The EFSUMB Guidelines and Recommendations for Musculoskeletal Ultrasound – Part II: Joint Pathologies, Pediatric Applications, and Guided Procedures

EFSUMB-Leitlinien und -Empfehlungen für den muskuloskelettalen Ultraschall – Teil II: Gelenkpathologien, pädiatrische Anwendungen und geführte Verfahren

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1. Joint pathology

1.1. Shoulder

**Background**

US has been used extensively in the diagnosis of various intra- and periarticular pathological conditions of the shoulder.

**Clinical applications**

US is an essential imaging method of glenohumeral joint (GHJ) evaluation, as shoulder swelling is unusual and effusion is not detected by X-ray [1, 2]. US detects intra-articular effusion/synovitis – frequently in RA and polymyalgia rheumatica (PMR) [3, 4], but rarely in osteoarthritis (OA) and spondyloarthritis (SpA) [5]. Effusions are not found in asymptomatic patients and are rarely observed in random painful shoulders [6, 7]. Although magnetic resonance imaging (MRI) detects effusions more often than US, it is not compatible with dynamic shoulder examination [2, 8].

Proliferative synovitis of GHJ can be detected in the posterior recess, axillary recess, or biceps tendon (BT) sheath in inflammatory arthritis, although synovitis in the BT sheath has low specificity for RA [3]. The power Doppler signal can be detected inside the posterior recess or around the BT but not in the axillary recess [3]. The power Doppler signal around the BT can distinguish RA from OA [9]. In particular, power Doppler detection of the synovial signal in the posterior GHJ recess has shown excellent reliability [10].

Rotator cuff disease (tears, tendinopathy, impingement) is the most common cause of shoulder pain, accounting for 65% to 70% of cases [11]. There is consistent data on similar diagnostic accuracy of US and MRI in rotator cuff tears [12]. A meta-analysis comparing US to MRI and MR arthrography (MRA) showed that US...
diagnostic performance is equal to that of MRI but inferior to MRA. The pooled sensitivity and specificity of US for detecting full- and partial-thickness rotator cuff tears was reported to be 92.3 % and 94.4 %, and 66.7 % and 93.5 %, respectively [13]. In addition, US was found to be highly specific for the detection of recurrent rotator cuff tears and more specific than MRI for the detection of partial-thickness tears [14, 15]. US was shown to have a low level of interobserver variability for the detection, classification, and localization of rotator cuff tears [16] as well as for assessing fibrillar disruption, neovascularity, and the number and length of calcifications in rotator cuff tendinopathies [17]. A supraspinatus tendon thickness of > 6 mm or abnormal tendon echo-structure can be used with equal accuracy to MRI to diagnose supraspinatus tendinopathy [18].

The diagnosis of adhesive capsulitis (AC) of the shoulder is based on clinical findings but imaging modalities can be used to confirm the diagnosis [19]. US may help identify several morphological and functional alterations at the level of the GHJ capsule, rotator interval [19–22], and supraspinatus and subscapularis tendon gliding [23]. The coraco-humeral ligament (CHL) and inferior GHJ capsule were reported to be significantly thickened in AC when compared to other shoulder pathologies and asymptomatic shoulders [20, 23, 24] and correlated with MRI measurements [19]. Capsular enhancement was detected using contrast-enhanced US and this parameter was comparable to MRI findings [21]. Limitation of the rotator cuff tendon gliding and the presence of hypechoic vascular soft tissue at the rotator interval level is found in AC [25].

Shoulder instability primarily affects young active people as a result of an acute injury or oversew [26]. MRI is more accurate in comparison to other imaging techniques [27], but US can add important information during pre- and postoperative shoulder assessment [28–30].

US is a sensitive and specific imaging tool for identifying shoulder dislocation and reductions [28, 31] and may deliver real-time pre- and postoperative information about the structural alterations of the labrum, glenoid rim, humeral head, and capsule as well as about shoulder dynamics [29, 30].

Dynamic US maneuvers are valid and reproducible for the assessment and quantification of inferior GHJ laxity when compared to stress radiography [32] enabling the identification of athletes at risk of shoulder instability [33].

Practical points, limitations, and artifacts in shoulder pathology are detailed in Supplementary Tables 1 and 2.

Recommendations

1. US should be used to elucidate the origin of both inflammatory and noninflammatory shoulder pathologies (LoE 1, SoR strong). Broad consensus (26/5/5, 84 %)
2. Color/power Doppler should be used to quantify the degree of inflammation in the rheumatoid shoulder (LoE 1, SoR strong). Broad consensus (26/8/2, 77 %)
3. US should be considered the first-line imaging modality in rotator cuff pathology evaluation (LoE 1, SoR strong). Strong consensus (33/1/2, 97 %)
4. US should be considered for identifying shoulder dislocation and reduction (LoE 1, SoR strong). Broad consensus (25/8/3, 76 %)

1.2. Elbow

Background

US findings supporting the diagnosis of elbow pathology complement those of clinical examination and other imaging methods. Dynamic maneuvers during examination, facilitated by patient positioning, are feasible and offer an advantage over MRI examination. High-frequency US is sensitive for detecting intra-articular alterations in the elbow joint (effusions, synovitis, loose bodies, cartilage degeneration) and for assessing medial joint stability [34].

Clinical application

Effusions accumulate in the coronoid and radial fossa, examined via the anterior approach with the elbow extended. For the olecranon fossa assessment, examination with the elbow in flexion allows identification of 1 to 3 ml of fluid, thus rendering US more sensitive than radiography for diagnosing effusions. MRI, however, remains the most sensitive for identifying effusions, regardless of joint position or location [35, 36].

In inflammatory rheumatic diseases (e.g., RA), comparison of clinical examination and US evaluation showed only fair agreement, with US improving the accuracy of diagnosing synovitis compared to clinical examination [37, 38]. Furthermore, when comparing US to radiography, sonographically visible changes were detected in 24 % of patients graded Larsen 0 [39]. Therefore, US is particularly valuable for detecting early stages of synovitis and minor erosions, showing intra- and interobserver reliability of 90.8 % and 88.8 %, respectively [40].

OA affects mainly the radiohumeral joint, where US allows for the humeral and radial cartilage thickness measurement with a mean of 1.2 mm, showing significantly reduced values in OA [41]. Also, the posterolateral radiohumeral plica may be evaluated, showing that OA may result in plica reduction associated with morphological changes [41]. In addition, lateral synoval fringe impingement at the radiohumeral joint may be assessed [42, 43]. US can detect loose bodies located between the cartilage and anterior or posterior fat pad, rarely in the small radial recess [44].

