care ultrasound (POCUS)—that is, ultrasonography performed and interpreted by the

Abbreviations: CT, Computed Tomographic; TTE, TransThoracic Echocardiography; TEE, TransEsophageal Echocardiography; IE, Infective Endocarditis.

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clinician at the bedside. Some medical schools are now training to their students with handheld ultrasound devices during clinical rotations.[1]

Although computed tomographic (CT) scanning remains the reference standard imaging tool for many diseases, the radiation exposure is recognized as a potentially major cause of cancer.[2] Ultrasonography has been used in obstetrics since the beginning without evidence of harmful effects. However, ultrasonography is a user/equipment-dependent technology, and as usage spreads, there is a need to ensure competence, define the benefits of appropriate use, and limit unnecessary imaging and its consequences.[3]

Ultrasonography has been used in different clinical setting, including infectious diseases. Sepsis is a recognized cause of mortality. Less than one-half of the patients who have signs and symptoms of sepsis have positive blood culture or other microbiological proof of an infectious focus.[4] Bloodstream infections are a major concern to physicians because of high levels of antibiotic consumption and of the increasing prevalence of antimicrobial resistance. Thus, they lack accuracy to tailor subsequent therapy.[5] Determining the origin and cause of a septic process is the main objective to choose appropriate antimicrobial treatment. Several times, the clinician use standard diagnostic methods (radiology, blood cultures, urine tests, etc.) those are typically limited in their scope and accuracy when faced with the myriad of possible causes of sepsis. Reliance on sophisticated and expensive diagnostic for relatively simple sources of infection, demonstrates a critical need for improved simple diagnostic bedside tools, as ultrasound.[6] One of the most important application, is the potential to both visualize and immediately perform on-site interventional procedures on infectious sites.

This article provides an overview of the current use of ultrasonography in the diagnosis and treatment of infectious diseases pathologies, with examples and discussion of its use.

We sought to summarize the existing evidence in published literature and characterize the diagnostic accuracy of POCUS and secondary level care ultrasound for infectious diseases in adults.

POCUS

Bedside POCUS is considered as an important adjunct to clinical examination in different fields as emergency medicine, critical care, and internal medicine.[7] Multiple etiologies can be investigated, improving diagnostic accuracy and specific treatment, in a matter of minutes.[8] An infectious disease can be diagnosed not only by microbiologist work-up, but also with images such as ultrasound.

Pneumonia

Chest X Ray and thoracic CT scan are common diagnosing tests, but they are irradiating and are high cost tests. Lung ultrasound has long been used in pulmonary diseases with promising results.

Ultrasound is actually better than bedside supine radiography for detecting consolidation, demonstrating an accuracy of 97% vs. 75%, in critically ill patients admitted at Intensive Care Unit (ICU).[9] The majority (98.5%) of cases of pneumonia is located about the lung surface.[10] So, a lung ultrasound can be used to detect the presence of pneumonia by identifying alveolar consolidation. The alveolar consolidation is an area of complete loss of aeration, that may be caused by fluid (transudate, exudate, blood, water) that fills a group of alveoli,[11] or alternatively, a pure loss of alveolar air (atelectasis). Simply detecting a consolidation, however, is not sufficient evidence to diagnose pneumonia. Only the correlation with the clinical data increases the accuracy of lung ultrasound for pneumonia.[12]

Consolidation of the lung may be the result of an infectious process, hydric surcharge, cardiogenic pulmonary edema, an infarction due to pulmonary embolism, a localization of cancer and metastasis, compression or obstructive atelectasis, or a contusion in thoracic trauma.[13]

The consolidated region of the lung is visualized as an echo-poor or tissue-like image (hepatization), depending on the extent of air loss and fluid predominance.[10] (see Fig. 1) The lung consolidations may have different causes (infection, embolism, neoplasia, atelectasis, and contusion).[14] Lung ultrasound can differentiates consolidations due to embolism, pneumonia, or atelectasis. Air bronchograms may be seen within the pneumonia, in the form of linear or punctiform, hyperechoic areas.[15]

