

Acute Pyelonephritis Today

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ABSTRACT

Acute urinary infections often involve the low tract, but in a good part of cases they run up to the kidney, becoming an important problem potentially cause of further complications. However, in these cases imaging target is not to diagnose a pyelonephritis, since clinic data are sufficient in non-complicated forms, but rather to evaluate the extension of the parenchymal damage and possible complications as abscesses. Urinary tract infections can be distinguished in APN, renal and perirenal abscesses, pyonephrosis, emphysematous pyelonephritis and emphysematous cystitis. Those infections are very diffuse and often cause patients hospitalization. In the current review it will be illustrated the most useful imaging techniques to recognize

and evaluate pyelonephritis in the most effective way comparing sensitivity, specificity and diagnostic accuracy of the various techniques available to the radiologist.

Key words: Pyelonephritis; Acute pyelonephritis; Contrast Enhanced Ultra-Sound; Computed Tomography; Magnetic Resonance Imaging

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INTRODUCTION

Infections of the upper urinary tract can be distinguished in simple and complicated: the first ones occur in an anatomically and functionally normal urogenital system, in absence of previous surgical interventions on the urinary tract, in immunocompetent patients; generally they involve women between eighteen and forty years old. Women are mainly predisposed to bacterial colonization of urethra and urinary bladder for anatomical reasons. Moreover, the sexual intercourse increases the risk of infections due to the trauma on the urethral meatus and probably also to changes in the vaginal bacterial flora. Non-complicated infections can occur in older women as well, probably due to decreasing of circulating estrogens with consequent atrophy of vaginal mucosa, reduction of the vaginal physiological bacterial flora, difficulties in bladder emptying or low intimate hygiene in elderly patients^[1]. [Sheffield].

Complicated infections occur in a structurally or functionally anomalous genito-urinary system, or in presence at least of one local or systemic factor that can reduce the efficacy of antimicrobial therapy, with possible persistent pathology or distant recurrences. In those cases occult pyelonephritis are more frequent, devoid of typical signs and symptoms, difficult to recognize and promptly treat and, in consequence, at a major risk of systemic and local complications. Miller and Hemphill define urinary infections as complicated "infections in a patient with structural and functional anomalies that reduce antimicrobial efficacy" and list as possible

causes of treatment failure in those cases the formation of abscesses, renal lithiasis, disseminate intravascular coagulation (CID), acute respiratory distress syndrome (ARDS), sepsis and development of chronic failure renal^[2].

Diagnosis of APN is mostly clinical. Typical pyelonephritis symptoms include fever with chills, flank pain, nausea and vomit, dolorability in costo-vertebral angle, associated or no to symptoms suggestive of cystitis (dysuria, stranguria, pollakiuria).

Symptoms of “high” infection can be isolated or associated, with variable intensity gradations, as: (1) Flank pain, unilateral or bilateral. It is possible also to observe a lumbar or suprapubic pain. Inguinal pain suggests the passage of a kidney stone into the ureter (in this case it would be therefore a complicated infection). The superior abdominal quadrants, instead, are an unusual site of pain and should suggest a different diagnosis. (2) Fever, of a variable entity, from mild to more than 39,4°C, can also be absent (for example in more than one third of elderly patients); the patient can refer a feeling cold or having chills also in absence of fever. In presence of negative Gram’s sepsis, is furthermore possible observe an hypothermia. (3) Malaise, weakness and myalgias: they are aspecific and very variable symptoms, even if the patient with high urinary tract infections is generally much suffering. (4) Gastrointestinal symptoms: anorexia is common; nausea and vomit vary in frequency and intensity indeed can be absent but also severe. Diarrhea is rare and should suggest and infective gastroenteritis or another intestinal pathology^[3]. [Shoff]

Along with the clinic evaluation also the urine analysis and urine culture represent fundamental diagnostic instruments to identify urinary tract infections.

Imaging is not routinely indicated in urinary tract infections, however with severe symptoms, high-risk immunocompromised state, diabetic patients and antibiotic non-responders, it become necessary^[4].