Assessment of medial elbow stability [45], indicative of the risk of ulnar collateral ligament (UCL) injury among professional sport players [46], requires US dynamic maneuvers. The thickness of the anterior bundle of the UCL and the width of the ulno-humeral joint can be measured in flexion, both at rest and with an applied valgus load. The anterior bundle of the UCL was found to be significantly thicker and the ulno-humeral joint space was significantly wider in the dominant arm both at rest and with applied valgus load, in asymptomatic and symptomatic baseball players alike [47, 48]. Hypoechoic foci and calcifications were found to be significantly more common in the dominant arm [45, 49, 50].

Practical points, limitations, and artifacts in elbow pathology are detailed in Supplementary Tables 1 and 2.
Statement

1. The sensitivity of elbow joint US examination to detect effusion and synovitis can be increased by dynamic evaluation, using the volar approach in extension for anterior recesses and the dorsal approach in flexion for the olecranon recess (LoE 2). Strong consensus (29/1/6, 97 %)

Recommendations

1. US is recommended to assess synovitis and erosions in inflammatory disease of the elbow (LoE 2, SoR strong). Broad consensus (32/2/2, 94 %)

2. US imaging should be used to assess medial elbow instability as a result of ulnar collateral ligament injury (LoE 2, SoR strong). Broad consensus (26/3/7, 90 %)

1.3. Wrist and hand

Background

Introduction of high-frequency probes led to obtaining high-resolution images of small hand and wrist structures, allowing US to rival MRI for many indications. US can be used as the primary imaging modality for many conditions in the hand and wrist with the advantage of dynamic imaging abilities providing insights into pathologies inaccessible with static imaging modalities such as MRI and computed tomography (CT). High-frequency US is sensitive for detecting intra-articular alterations in hand and wrist joints such as effusions and synovial hypertrophy. Normal joint recess thickness has been described as ≤2.9 mm for the dorsal wrist, 3.4 mm for the volar wrist, <1.9 mm for the volar metacarpophalangeal (MCP) joint, and ≤1.6 mm for the proximal interphalangeal (PIP) joint [51]. The sensitivity of the US examination can be increased by using both the palmar and dorsal approach [52]. Knowledge of pitfalls is essential [53].

B-mode and Doppler US have shown validity and reproducibility for detecting and quantifying synovial inflammation in wrist/finger joints when compared with histological findings in RA [54–58]. US contrast media allows finger joint vascularity assessment and quantification at the microvascular level [59–62].

Cartilage assessment was shown to be feasible in both degenerative and crystal deposition disease [63, 64]. US assessment of articular cartilages and detection of RA erosions in accessible aspects of finger joints has been successfully validated using cadaver specimens [63] and CT/micro-CT [65, 66], respectively.

Clinical applications

US is able to detect subclinical synovitis, even in RA patients in synthetic or biological therapy-induced clinical remission [67]. This can predict joint structural damage appearance and progression [68] as well as disease flare [69]. In addition, US is substantially more sensitive than conventional radiography for detecting early bone erosions [70] and cartilage damage [71] in RA target joints of the hand.

The predictive value of US in relation to the development of Doppler-positive synovitis in the target areas, such as the wrist and MCP joints, or early erosions in specific sites of MCP joints in patients with inflammatory arthralgia or in those with early undifferentiated arthritis has been proven [72, 73].

US assessment of synovitis in the wrist and fingers has shown the best accuracy-feasibility balance in reduced joint count scores at the patient level for US monitoring [74] and subclinical inflammation detection [75] in RA patients.

In addition to synovitis, psoriatic arthritis (PsA) is characterized by enthesitis, tenosynovitis, and dactylitis, all of which are readily detectable on US. US detects both articular and peri-articular inflammation in early [76] as well as established [77] disease, which correlates with clinical disease activity [78] and was shown to be sensitive to change [77]. Similar to RA, US-detected subclinical synovitis is very common in early PsA and led to the majority of oligoarthritis patients being reclassified as having polyarthritis [76].

In connective tissue diseases such as systemic lupus erythematosus (SLE) [79, 80], primary Sjögren’s syndrome (pSS) [81], and mixed connective tissue disease (MCTD) [82], US reveals subclinical synovitis located especially on the MCPs and wrist in patients without joint symptoms and correlates with clinical disease activity indices [83, 84]. Tenosynovitis is the most common finding in systemic sclerosis [85] and, similarly to SLE, mostly affects the wrist and MCP joints [86].

In hand OA, US-detected features of inflammation, in particular power Doppler signals, are associated with the development of erosions, more severe radiographical damage, and reduced cartilage thickness [87–89]. Both Doppler flow and grayscale signs of synovitis are associated with pain [90, 91]. US is a reliable and more sensitive imaging modality than conventional radiography for detecting erosions and osteophytes [92, 93].

US is helpful in the diagnostic workup of finger joint trauma by detecting collateral ligament tears, palmar plate injuries, thumb sesamoid fractures, clinically unsuspected synovial cysts, thickened joint capsules, fibrous tissue, and fluid collections, especially during dynamic examination and thus may help improve outcomes [94–96].

Practical points, limitations, and artifacts in wrist and hand pathology are detailed in Supplementary Tables 1 and 2.

Recommendations

1. US should be considered to detect joint inflammation in rheumatoid arthritis in order to optimize management, particularly in clinical scenarios such as early diagnosis or evaluation of residual inflammation in clinical remission (LoE 2, SoR strong). Strong consensus (34/0/2, 100 %)

2. US should be considered to detect the articular and peri-articular involvement of the wrist and hand in early and established psoriatic arthritis and to provide information on disease activity (LoE 2, SoR strong). Broad consensus (31/2/3, 94 %)

3. US may be used to detect both synovitis and tenosynovitis in connective tissue diseases. (LoE 2, SoR weak). Broad consensus (31/2/3, 94 %)

4. US should be considered to detect inflammation in hand osteoarthritis (LoE 2, SoR strong). Strong consensus (33/1/2, 97 %)
1.4. Hip

**Background**

The hip joint can be affected by inflammatory and degenerative conditions leading to effusion and synovitis. Furthermore, proliferative morphologic bone alterations whether developmental, traumatic, related to childhood orthopedic conditions, iatrogenic, or idiopathic (e.g., OA) may, along with labral changes, cause impingement or decreased range of motion often requiring surgical intervention. In the postoperative period, hip symptoms are not infrequent, and US may be useful in assessing the cause of the symptoms. Hip pathology may also be seen in trauma leading to hematoma and/or anterior labral tear.