The dynamic air bronchogram[10] means that air present in the bronchi receives a centrifugal inspiratory pressure, making it move toward the periphery, indicating that the consolidation is not retractile and rules out atelectasis. The lung sliding may be abolished, possibly due to decrease in lung expansion or adherence, but not always happens. Through abolished lung sliding, the cardiac activity becomes immediately visible arising from the pleural line in rhythm with heartbeat, which is called "lung pulse" and rules out pneumothorax.[16]

For pulmonary ultrasound it is important to recognize the B-lines, which are defined as discrete vertical hyperechoic reverberation artefacts that arise from the pleural line, extend to the bottom of the screen without fading, and move sinchronously with lung sliding. Multiple B-lines are the sonographic sign of lung interstitial syndrome, and a focal sonographic pattern of interstitial syndrome may be seen in the presence of pneumonia, but also in pneumonitis, atelectasis, pulmonary contusion, pulmonary infarction, pleural disease, and neoplasia.[14]

A recent meta-analysis (ten studies with 1172 subjects from emergency departments and ICU) about the diagnosis of pneumonia showed a high sensitivity: 94% (95% CI: 92%—96%); high specificity, 96% (95% CI: 94%—97%); positive likelihood ratio, 16,8 (95% CI: 7.7—37); negative likelihood ratio, 0.07 (95% CI: 0.05—0.10); and the receiver operating curve was 0.99 (95% CI: 0.98—0.99).[17]

Pleural effusion

Ultrasonography can detect the presence of as little as 5—50 mL of pleural fluids and is superior to radiography for this condition. The search for pleural effusion is a classic application of ultrasound. Bedside ultrasound has proved superior to radiography for this condition.

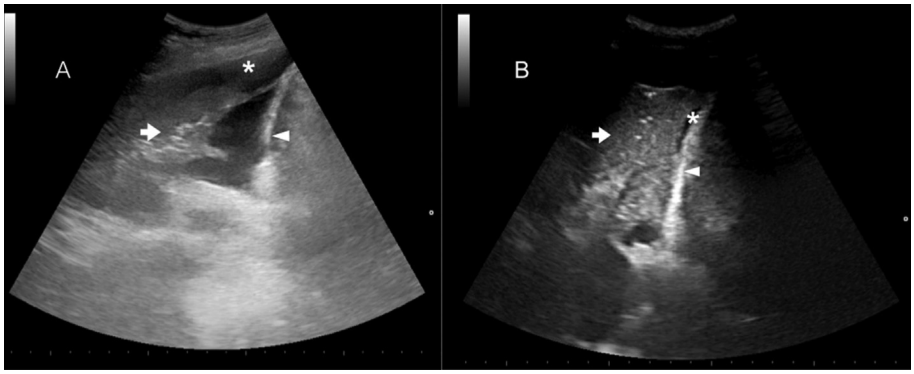

Figure 1 Pneumonia and pleural effusion in a patient with cough and fever. Ultrasound image shows pleural fluid (*) and consolidation (arrow head). Diaphragm is indicated by the arrow head.

Using CT scan as the gold standard, bedside ultrasound has demonstrated a sensitivity of 93%, compared with 39% for radiography.[9,18] Ultrasonography can be used under several different situations, including the following: identification of the appropriate location for thoracentesis, pleural biopsy, or chest tube placement; identification of pleural fluid loculations; distinction of pleural fluids from thickening; differentiation of a pyopneumothorax from a lung abscess; and evaluation of the trauma patient for the presence of a hemothorax or a pneumothorax.[19]

Pleural fluids on ultrasonography can be identified as echo free (anechoic), complex septated (fibrin strands or septa), complex non-septated (heterogeneous echogenic material), or homogeneously echogenic. If echogenecity is extremely high, immediate thoracentesis is required for differentiation of empyema or hemothorax (see Fig. 2).[19]