Imaging has the task to evaluate the extension of renal damage and the presence of possible complications through techniques as CEUS, Magnetic Resonance and Computed Tomography.

Currently, the most accepted imaging technique that the scientific community considers as the most sensitive and specific, to diagnose an acute pyelonephritis (APN) and its complications when imaging support is needed is the Computed Tomography (CT)^[5]. Although alternative techniques that not require ionizing radiations like contrast enhanced ultra-sonography (CEUS) and magnetic resonance (MRI) are becoming always more important, also thanks to the fact that the major part of APN patients are children and women in fertile age. The problem of exposure to ionizing radiation is a very real issue so in the most recent pediatric guidelines, CT is not even mentioned and is substituted by the only ultrasound examination or in some cases by MRI^[6].

Contrast enhancement ultrasound (CEUS)

Contrast enhancement ultrasound (CEUS) uses microbubbles as contrast agents and acquisitions of impulses of second harmonic to evaluate the parenchymal perfusion. CEUS advantages are well documented and include its safety, simplicity, extreme compliance by the patient, absence of ionizing radiations and capacity to provide a real time imaging. CEUS, like all the US-based techniques, has limitations similar to those of traditional US, for example those related to patient’s habitus, excess of intestinal gas, or scarce collaboration from the patient. CEUS permits to overcome some typical limitations of the traditional B-Mode US, consenting a perfusion assessment of the renal parenchyma (such as for other organs).

After the injection of a US contrast agent bolus, it’s possible

evaluate the early arterial phase by observing the corticomedullar differentiation, lasting between 20 and 40 seconds after injection, followed by a tardive sinusoidal phase in which this differentiation is lost and an homogeneous contrast enhancement through cortical and medullar regions is observed. This phase lasts 45-120 sec. after contrast media administration; the relative vascularization of a lesion is studied through confronting it with the close parenchyma: the vascular lesions appear more echoic and the avascular ones appear more hypoechoic than the normal renal parenchyma.

CEUS is therefore an useful technique to reveal possible alterations of renal perfusion, potentially characterizing anomalies of vascularization as happens in the APN.

According to Correia, the usage of US with contrast media increases the sensibility of the 33% in the diagnosis of pyelonephritis respect to the B-Mode examination alone⁷. It permits the evaluation of areas of minor vascularization, typical of initial either mild or severe forms of pyelonephritis, in which the risk of abscessual evolution is much greater^[7] (A. Nilsson). With CEUS studying the APN, the renal parenchyma is characterized by hypoperfused areas, generally triangular shaped. Abscesses are visible, even if they are small, as rounded hypoechoic or anechoic lesions avoid of contrast enhancement, sometimes with an hypervascularized peripheral rim.

The aim of use US in APN is essentially to document kidney’s size, evaluate cortical scars that are suggestive of previous episodes, to define a structural anomaly or etiology and to confirm or to reject

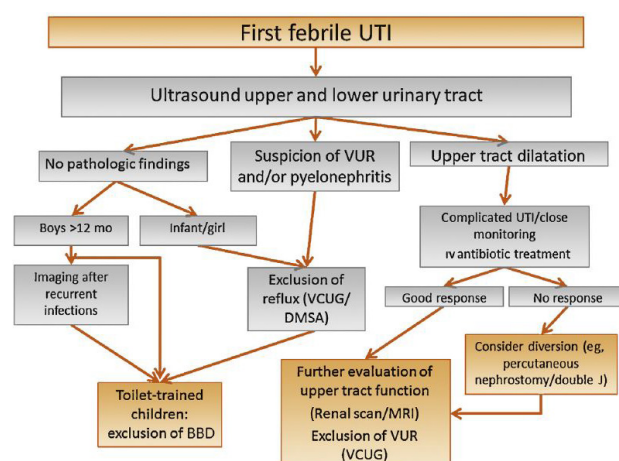


Figure 1 from Stein R, Dogan HS, Hoebeke P, Kočvara R, Nijman RJ, Radmayr C, Tekgül S. Urinary tract infections in children: EAU/ESPU guidelines Eur Urol (2014). Algorithm for assessment and treatment of first febrile urinary tract infection. BBD: Bladder Bowel Dysfunction; DMSA = dimercaptosuccinic acid; IV: intravenous; MRI: magnetic resonance imaging; UTI: urinary tract infection; VCUG: voiding cystourethrography; VUR: vesicoureteral reflux.