**Clinical application**

**Arthritic conditions**

US is more sensitive than clinical examination for the assessment of synovitis and effusion in the hip [97, 98] but less sensitive compared to MRI [99, 100]. US is a reproducible method for the assessment of changes in the osseous surface, synovitis, and effusions [101, 102]. The anterior column-capsule distance has been reported to be ≥7 mm, showing good sensitivity for effusion/synovitis, whereas a cut-off ≥9 mm improves the specificity [99, 103]. In suspected crystal arthritis, US should be regarded as the first-line imaging technique for hip assessment because of its reliability in detecting crystal deposits and its safety compared to conventional radiography [104, 105]. US may be used to monitor treatment in inflammatory arthritis [102, 106–108].

**Femoroacetabular impingement (FAI)**

FAI is an important cause of hip pain in younger patients. In juvenile males a strong association has been noted between high intensity weightbearing sports and cam morphology, which is a strong risk factor OA and hip replacement [109–111]. The diagnosis of FAI is based on clinical symptoms, physical examination, and initial conventional radiography. US has been evaluated for the diagnosis of cam deformity and in follow-up after surgical resection and has compared favorably to X-ray, MRI, and the gold standard MRA [112–115]. US evaluation of the morphologic appearance of the head-neck junction and measurement of the “α-angle” (along with other measurements) have been assessed and found to be comparable with other imaging techniques [114–116].

**Anterior labrum tear (ALT)**

Using US, labral tears may appear as labral enlargement with intra-substance hetero-echogenicity, labral displacement or the absence thereof, hypoechoic clefs or labral inrasubstance or para-labral cysts [117]. US is comparable to MRI for labral tears but inferior to MRA or CT arthrography (used when MRA is contraindicated) [118–120].

**Total hip arthroplasty (THA)**

US of the postoperative hip joint allows assessment of the prosthesis area of the hip and surrounding tissues. In the early postoperative phase, US can detect fluid collection and hematoma, thereby helping to determine further treatment [121–123]. In the later postoperative phase, US can help in the diagnosis of pathology such as ilipsoas bursitis, muscle atrophy, fluid collections as well as in the detection and routine monitoring of pseudotumors after a metal-on-metal (MoM) hip arthroplasty [124–126]. Metal artifact reduction sequence MRI (MARS MRI) is the gold standard for the assessment of postoperative hips. US, with its reported high sensitivity for detection, can play a critical role in the diagnosis and routine monitoring of pseudotumors in asymptomatic patients [126–128].

**Practical points, limitations, and artifacts** in hip pathology are detailed in Supplementary Tables 1 and 2.

**Statement**

1. Ultrasound of the hip is more sensitive than clinical examination but not as sensitive as MRI for detecting synovitis and effusion (LoE 4). Broad consensus (30/4/2, 88 %).

**Recommendations**

1. US might be used to monitor the treatment of hip inflammation. Timing of repeat US is dependent on the clinical circumstances (LoE 2, SoR weak). Broad consensus (26/6/4, 81 %)

2. Following metal-on-metal total hip arthroplasty, US is recommended as the initial screening tool and for regular surveillance in pseudotumor diagnosis in asymptomatic patients, as US has the same diagnostic accuracy as metal artifact reduction sequence MRI (LoE 2 SoR strong). Broad consensus (29/2/5, 94 %)

3. US may be used to evaluate patients clinically suspected for femoroacetabular impingement (LoE 4, SoR weak). Broad consensus (27/7/2, 79 %)

4. US may be used for detecting hip anterior superior labrum tears (LoE 4, SoR weak). Broad consensus (28/7/1, 80 %)

1.5. Knee

**Background**

US detection and quantification of inflammatory findings in the knee have been validated using MRI [129] and histology [130]. US has also shown great value in the detection of crystal deposition in several structures of the knee such as the articular cartilage, menisci, and tendons [131–133]. In OA, the assessment of meniscal protrusion, articular cartilage degeneration, synovitis, osteophytes, and Baker’s cysts (popliteal cyst) are the main uses of US. After history and clinical examination, US is the first choice for imaging of knee injuries, e.g., sprains and direct impact.

**Clinical application**

**Inflammatory arthritis**

US has shown a greater sensitivity than clinical evaluation for the detection of knee inflammation, i.e., intra-articular effusion, synovial proliferation, and synovial inflammatory activity, i.e., synovial blood flow in immune-mediated arthritis such as RA [134] or SLE [135] as well as in crystal arthritis such as gout and...
calcium pyrophosphate deposition disease (CPPD) [136]. US is also more sensitive than clinical examination for detecting Baker’s cysts [134].

Crystal arthrits

US allows differentiation between CPPD and urate crystal deposits based on the distribution of the pathological findings. These are hyperechoic foci within the articular cartilage substance in CPPD [133, 136, 137] and a thick hyperechoic enhancement of the synovial surface of the cartilage irrespective of the insonation angle of the US beam (the double contour sign) [138, 139] in gout. It has been widely demonstrated that the capacity of US to detect intra-articular CPPD crystals in the knee is superior to that of conventional radiography [131, 132, 140, 141].

Osteoarthritis

US and clinical findings (e.g., pain, function) correlate in knee OA [142, 143]. US has demonstrated good reproducibility in the assessment of the osteoarthritic knee [144]. While prompt detection of fluid is contributory to subsequent intervention [145], the presence of US-detected effusion greater than 4 mm has also been reported to predict subsequent joint replacement [146].

Similarly, an initial US finding of meniscal protrusion was found to be predictive of radiographic OA [147]. Of note, both quantitative and semiquantitative assessments of meniscal protrusion seem reliable when compared with MRI [148]. Undoubtedly, dynamic scanning is better for functional assessment of meniscal protrusion [149].

For the detection of osteophytes, US provides superior sensitivity compared to conventional radiographs for the detection of osteophytes [150]. Grading scales for medial femoral osteophytes have also been developed, with good agreement with the Kellgren-Lawrence grading [151].

US and MRI were found to be comparable with respect to assessing cartilage defects [152]. Semi-quantitative grading and thickness measurements of the articular cartilage were sufficiently correlated with MRI [153] and histological findings [154]. Normative reference values for any of the aforementioned data can be readily established among populations [155].