Soft tissue infections

Uncomplicated soft tissue infections include cellulitis, folliculitis, simple abscess and minor wound infections. These infections respond to either source of control management (drainage or debridement) or antibiotic therapy. The physical examination is often limited to differentiate between abscess, cellulitis, or fasciitis. Ultrasound is readily able to make this distinction and help to drain a collection. Ultrasound appearances of cellulitis range from diffuse swelling and increased echogenicity of the skin and subcutaneous tissues to a variable cobblestone appearance.[20]

An abscess is usually well defined, focalized, and hypoechoic. (See Fig. 3) The necrotizing fasciitis is characterized by layering fluid along the fascial plane and "dirty shadows" indicating the presence of air within the area of inflammation a diffuse. A disorganization of the muscular fibers indicates myonecrosis, whereas gangrenous fasciitis preserves the muscle.[21] (See Fig. 4) Ultrasound of pyomyositis reveals diffuse muscle swelling with edema (muscle hyperechogenicity with or without localized hypoechogenicity) and diffuse hyperaemia.[22] Also, it is possible to make a diagnostic approach of nodule-like lesions according to its echogenic pattern: synovial cysts, ganglions or subcutaneous nodules can be differentiated from abscesses or even parasitic infestations. Those diagnoses can be performed easily and fast even in an emergency or primary health care environment in order to conduct specialized further studies. (See Fig. 5) Finally, by using ultrasound assessment over soft tissue infections, helps to make a source control such as eco-guided drainage of an abscess or incision into the

Figure 2 Pleural effusion. Pleural fluid (*) is noted as well as septations (arrow) and loculations.

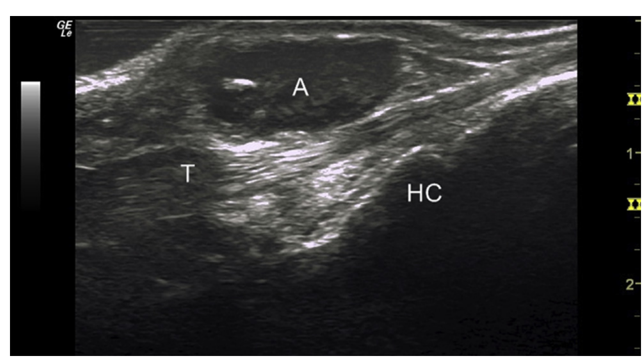

Figure 3 Wrist abscess secondary to *S. aureus* infection. Longitudinal view of the dorsal aspect of the ulnar margin of the wrist of a 78 years old female who presented 7 days after a mosquito bite. A: Isoechogenic rounded structure located inside fat tissue over ulnar tendon. T: Ulnar extensor tendon demonstrating upper compression and hyperechogenicity just below the abscess. HC: Carpal bones of the wrist.

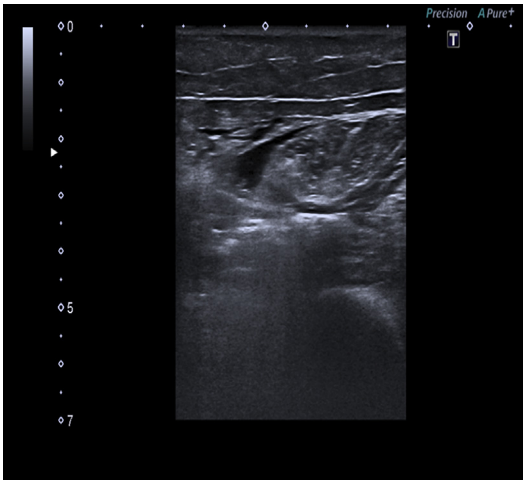

Figure 4 Necrotizing Myositis secondary to *C. perfringens*. Longitudinal view of the thigh of a patient with leukemia and neutropenia. Edema and fluid bands around the anterior thigh muscles with air-on-fascia between rectus femoris and vastus medialis.

abscess cavity. Visualization of major vessels through eco-Doppler is safer than a blinded procedure.