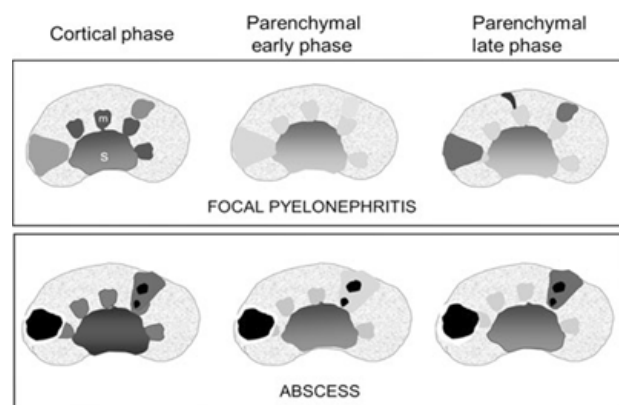


Figure 2 from Fontanilla T, Minaya J, Cortés C, Hernando CG, Aranguena PR, Arriaga J, Carmona MS, Alcolado A. Acute complicated pyelonephritis.

obstructions or abscesses.

According to Fontanilla, CEUS is indicated to study patients with complicated APN, while performing CT only in selected cases, in order to avoid radiation, so that they perform renal CEUS in the first place, with follow-up at 1 week and 1 month, while following it up at 3 months and a year depending if the initial lesion was abscess or not and to assess the evolution of the lesion and its complete resolution or the development of scars^[8].

CEUS diagnostic accuracy seems to be inferior in the diffuse pyelonephritis due to the impossibility of confronting contemporarily both kidneys, while in the focal and monorenal multifocal forms has been reported a notable diagnostic accuracy (with a positive predictive value of 100% and a negative one of 89%).

CEUS is demonstrated to be a great technique in the close follow-up of young patients to evaluate the evolution of APN under antibiotic treatment towards healing, or in case of antibiotic inefficacy towards complications.

According to Fontanilla, CEUS can be used safely also in patients with marginal renal function, because US contrast media are not nephrotoxic. Detection of complicated APN is extremely important in renal transplant recipients because it could determine deterioration of graft function, but at the same time to minimizing the risk of nephrotoxicity is needed so that CEUS provides both advantages^[8].

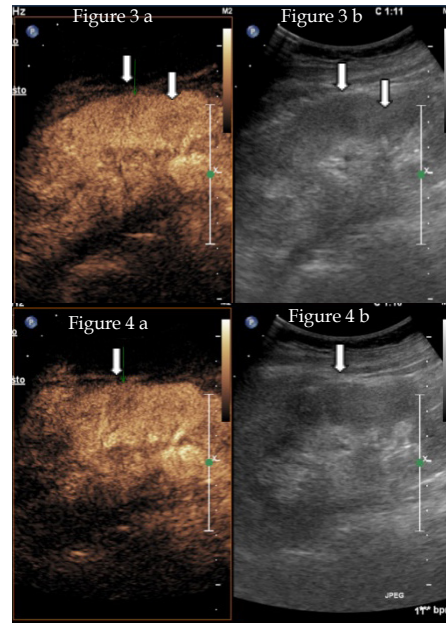
Radiological findings for APN and its complications in CEUS are the following:

Focal pyelonephritis appeared most frequently on grey-scale ultrasound as a hyperechoic focal lesion with cortical bulging. This represents the presence of numerous interfaces mostly due to the presence of abundant inflammatory cells in the interstitium and tubules^[9]. Besides the inflammatory infiltrate and edema, severe capillary damage has been demonstrated, with presence of intraluminal leukocyte and fibrin plugs^[9]. This explains the CEUS hypoechoic appearance of these lesions in comparison to the surrounding cortex, due to diminished enhancement. CEUS allows real-time assessment of renal perfusion, obtaining valuable temporal information. Focal pyelonephritis areas are most conspicuous during the late parenchymal phase, because these areas (wedge or round-shaped) appear more hypoechoic during this phase. Even tiny lesions (smaller than 1 cm), may be detected.