Knee injuries

If a fracture in the area of the patella and the tibial head is suspected, US scanning of the most painful region in two planes has shown a high sensitivity and specificity for detecting a cortical break [156]. Nevertheless, X-rays are mandatory in these cases. Muscle contusions, joint effusions and popliteal cysts are reliably detected by US [157]. A distortion injury can lead to rupture of the capsule, the medial patellofemoral ligament, the medial and lateral collateral ligament, the tendons of the semimembranosus, semitendinosus and gastrocnemius on the inside and the popliteus on the outside of the knee. The ability of US to detect these lesions is comparable with that of MRI.

US of the meniscus, especially medially, has a high negative predictive value of 93 % and an acceptable specificity for meniscal lesions [158]. However, if damage to the meniscus with a possible requirement of an operative procedure is suspected, MRI is necessary [159]. Although in the area of the medial meniscus, the anterior horn, the pars intermedia, and the posterior horn can be assessed sonographically with regard to the outer contour, the internal structure is not sufficiently reliable to differentiate a radial and a horizontal tear [160]. If the meniscus is subluxed or even dislocated, this can be reliably detected with US, but the cause cannot always be specified. Dynamic examination of the posterior corner of the capsule and the posterior horn of the meniscus is particularly helpful. A bucket-handle tear of the medial meniscus is clearly recognizable [161]. A discoid meniscus, which typically affects the outer meniscus, can be easily visualized.

All ligaments of the knee joint except the two cruciate ligaments are superficially opposed and thus amenable to US assessment. Ruptures and distortions with intra-ligamentary fluid accumulation may be differentiated through morphological structural changes and abnormalities on power Doppler [162]. The medial collateral ligament and the medial patellofemoral ligament are particularly accessible [163]. The anterolateral ligament, visible on US, has been extensively examined due to its importance for the anterolateral rotational instability in ruptures of the anterior cruciate ligament [164]. After a patella dislocation, the visualization of the ruptured medial patellofemoral ligament is of great importance and can be performed sonographically [165]. The posterior cruciate ligament can be easily assessed by direct visualization of the distal two-thirds aspect [166]. This is not reliable in the clinically more important proximal third or the proximal two-thirds of the anterior cruciate ligament [167]. In the dynamic assessment of the two cruciate ligaments, a number of studies have left no doubt as to the value of the US Lachman test [168–170].

Practical points, limitations, and artifacts in knee pathology are detailed in Supplementary Tables 1 and 2.

Recommendations

1. US could be used to detect and characterize knee inflammatory abnormalities when clinical assessment is insufficient or inconclusive (LoE 3, SoR weak). Broad consensus (26/3/7, 90 %)

2. In crystal-related arthritis of the knee (with or without symptoms), US is recommended to increase diagnostic accuracy (LoE 2, SoR strong). Strong consensus (31/0/5, 100 %)

3. US should be used to detect effusion/synovitis, cartilage damage, early bone proliferation and meniscal protrusion in the diagnosis and management of knee osteoarthritis (LoE 2b, SoR strong). Strong consensus (33/1/2, 97 %)

Ankle and foot

Background

Due to the high number of joints found in the ankle and foot and the complexity of local anatomy, US examination needs to follow standardized protocols [171, 172]. In healthy subjects, synovial fluid and synovial hypertrophy in the ankle and especially in the foot joints have higher prevalence compared with other joints, in correlation with biomechanical factors, age, and pregnancy [173, 174].
Clinical application

In contrast to the high interest in US of the hand and wrist in RA patients, fewer studies on ankle and foot involvement have been published [175]. Clinical detection of synovitis is more difficult than in the wrist and hand [176]. However, US is more sensitive for detecting ankle and foot synovitis compared to clinical examination [177, 178]. The added value of US in detecting inflammatory lesions [176, 179, 180] is proven, showing the importance of the method in characterizing disease activity. In the ankle and midfoot, the tibiotarsal (TT) and talonavicular joints are the most frequently affected joints [181–184] while in the forefoot the metatarsophalangeal (MTP) joints, especially MTP II-V, are most affected [183, 185]. Using US, subclinical synovitis was found in 25 % of RA patients in clinical remission [186] and the presence of the power Doppler signal in MTP joints showed predictive value for unstable remission [186] and radiographic progression [187]. Compared to X-ray, US performs better in the evaluation of MTP joint articular cartilages [188] and erosions [189]. US and MRI had comparable sensitivity for the detection of synovitis in MTP or tarsal joints [190–192] and very good agreement (96 %) for MTP erosions [190]. Interobserver agreement was very good or good for the US detection of ankle and foot synovitis [193].

In PsA, US more frequently detected features of active disease at the MTP level compared to clinical examination [194]. The presence of MTP synovitis, erosion, and subluxation was predominately responsible for painful MTP [195]. US and MRI had high concordance (85 % to 100 %) for destructive changes and moderate concordance for inflammatory findings (73 % to 100 %), with both techniques being more sensitive compared to X-ray and clinical examination [196]. Compared with MRI, X-ray, and scintigraphy, the specificity of US was between 84 % and 94 %, depending on the pathological joint [197]. Agreement between US and MRI was higher regarding effusion and synovitis in MTP I, II, and IV, compared with MTP III and IV [197]. MTP joints were included in US composite scoring systems which have shown utility in monitoring response to therapy [198, 199]. US-detected persistent synovitis or enthesitis after 6 months of treatment proved to be an independent predictor of future structural progression [200]. Also, detection of at least one joint with active power Doppler synovitis (including TT and MTP) in PsA patients in remission, led to flare during follow-up in 65 % of cases (relative risk = 11, 95 % CI 2.8–44, p < 0.001) [201].

In gout, MTP I and TT are the most frequently affected joints. US is a sensitive imaging technique for the evaluation of joint pathology in acute gout attacks, the early detection of erosive joint damage, the assessment of monosodium urate deposits, and the guiding of intra-articular injections, with high sensitivity and specificity [202–206]. High intra-observer agreement was found for elementary lesions in gout [207], and the presence of the double contour sign in the first metatarsal, talar, second MCP, or femoral articular cartilage has good sensitivity and specificity for the diagnosis of gout [208].

An early study, focused on joint involvement in SLE [209], reported that MTP joints (especially MTP II) were the most affected site (72.6 %) with significant differences compared with the wrist, MCP, and PIP (joint effusion, synovial hypertrophy, or synovitis).