Abdominal infections

Acute cholecystitis is an important cause of sepsis and abdominal complication. Unfortunately, physical examination and laboratory evaluation are poorly sensitive and specific for this diagnosis.[23] Because clinical signs are often variable, radiology-performed ultrasonography, described since 80′s decade,[24] is a common first step. However, this test is not always promptly available and requires transport to radiologist facilities. Criteria for the diagnosis include a cholelithiasis, thickened wall more than 4 mm, enlarged gallbladder, sludge, and perivesicular fluid.[25] (See Fig. 6).

However, POCUS is useful to detect cholelithiasis, other signs such as thickened wall, pericholecystic fluid and emphysematous gallbladder, are not specific for acute acalculous cholecystitis, particularly in ICU patients.[26] In a retrospective study including critically ill trauma patients, the sensitivity was 30% and specificity of 93% for ultrasound evaluation.[27]

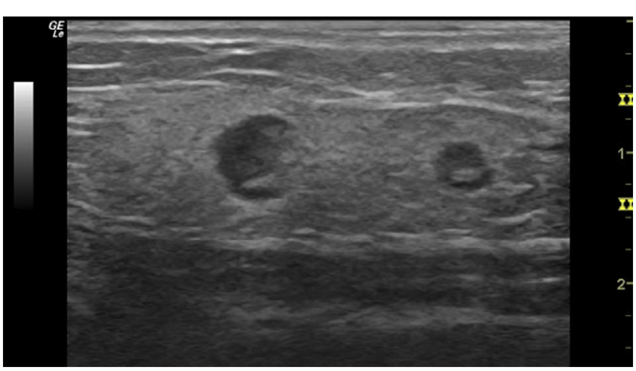

Figure 5 Subcutaneous nodules located in the radial border of the right forearm of a 40 years old female from Bolivia. Ultrasound shows two rounded structures across fat tissue with intense inflammatory reaction around. Inside the structures can be distinguished at least to different echogenic pattern. Surgical specimens were identified as *cysticerci*.

Emergency physicians used bedside gallbladder ultrasonography to improve the diagnosis of abdominal pain. In retrospective and prospective studies, patients who received bedside ultrasonography performed by trained emergency physicians for suspected biliary colic had a significantly shorter length of stay than patients undergoing radiology ultrasonography.[28]

Another important use of abdominal ultrasound is for the diagnosis of appendicitis and peritonitis. Using ultrasound as a screening test in suspected appendicitis by surgeons achieves a sensitivity of 92% and specificity of 96% in a metaanalysis.[29] However, the use of ultrasound for the diagnosis of peritonitis or perforated viscus is limited.[26] Abdominal ultrasound is based on artifacts imaging[30] and free intraabdominal air may not be differentiated from gas-filled intestinal loops, increased hepatic echogenicity, subcutaneous artifacts, basal pneumothorax or experience of the examiner.[31] Finally, intestinal perforation does not always imply free peritoneal air.[32]

Finally, ultrasound has previously been under used in the imaging of the bowel wall due to the, often marked, artefact from intraluminal gas particularly in those patients with acute abdominal distension. In this group of patients extensive wall thickening causing luminal effacement and exudates exclude lumenal gas thereby making these inflamed loops easier to identify sonographically.[33] A routine ultrasound exploration with convex or linear probes, and gentle compression is enough to visualize intestinal wall thickening of 6–26 mm. Another feature noted more frequently on ultrasound imaging is ascites, described in approximately 75% of patients on ultrasound.[34]

Figure 6 Cholecystitis. Longitudinal view of the right upper quadrant of a patient with abdominal pain, and fever. Thickened gallbladder wall (arrow) with pericholecystic fluid (arrow head), and stone (star).