Abscesses: they are necrotic cavities containing pus and debris, always seen as anechoic areas, with or without rim or septal enhancement, alone or within areas of pyelonephritis. In Fontanilla's series, both rim and septal enhancement diminished during the parenchymal phase^[8]. Care must be taken and all of the phases must be carefully analyzed because during the late phase, if the pyelonephritis area is very hypoechoic, small abscesses may not be distinguished from the surrounding pyelonephritic area, or else the size of the abscesses may be overestimated.

Infarctions: may be distinguished from focal APN either because the last one always shows some degree of enhancement with a typical temporal pattern, whereas focal infarctions are seen as non-enhancing areas (although rarely there may be peripheral partially enhanced areas)^[8]. Infarctions are usually wedge-shaped, whereas abscesses are round, geographical or coalescent. Also, infarctions usually do not produce cortical bulging, whereas large or medium size pyelonephritis, with or without abscess, usually does. Another distinctive feature is that infarctions may show a characteristic enhanced external border due to the presence of cortical collaterals^[10]. In the end, infarctions may produce scars indistinguishable from pyelonephritic scars

Residual post-pyelonephritic scars: although they are hypoechoic



Figures 3, 4 APN in a 30 yo female. CEUS showing two hypoechoic foci at the upper pole (figure 3a) and at the middle-third (figure 4a) of the right kidney (arrows). In figures 3b and 4b the correspondent B-mode image are shown (arrows).

on CEUS, they are not difficult to distinguish from complicated APN, because they lack the characteristic temporal pattern and there is focal atrophy of the cortex. Other hypovascular lesions that can potentially mimic APN lesions in CT are renal lymphoma; lesions in autoimmune pancreatitis or Wegener granulomatosis, but there are scarce or no reports on CEUS findings in these entities^[11,12].

Magnetic Resonance (MRI)

Magnetic resonance (MRI) is a technique based on the usage of magnetic fields and radiofrequency impulses. To execute this examination, the patient is introduced in a homogeneous magnetic field; the hydrogen atoms naturally present in the tissues, absorb the electromagnetic energy administrated with a certain frequency and then they release it during the relaxation phase. Relaxation times of tissues are influenced by their molecular composition, in particular by their fat and free water content. It's possible to distinguish two relaxation time constants: T1 (longitudinal relaxation) and T2 (transversal relaxation); T1 or T2-weighted images consent to highlight what tissues relax in their respective times. At T1 the adipose tissue and parenchymal structures are highlighted; at T2 the fluids.

MRI doesn't need contrast agents media, if not in very doubtful cases, for the diagnosis, the evaluation of complications and follow-up of patients with APN. This is possible thanks to the diffusion-weighted imaging (DWI). DWI is a technique of MRI that permits to evaluate the free movement of water molecules. In cases of APN, due to the microvascular alterations consequent to phlogosis, exists a reduction of the free movement of water molecules and consequently a high signal. Furthermore, it is possible to re-elaborate the diffusion-weighted images thanks to colorimetric maps representing the apparent diffusion coefficients (ADC); they are obtained by modifying the diffusion-weighted images with an algorithm that permits also the attribution of a numeric objective value to the studied areas. The lower the ADC value, the lower will be the free movement of water molecules and viceversa (Figures 5-8).