US inflammatory scores, as indicators of severity of local joint involvement, have the highest value for the MTP joints. Synovitis and synovial power Doppler vascularity were more commonly detected in MTP II and IV [210]. The presence of MTP synovial hypertrophy in 80 % of the SLE cases with power Doppler signal in only 10 % of cases, was related to mechanical tissue irritation [211].

In Löfgren syndrome with ankle involvement, articular synovitis is rare, mild, and without significant power Doppler activity [212, 213]. Talocrural, subtalar, and Lisfranc joints can be affected (25 % effusion, 17.5 % synovitis, and 7.5 % power Doppler signal), with bilateral arthritis rarely being present [139].

Elementary lesions of foot OA, including inflammatory lesions (synovial hypertrophy, joint effusion, power Doppler signal) and structural abnormalities (cartilage damage and osteophytes) have been evaluated leading to the conclusion that US is a reliable tool for assessing inflammatory lesions in foot OA [214]. The prevalence of US pathological findings in patients with foot OA is high, both in the forefoot and midfoot [215]. Osteophytes are associated with the presence of MTP I pain and together with power Doppler synovitis, with worse patient-reported function [216].

In marathon runners, the acute physical stress does not produce significant changes or effusion in the talocrural joints [217]. In contrast, in patients with ankle sprains, the presence of talocrural effusion on US indicates severe ankle sprain [218].

Practical points, limitations, and artifacts in ankle and foot pathology are detailed in Supplementary Tables 1 and 2.

Recommendations

1. In patients diagnosed with RA, PsA, LES, and gout presenting with ankle or foot joint symptoms, US should be used for the differential diagnosis and management of the arthritis (LoE Zb, SoR strong). Strong consensus (33/1/3, 97 %)

2. US might be used as a complementary imaging technique for the evaluation of the traumatic ankle and foot joint lesions (LoE 5, SoR weak). Broad consensus (31/2/3, 94 %)

2. Pediatric applications

Background

MSUS is a particularly attractive imaging technique in the pediatric population. Besides benefits for children (no ionizing radiation or sedation required), the use of US in evaluating disease has been steadily increasing throughout the world because of its accessibility for clinicians, portability, real-time imaging capabilities and low economic cost.

In addition to a detailed anatomy description of joints and soft tissues on B-mode, Doppler US provides real-time assessment of the blood flow and its anomalies [219–221]. Establishing US normality in children is key to both US standardization and accurate diagnosis.

For many years, US has been used for the diagnosis of developmental dysplasia of the hip (DDH) [222]. US is well suited for imaging all peripheral joints. It enables the identification and differentiation of intra- and peri-articular structures and, consequently,
enhanced disease assessment. Therefore, it is particularly useful in patients with Juvenile Idiopathic Arthritis (JIA) [223]. Moreover, US can be used for guiding biopsies of tumors and cystic lesions and for supporting therapeutic strategies [224, 225]. US is also becoming widely used for superficial tissue evaluation (skin and subdermis) in children with scleroderma and dermatomyositis. However, US is limited in the assessment of deeper lesions and the ones proximal to the airway, gastrointestinal tract, and skeletal structures [222]. Unlike in adults, to date, the use of imaging for research purposes has been scarce in children, mainly due to the limited standardization of imaging techniques and the paucity of validation studies.

This chapter will focus on the role of MSUS in diagnosing and monitoring several pediatric musculoskeletal disorders, excepting DDH. Today’s standards of hip US in DDH are well established. The Graf’s (morphological/static) and Harcke’s (dynamic) methods have been the focus of ongoing development as a result of using US screening for the past 30 years [226].

2.1. Normal sonoanatomy of the musculoskeletal system

Clinical applications

Several studies in children provided relevant information of age- and gender-specific sonoanatomy crucial for pathology recognition. Two of them addressed the development of definitions for the US appearance of joints (i.e., hyaline cartilage, epiphyseal secondary ossification center, joint capsule, normal synovial membrane, the ossified portion of articular bone, physiological vascularity, and the fat pad tissue) in healthy children through a consensus process and validation in several practical exercises [219, 220].

A small amount of physiologic fluid located at several joint recesses and the flexor tendon sheaths has been described as a mode of cartilage thickness (JCT) [230–235] and it seems to be significantly greater in boys than in girls in peripheral joints [231, 232]. Conversely, Samanta et al. did not find any significant difference at the wrist joint [233]. Intra- and inter-observer variations in JCT measurement have been documented as acceptable in several studies [230, 234, 235]. A strong association between the mean tendon thickness of lower limbs and age has been reported (p≤0.001) [226, 236, 237].

Several studies reported that the joint cartilage thickness (JCT) shows a steady decline with age [230–235] and it seems to be significantly greater in boys than in girls in peripheral joints [231, 232]. Conversely, Samanta et al. did not find any significant difference at the wrist joint [233]. Intra- and inter-observer variations in JCT measurement have been documented as acceptable in several studies [230, 234, 235]. A strong association between the mean tendon thickness of lower limbs and age has been reported (p≤0.001) [226, 236, 237].

Several studies reported on physiological vascularity using the Doppler technique, mainly detected at physeal and epiphyseal cartilaginous structures in joints and entheses [220, 227, 236, 237]. Chauvin et al. documented the Doppler signal at asymptomatic sites in two locations: 1) peri-entheseal (1–3 color spots displayed) in peripheral children and 2) intra-entheseal in the quadriceps tendon in younger children (4–9 y. o.) [227]. Roth et al. found similar results [236], whereas Jousse-Joulin et al. did not find US vascularity in any of the healthy entheses evaluated [237].

Statement

1. US is able to show children’s age-related variations in the sonoanatomy of healthy joints and tendons (LOE 4). Broad consensus (23/7/6, 77 %)

2.2. Inflammatory arthritis

JIA represents the most common rheumatic disorder in childhood. Consensus-based recommendations on the use of imaging in JIA were recently published [223].

Clinical applications

The diagnosis of JIA is mainly based on clinical features and the exclusion of other conditions mimicking chronic arthritis. US has the potential role to narrow the differential diagnosis [223, 238].