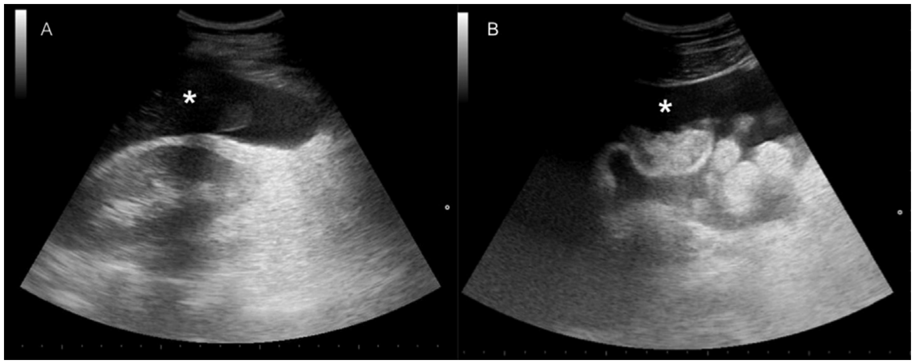

Figure 7 Peritoneal Tuberculosis. Longitudinal view of the right lower quadrant of a patient with abdominal pain and fever, showing ascites (*) and bowel loops. An ultrasound-guided paracentesis was performed and *Mycobacterium tuberculosis* was isolated on culture.

Sepsis

Bedside ultrasound shows the sepsis site at the bedside: infected pleural effusion, pneumonia, peritoneal collection, acute cholecystitis, biliary or urinary obstacle, abscess (soft tissue, liver, spleen, kidney), pericarditis, endocardial vegetation in most instances, etc.[6] Nearly all of these findings can benefit from ultrasound-guided diagnostic procedure in a safety way, and the biological samples can promptly be sent to the laboratory. Thus, antimicrobial treatment can be initiated immediately,[35] while calling to the specialist (radiologist, surgeon) if needed. The use of ultrasound, either at the hemodynamic and diagnostic step, has been demonstrated in the early differential diagnosis, which is determinant for a correct and prompt treatment. Bedside ultrasound can be a useful diagnostic tool to discriminate the etiology of hypotension. The RUSH exam (Rapid Ultrasound in SHock examination) is another comprehensive protocol used in critical care for the management of patients in shock, including septic shock.[36]

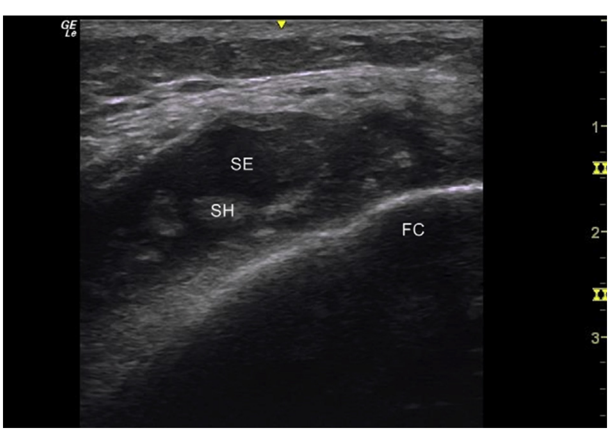

Figure 8 Septic arthritis of the knee secondary to *S. aureus*. Longitudinal view of the lateral recess of the knee of a 51 years old male who consulted by fever and intense swollen of his left knee. Synovial effusion (SE) is viewed as an anechoic distention of the synovial capsule. Synovial hyperplasia (SH) is observed as relative hyperechogenic digital proliferation. FC: Femoral condyle.

Bedside echocardiography can identify a decrease in ejection fraction and increased end-diastolic volume in patients with septic shock.[37] In addition, there is a universal reduction in left ventricular ejection fraction resulting in a severe reduction in the left ventricular stroke volume. Sepsis may also be associated with diastolic dysfunction,[38] and depression of left ventricular intrinsic contractility.[39]

In emergency settings, the availability of POCUS data can appropriately guide the clinical approach in patients with undifferentiated hypotension. A real-time point-of-care ultrasonographic assessment can influence early management decision-making. A simple technique (including cardiac function, inferior cava vein diameter, pulmonary congestion, abdominal free fluid, aortic aneurysm, and leg vein thrombosis) was significantly agreed with a final clinical diagnosis of hypotension.[40]