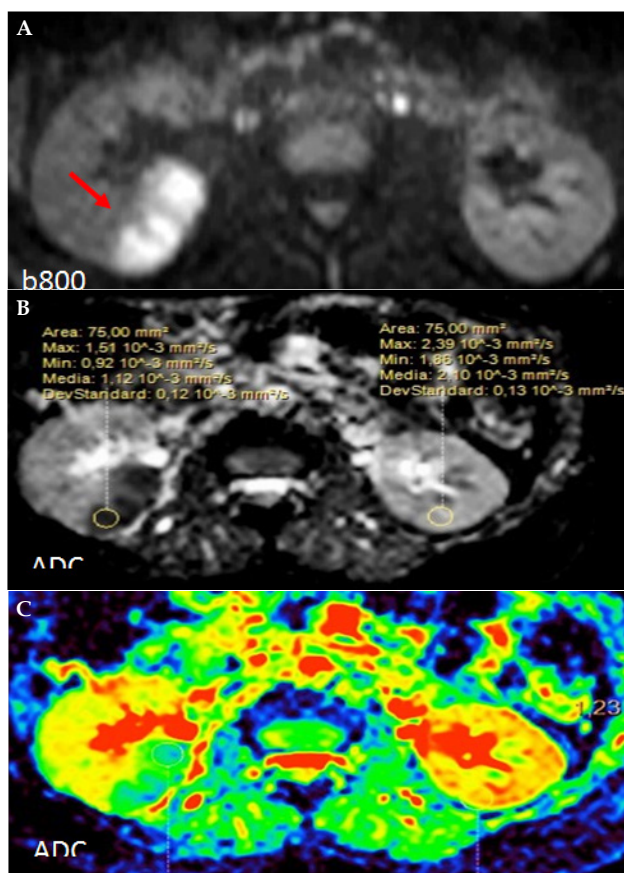
MRI is used mostly in the second instance to confirm APN

diagnosis in those patients with contraindication to iodinate contrast and/or transplant recipients. In the latter ones DWI-MRI has an important role to play as contrast may be contraindicated due to the alteration of renal function. According to Chandan, the magnetic resonance is indicated also in pregnancy^[13]. MRI without contrast media, particularly diffusion weighted magnetic resonance imaging (DW-MRI) and the apparent diffusion coefficient (ADC) value have already been shown capable to distinguish healthy kidney functions from pathologic ones in native kidneys. According to Chandan, DWI-MRI is useful to detect abscesses as they show restriction of diffusion^[13]. Furthermore, it is particularly useful to differentiate hydronephrosis from pyonephrosis as pyonephrosis tends to show restricted diffusion^[14]; beyond that, it has an important role in detecting infected cysts and tumors. In particular, it has been noticed that the normal renal parenchyma presents an ADC value of 2.06 ± 0.16 , while in cases of pyelonephritis the ADC value is of 1.43 ± 0.32 ^[15]. Very similar values for healthy renal parenchyma and APN have been detected in the ADC map also by Albarello F. *et al.*... where the renal parenchyma presented a value of 2,19 and the APN of 1,52. Moreover, these authors evaluated also the abscess value, that resulted of 0,89^[16]. According to Faletti *et al.*..., DWI-MRI along with ADC map are very useful also to evaluate the presence of APN in renal transplant recipients in follow-up^[19].

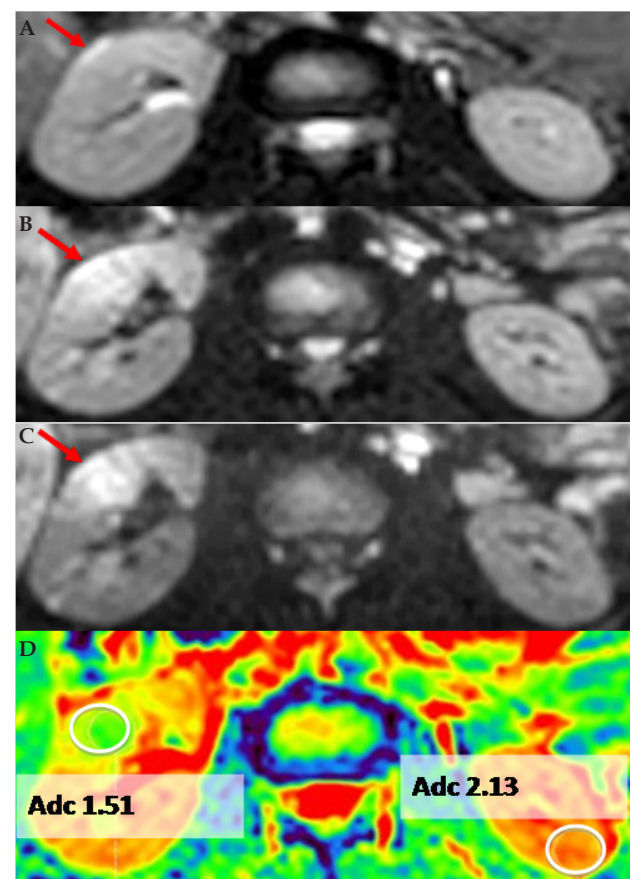
Computed Tomography (CT)