US has a better sensitivity than clinical examination for the detection of inflammation in peripheral, particularly small joints [239–246]. US allows precise identification of the structures affected by the inflammatory process (joint, tendon, enthesis) with implication for JIA classification, extension, and treatment strategy (including US-guided local treatment) [225, 237]. US is sensitive for tracking treatment-induced synovial changes [225]. Lanni et al. reported a strong sensitivity to change for grayscale and power Doppler US scores (standardized response mean 2.44 and 1.23), suggesting their potential use as outcome measures [247].

Standardized US examination protocols for the JIA are currently available [248]. A reduced 10-joint US assessment has been proposed as it was found to be as valid and feasible as the 44-joint comprehensive US evaluation [249].

Studies comparing US with MRI have shown a poor sensitivity of US for the early detection of temporomandibular joint involvement [250, 251].

US studies have demonstrated persistent synovitis in a significant proportion of JIA patients with “clinically inactive disease” [252–255]. Pilot studies found that US-detected synovial abnormalities did not predict disease flare in clinically inactive JIA [252, 256, 257]. Conversely, De Lucia et al. showed an increased risk of flare (OR = 3.8, 95 % CI 1.2 to 11.5) [253], and Silva et al. study reported similar results [254]. Although US offers a more accurate evaluation of remission status over clinical examination, the prognostic value of subclinical synovitis is still being defined.

US has the potential to enhance the detection of structural damage over clinical examination and conventional radiography [258–261]. When comparing US with radiography, the same detection rate has been described in wrist erosive changes for both methods [258] and 1.4-fold in the assessment of knee joint space narrowing [260]. Evidence that US is a reliable tool for the assessment of cartilage damage in JIA has been supported by the excellent agreement achieved between MRI and US measurements of the distal femoral cartilage thickness [169].

Recommendation

1. US is more sensitive than clinical examination in the evaluation of inflamed joints. This technique should be integrated into clinical examination in a child with recent-onset inflammatory
2. US has demonstrated high sensitivity to show inflammatory changes and might be considered for monitoring joint inflammation in JIA patients (LoE 3, SoR weak). Strong consensus (30/1/3, 97 %)

3. US might be used to detect subclinical synovitis in JIA patients in clinical remission (LoE 3, SoR weak). Strong consensus (34/0/2, 100 %)

2.3. Infections

Clinical applications

US is useful for the early diagnosis of pediatric septic arthritis (SA), particularly in the hip joint. US shows high sensitivity and low specificity [261–264]. US features, such as predominant synovial (capsular) thickening associated with increasing joint effusion, high fever, and high serum CRP level are predictive of hip SA [265]. Two studies identified US as being the imaging technique of choice in the initial workup of the pediatric irritable hip or transient synovitis [265, 266].

Recommendation

1. When septic arthritis is clinically suspected, US can visualize the presence of joint effusion and guide fluid aspiration. However, differentiation between septic arthritis, transient synovitis, and early osteomyelitis is not possible based on US findings alone (LoE 4, SoR). Broad consensus (26/5/5, 84 %)

2.4. Overload syndromes

Osgood-Schlatter disease (OSD), Sinding-Larsen-Johansson syndrome (SLJS), and jumper’s knee syndrome are enthesopathies affecting the adolescent knee joint and usually have a good prognosis. The classic US findings associated with overload syndromes in the knee are: a hypoechoic/anechoic region in the enthesis, with or without thickening, tears, vascularity, and bone lesions, including fragmentation of the tibial tubercle ossification center (OSD) or the distal patellar pole (SLJS).

Clinical applications

OSD seems to be associated with the degree of bone maturation. Kaneuchi et al. showed that the risk of OSD significantly increased from the cartilaginous stage – unossified tibial tuberosity (TbT) – to the secondary ossification center stage (OR = 9.48) [266]. In addition to morphological changes in OSD, Doppler signal surrounding the TbT apophysis was detected along with knee pain (within the enthesis, bursa, and the Hoffa fat pad) [267]. Of note, the classic US findings in OSD have also been found in young athletes without symptoms [268, 269].

Recommendation

1. US might be considered a first-line imaging diagnostic technique in overload syndromes of the knee in adolescents (LoE 3b, SoR weak). Broad consensus (25/7/4, 78 %)

2.5. Pediatric Trauma

Clinical applications

US provides an alternative to conventional radiography in the investigation of pediatric trauma [270]. In extremity fractures (mainly humerus and forearm), the sensitivity, specificity, positive predictive value (PPV), and negative predictive values (NPV) for US were high [270, 271]. The agreement between radiography and US to detect fractures was reported in 93 % of cases. It was higher for the femur, nasal bones, and ribs/sternum (100 %), and lower for the bones of the hands and feet (75 %) [272].

In the detection of pediatric elbow fractures, a meta-analysis has showed a summary sensitivity of 96 % and specificity of 89 % and a pooled proportion of false-negative rate of 3.7 % for US [273]. For supracondylar fractures of the distal humerus (SCFs) US diagnosis in comparison to radiography showed a sensitivity, specificity, NPV, and PPV of 100 %, 93.5 %, 100 %, 95.2 %, respectively [274]. The presence of the posterior/dorsal fat pad sign (dFPS) predicted an elbow fracture with a sensitivity and specificity just under 100 % and a PPV of 90.2 % with an NPV of 97.4 % [275, 276]. Similar values of sensitivity and specificity were obtained in the detection of hand and foot bony fractures [277, 278].

A meta-analysis on occult ankle fractures in children with suspicious symptoms showed that the operating characteristic for US ranged in positive likelihood ratio from 9 to 20 and in negative likelihood ratio from 0.04 to 0.08 [279]. US is more sensitive than radiography (100 vs. 40 %) for the diagnosis of avulsion fractures of the anterior talofibular ligament which require urgent diagnosis and orthopedic consultation [280].

The US sensitivity and specificity values for the diagnosis of pediatric nasal bone and skull fractures were variable. They seem to be higher in children younger than 2 years old [281, 282].

US was used in the diagnosis and monitoring of congenital muscular torticollis [283].

US findings are often nonspecific in post-traumatic myositis ossificans [284].

Recommendation

1. US might be used in children with clinically suspected fractures to guide the diagnostic process (LoE 3, SoR weak). Broad consensus (30/3/3, 91 %)

2. US might be used as a screening tool for the evaluation of suspected elbow fractures (LoE 3, SoR weak). Broad consensus (24/4/8, 86 %)

2.6. Pediatric vascular anomalies

Clinical applications

Infantile hemangioma is the most common benign tumor in children. Clinical presentation and typical grayscale and Doppler US features may confirm the diagnosis of superficial soft-tissue hemangioma, thereby avoiding biopsies [221, 285–290]. Conversely, atypical and deep-seated hemangiomas show no specific US findings [287–299].