Extrapulmonary tuberculosis

Bedside ultrasound can identify common manifestations of extra pulmonary tuberculosis including pericardial effusion, pleural effusion, and abdominal tuberculosis. Cardiac tamponade secondary a tuberculosis pericarditis is the most severe clinical presentation and constitutes a life-threatening event that requires immediate medical intervention. Pleural effusion is easily visualized with linear or convex probe. Finally, typical ultrasound findings of abdominal tuberculosis include retroperitoneal and mesenteric lymphadenopathy with node diameter greater than 1.5 cm, multiple splenic hypoechoic nodules between 0.5 and 1 cm, and patterns of ascites. Ultrasound can rapidly identify abnormal signs, which in high prevalence settings, will be highly suggestive of extrapulmonary tuberculosis. The Focused assessment with sonography for HIV/TB (FASH) is a protocol that can be taught rapidly to physicians with little or no prior ultrasound experience. The examination takes only a few minutes and may provide important findings that should be interpreted by a clinician within the clinical and epidemiological framework applying to the individual patient. The protocol is intended for settings where the prevalence of HIV/TB co-infected patients is high.[41] (See Fig. 7).

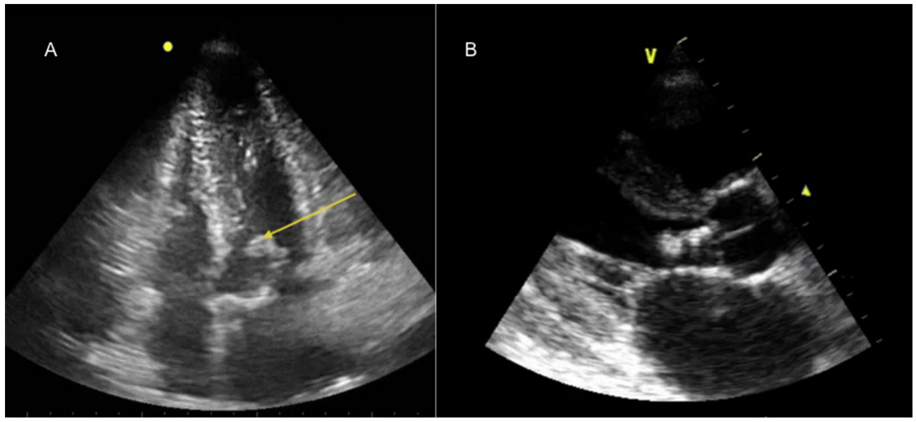

Figure 9 Endocarditis. Transthoracic echocardiogram. A: Apical four-chamber view showing a large echo bright vegetation (arrow) in the mitral valve of a patient with fever and a mitral murmur. *S. aureus* was isolated from blood cultures. B: Parasternal long-axis view showing a vegetation in the aortic valve.

Second level ultrasound examination

It is clear that the clinicians need the expert level knowledge of radiologist, cardiologist, and other specialists such as rheumatologist, and gynecologist for some infectious diseases. The domain of POCUS is limited and the competence of the examiner depends of skills and experience. Not every clinical question can be answered with POCUS. Some infectious diseases need expertise such as articular infections or infective endocarditis.

Septic arthritis and periarticular infections

Joint infection is a serious condition given the propensity for long-term morbidity due to destruction of the joint if not treated early. Ultrasound can detect the presence of a joint effusion in a patient with clinical signs of joint infection. Following recognition of an effusion is the guided-aspiration of joint fluid, which can be performed at an early stage thereby allowing early diagnosis and appropriate treatment. Joint fluid in septic arthritis may be hypoechoic and clearly demarcated from joint synovium and capsule or hyperechoic and less clearly demarcated from joint synovium or capsule.[20] In most instances, ultrasound cannot reliably differentiate infective from non-infective causes of arthritis, and, in the appropriate clinical setting, aspiration of joint fluid for analysis is helpful. Periarticular tissue can also be assessed by ultrasound when septic involvement is suspected. Infective tenosynovitis or peritenonitis are clinical entities that could be misdiagnosed as mechanical tenosynovitis.[42,43] (See Fig. 8).