Several studies report distinct US images for other lesions, such as congenital hemangioma [221, 292], locally aggressive tu-
mors, such as Kaposiform hemangioendothelioma [293], vascular malformations (capillaries, venous, lymphatic, and arteriovenous, or high-flow and low-flow lesions) and fibro-adipose vascular anomaly (FAVA) [221, 285, 288, 289, 294, 295].

Recommendation

1. US might be used as a first-line examination in the diagnosis of small and superficial vascular anomalies (LoE 5, SoR weak).

Broad consensus (25/5/6, 83 %)

2.6. US of spine in children

Spinal US is an ideal imaging technique for a preliminary workup of the spine in newborns and young children [296] and is used in the diagnosis of occult and non-occult spinal dysraphism and in the assessment of spinal cord abnormalities, vascular malformations, and birth-related trauma of the spine [297–301].

Clinical applications

US is the first-line imaging technique for the assessment of the spine and its content in the youngest children [296–304]. During the first 3–6 months of life, the incompletely ossified posterior vertebral arch offers a valuable acoustic window to spinal US. US allows an accurate depiction of neural structures in the spinal canal [305]. However, MRI remains the first-line technique in older children when ossification of the posterior arch is complete [306].

Newborns should undergo spinal US evaluation in the following circumstances: posterior midline cutaneous markers (midline or paramedian back masses or dimples higher than the intergluteal fold especially when associated with midline skin discoloration, skin tags, hair tufts, hemangiomias), foot abnormalities, anorectal and genitourinary malformations and neurologically abnormal lower limbs, spina bifida occulta, tethered cord, intracanal masses, raphe dysraphism including myelomenigocele, myelocoeles [296–304]. Nevertheless, the diagnosis should ultimately be confirmed and characterized by MRI.

Spinal US guides interventional procedures [307] and assesses complications of spinal tap [308, 309]. In addition, spinal US can provide an accurate measurement of the lengthening of magnetically controlled growing spinal rods [310, 311] and can show the Cobb angle changes of adolescents with scoliosis during follow-up [312].

M-mode US reveals oscillations of the cord due to respiration and the cardiac cycle [312]. The lack of movement of the terminal cord is an ancillary US sign of tethered cord [296, 300]. Color Doppler US displays the epidural venous plexus as well as the central branches of the anterior spinal artery [313]. New three-dimensional US probes and post-processing software offer a valuable opportunity to create multiplanar reconstructed images [314, 315].

The feasibility and reliability of intervertebral disc shear-wave elastography suggests it should be used as a routine tool for the early detection and monitoring of the progression of vertebral disc abnormalities [316].

Of note, normal variants mimicking spinal pathology such as ventriculus terminalis and transient dilatation of the central canal, pilar cyst, pseudo-sinus tract, and thick filum terminale (<2 mm) [317, 318] should be taken into account. Additionally, a false image of duplication of the spinal cord is a common artifact to consider when looking for spinal cord duplication [318].

Isolated sacral dimples of the intergluteal fold do not predict underlying spinal cord malformations, and spinal US should not be performed in neonates with simple sacral dimples [318].

Practical points, limitations, and artifacts in pediatric applications are detailed in Supplementary Tables 1 and 2.

Recommendation

1. For spine evaluation in newborns up to the age of 3–4 months, US should be used as a first-line tool (LoE 1a, SoR strong).

Broad consensus (27/2/7, 93 %)

3. MSUS-guided procedures

3.1. Arthrocentesis and therapeutic injections

Background

Over the past 20 years, US-guided intra-articular (IA) and peri-articular (PA) diagnostic and therapeutic injections have earned their place in clinical practice. The use of US to direct the needle improves accuracy, performance, and safety by facilitating visualization of the target area avoiding damage to vulnerable tissues such as nerves, vessels, tendons, ligaments and cartilage. In addition, US scan prior to injection enables a point-of-care morphopathologic assessment of the problem. US-guided injections can be performed indirectly (pre-recorded visualization) or directly either free-hand or with device guidance. US-guided musculoskeletal injections are typically performed free-hand with real-time visualization.

Clinical application

US-guided arthrocentesis and IA injections are more accurate than anatomical palpatory landmarks for fluid aspiration or for delivering drugs in many superficial, deep, large, and small joints [319–328]. Glucocorticoids (GC) and hyaluronic acid (HA) are currently the most frequent IA injectables used in clinical practice. However, whether US-guided IA injections improve efficacy warrants further investigation [323, 325, 327, 328]. Since 1952, GC have been injected into joints to decrease local joint synovial inflammatory response and pain in patients with inflammatory and degenerative arthritis [329, 330]. Data comparing the efficacy and safety of the different available preparations is limited [330]. Crystalline long-acting GC (methylprednisolone acetate, triamcinolone acetonide, and triamcinolone hexacetonide) preparations are commonly used because they are taken up by the synovial lining cells allowing continued local release plus small systemic absorption [330]. IA HA preparations relieve pain and can improve function in osteoarthritic joints by restoring the elastic and viscous properties of the synovial fluid [331, 332]. They have also been used in adhesive shoulder capsulitis [333, 334]. Those compounds with higher molecular weight and obtained from biological fermentation process seem to offer a better efficacy and safety profile [335].

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US-guided PA injections have continued to develop and expand, and multiple therapeutic options have become available, all with varying levels of supportive clinical evidence of their efficacy. US-guided intra-tenosynovial GC injections are more accurate, safer, and are more effective than palpatory GC injections for treating inflammatory tenosynovitis [336, 337]. When needed for diagnostic purposes, very small amounts of tenosynovial fluid can be easily aspirated using US guidance [338]. US-guided GC intra-bursal injection is effective and safe for treating refractory Achilles enthesitis in patients with SpA [339]. Intra-tenodinous US-guided injectables, such as dextrose, high-volume saline, platelet-rich plasma, are used to treat chronic tendinopathies. However, there is no evidence whether US guidance is more effective and/or safer than conventional blinded intratendinous injections [340–352]. Finally, several studies have shown good feasibility for US-guided pararadicular and facet joint injections at the cervical/lumbar spine [353–355] and superior sacroiliac joints [356].

Practical points, limitations, and artifacts in arthrocentesis and therapeutic injections are detailed in Supplementary Tables 1 and 2.