Infective endocarditis

The use of echocardiography in the diagnosis of infective endocarditis (IE) was reported first in 1973.[44] Endocarditis is an infection of the innermost muscle layer of the heart. The characteristic finding is a shaggy, dense band of irregular echoes in a non-uniform distribution on one or more leaflets, with full motion of the valve. (See Fig. 9) If the vegetation is calcified (which may occur early) the sensitivity of the echocardiography may be increased. Echocardiography can localize vegetations in culture-negative cases and it is useful to detect large friable vegetations such as fungal IE.

The Duke criteria are widely known and well established for diagnosing IE with one of the major criteria being evidence of an intracardiac vegetation, abscess, or new valvular regurgitation on echocardiogram. Therefore, ultrasound plays an essential role in the diagnosis of this disease entity. The two methods of cardiac ultrasound for the evaluation for IE are transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE).

Many reports have evaluated the role of TTE as the initial imaging study to evaluate the diagnosis of suspected IE, followed by TEE if needed. Technical limitations to perform TTE are obesity, chronic obstructive pulmonary disease, or chest wall deformities.

TTE has variable sensitivity for the detection of vegetations. The sensitivity is highest in right-sided endocarditis because the tricuspid and pulmonary valves lie close to the chest wall.[45] TEE is more sensitive than conventional TTE in the detection of vegetations (90—65%), particularly in the setting of prosthetic valves (98%). Although negative results on TEE do no exclude IE.[46] TEE is only indicated if there is suspected pulmonary valve endocarditis, an implanted cardiac device, moderate to high clinical suspicion of right-sided endocarditis with a nonsuggestive TTE, or poor acoustic TTE windows.[26]

Bedside ultrasound may allow for earlier diagnosis by demonstrating cardiac valvular vegetations.[47] Positive findings suggestive of IE on bedside ultrasound can enable to more rapidly initiate appropriate antibiotics and to obtain prompt specialty consultation without undue delay for a diagnosis that is not often made in the ward.[48] IE is an infection with serious morbidity and mortality. Due to the high in-hospital mortality risk of IE (can be as high as 18%),[49] early recognition and diagnosis are essential for a definitive treatment (surgical or medical). Because larger IE lesions (>10 mm) may be most detected on bedside ultrasound, focused ultrasound may be helpful in identifying those patients who are at greatest risk from this disease, even considering its low sensitivity.[50]

Limitations

Probably, the most important limitation of ultrasonography is related to the fact that is highly operator-dependent (acquisition of accurate images depends on the operator). Sometimes, the examination is patient-dependent (obese patients may be more difficult to examine due to the thickness of soft tissues). POCUS does not replace the history or the physical examination in infectious diseases. History, clinical signs, and microbiology isolation are fundamental for the correct diagnosis. Unlike the radiologist, the clinicians integrate all aspects of the physical examination in conjunction with POCUS in order to establish a rational diagnostic and management strategy. Although it is important to realize our own competence and refer to specialist as needed.

Conclusion

With appropriate use, POCUS can decrease medical errors, provide more efficient real-time diagnosis, and supplement or replace more advanced imaging in appropriate situations. In addition, focused ultrasonography may allow more fast, widespread, safe, and less-expensive screening for defined indications in emergency situations. Ultrasound, in some cases, can obviate the need for more expensive imaging test performed by a consulting radiologist, avoiding waiting periods for radiologist investigation and reduced hospital stay. As a user-dependent technology, bedside ultrasonography requires consideration of appropriate training and quality assurance.[3] POCUS has important limitations related to operator skills and it is not useful in all infectious diseases. Refer to the consultative radiologist or cardiologist is needed in some cases.

The use of POCUS will continue to diffuse across medical specialties, including infectious diseases. Future challenges for an infectious diseases specialist include gaining experience about the appropriate use (when and how) of point-of-care ultrasonography. Ultrasound training is required to ensure competent use of this technology, and structuring policy and reimbursement to encourage appropriate and effective use.

Conflict of interests

The authors declare no conflict of interests.

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