Recommendations

1. US guidance should be considered for fluid aspiration (LoE 1, SoR strong). Strong consensus (34/0/2, 100 %)
2. US guidance should be considered to improve the accuracy of intraarticular injections (LoE 1b, SoR strong). Strong consensus (34/0/2, 100 %)
3. US guidance should be used in intra-tenosynovial glucocorticoid injection for inflammatory tenosynovitis (LoE 1b, SoR strong). Strong consensus (34/0/2, 100 %)
4. US-guided procedures such as high-volume injection in painful Achilles chronic tendinopathy and platelet-rich plasma in plantar fasciitis, patellar tendinopathy, and epicondylitis might be considered (LoE 2b, SoR weak). Broad consensus (31/3/2, 91 %)
5. US-guided therapeutic injections of the cervical/lumbar spine and SI joints might be considered as an alternative for CT or fluoroscopy guidance (LoE 2, SoR weak). Broad consensus (29/4/3, 88 %)

3.2. Musculoskeletal biopsy

Background

Synovial biopsies are performed commonly for clinical purposes or translational research [357–359]. Synovial tissue samples are taken from joints or tendon sheaths in order to perform cellular and molecular analysis. US guidance is widely used in order to guide the biopsy needle or forceps into the biopsy area (joint synovitis, tenosynovitis), but other techniques exist, especially arthroscopic guidance [360].

It is important to determine the biologic potential of soft-tissue tumors before surgery, due to the impact on patient management and prognosis [361–363]. This often requires histologic confirmation [363, 364]. Percutaneous core needle biopsy (PCNB) of muscle and soft tissue tumors is often performed under US guidance [365, 366] and contrast-enhanced US can be considered for guiding the biopsy in significant areas (vascularized areas) of the tumors [367, 368].

Clinical application

Sampling of synovial tissue or tendon sheaths can be very useful in the clinical context of suspicion of joint infection while making it possible to perform histological and bacteriological analyses. In published case series and cohorts, synovial and tendon biopsy allowed a definite diagnosis in 16.2 % of cases [358] and had a direct diagnostic impact in 37 % of cases, with a positive predictive value of 100 % and a negative predictive value of 95 % for infection [359].

PCNB of soft-tissue tumors is more cost-effective and less invasive compared with biopsy, has lower complication rates, and provides comparable yield rates [362, 369–371].

Practical points, limitations, and artifacts in musculoskeletal biopsy are detailed in Supplementary Tables 1 and 2.

Recommendation

1. US-guided synovial biopsies can be performed safely and might be helpful in the clinical setting for the diagnosis of joint infection when synovial fluid analysis is not available or is non-conclusive (LoE 3, SoR weak). Strong consensus (32/1/3, 97 %)
2. US-guided core needle biopsy of soft-tissue tumors must be done along the planned surgery incision in collaboration with the orthopedic oncologist, obtaining at least four specimens, each with a length of more than 10 mm. The target must be viable tumor regions. Unaffected compartments or neurovascular bundles must not be contaminated by the biopsy tract (LoE 2, SoR strong). Strong consensus (33/1/2, 97 %)

3.3. Perineural injection

Background

Perineural injections (nerve blocks) are performed routinely by anesthetists and pain specialists to block nerve conduction to/from an affected area.

Nerve blocks encompass both central: neuraxial blocks (spinal, epidural, combined spinal-epidural, paravertebral) – outside the scope of this body of work – and peripheral: plexus and terminal nerve blocks. The technique is applicable to individual anatomical locations [372]. The strategy of selection of the optimal block for a specific surgical procedure is “as distal as possible and as proximal as necessary” [373].

Clinical application

Perineural injections aim at depositing local anesthetics with or without additives (epinephrine, steroids, alpha2 agonists, etc.) in the vicinity of a plexus or nerve with the goal of achieving analgesia or complete surgical anesthesia (thus rendering an area insensitive allowing surgery and obviating the need for general anesthesia). Historically, various other nerve localization modalities have been employed, such as paresthesia, anatomical landmarks, peripheral nerve stimulators, loss of resistance (‘pops’), and trans-arterial techniques.
US-guided nerve hydrodissection using local anesthetics, saline, 5% dextrose, glucocorticoids, hyalurondiase, or platelet-rich plasma, has recently emerged as a potential minimally invasive non-surgical treatment for nerve entrapment syndromes [374]. US guidance has been shown to increase the efficacy of perineural injections due to more precise injectate deposition, as quantified by more blocks deemed sufficient for surgery following sensory or motor testing and fewer blocks requiring supplementation or conversion to general anesthesia [375–378]. Also, it improves their safety profile by reducing, although not eliminating, the incidence of nerve injury and inadvertent intravascular injections. While the fewer needle passes do not translate into fewer postoperative neurologic symptoms [379], US is effective in reducing local anesthetic systemic toxicity across its clinical presentation continuum [380].

In addition, US appears to hasten block performance and onset time of peripheral nerve blocks, especially in the lower extremity [376–378].

Practical points, limitations, and artifacts in perineural injections are detailed in Supplementary Tables 1 and 2.

Recommendations

1. Real-time US guidance should be considered for perineural injections (LoE 1, SoR strong). Strong consensus (34/0/2, 100 %)
2. US monitoring of the needle tip should be performed throughout the injection in order to avoid intraneural needle tip placement (LoE 2, SoR strong). Strong consensus (30/1/5, 97 %)
3. US visualization of tissue expansion/injectate spread without resultant increase of the cross-sectional area of the nerve should be sought (LoE 2, SoR strong). Strong consensus (29/0/7, 100 %)

Conclusion

In conclusion, this international multidisciplinary task force has produced, under the auspices of EFSUMB, an evidence-based comprehensive update on clinical applications of MSUS as well as consensus-based recommendations in the field. We expect this EFSUMB product to be useful to the MSUS community.

Conflict of interest

Fernando Allageme Speaker honoraria: GE, Mindray; Equipment support: Esaote
David Bong No Conflicts of interest
Angel Bueno No Conflicts of interest
Vito Cantisani Speaker honoraria: Bracco, Samsung, Canon
Paz Collado No Conflicts of interest
Maria Antonietta D’Agostino No Conflicts of interest
Daniela Fodor No Conflicts of interest
Javier de la Fuente No Conflicts of interest
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Hilde Hammer Speake honoraria and/or consultancy; AbbVie, Lilly, Roche, Novartis
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