Currently the CT is the gold standard to diagnose APN thanks to

a high accuracy of anatomical study of renal parenchyma and its vascularization. CT is currently the imaging technique with the most solid radiological semeiotics. The radiological APN signs are: focal or global renal enlargement based on the difference in size between the right and left kidney, stranding of perinephric fat, thickening of Gerota's fascia, obliteration of the renal sinus, pelvicalyceal wall thickening, urinary tract stones, pelvicalyceal air, abscess (well-defined hypo-attenuated mass with irregular wall), and hydronephrosis^[17]. CT imaging gives better results than B-mode ultrasound and power Doppler in the detection and characterization of the APN lesions; furthermore it performs better to identify lithiasis or anatomic congenital alterations thanks to a more panoramic view and sensitivity than US in detecting calculi and concomitant urinary tract anatomic abnormalities that could be unnoticed by CEUS^[8]. Occasionally some cases of mild non-complicated pyelonephritis can be unacknowledged, appearing normal to CT with and without contrast media^[18] [Talner]. In many cases of mild PNA, either CECT or ultrasonography may show no abnormal findings^[13]. The sensibility of CT in diagnosing pyelonephritis in literature is reported to be of 86.8%, while the specificity of 87.5%. Nonetheless, an accurate diagnosis is needed, it is important considering the relatively high radiation dose to the patient implicated in CT. Moreover, patients with renal lesions go under multi-step phases of study and follow-up and it has to bear in mind that iodinated contrast agents are potentially toxic in patients at risk of renal failure.



Figures 5 case of APN in a 39 yo woman in the right kidney. In (A) it is shown in a DWI with a b-value of 800 as a signal hyperintensity in the postero-medial portion of the right kidney (arrow). In (B) it is shown in the ADC map in grey scale with the value of 1,12 in the APN focus compared with the value of 2,1 of the normal parenchyma of the contralateral kidney (circles). In (C) it is shown the colorimetric ADC map (green corresponds to low ADC values).



Figures 6 case of APN in a 35 yo woman in the right kidney. In (A) it is shown in a T2w image and appears isointense with the normal parenchyma (arrow). In (B) it is shown in a DWI with a b-value of 400 as a signal hyperintensity in the anterior portion of the right kidney (arrow). In (C) it is shown in a DWI with a b-value of 800 as a even greater signal hyperintensity (arrow). In (D) it is shown the colorimetric ADC map (green corresponds to low ADC values) with the ADC value of 1,51 in the APN focus while it is of 2.13 in the contralateral normal parenchyma (circles).

The CT protocol execution in the clinical suspicion of APN is based on a first basal scan, followed by a 50-90 seconds scan after contrast media injection, completed by a delayed acquisition only if an urinary tract obstruction is suspected^[19] [Craig]. Although, in a lot of cases, in absence of a correct clinical diagnosis, a quadriphasic study is often applied (basal, arterial, venous and delayed).

The inflammatory foci are rarely identifiable in basal scans, in which only predisposing factors or infectious process complications can be observed, such as gas along the urinary tract, lithiasis, hemorrhages and obstructions^[19] [Craig]; therefore, in case of APN, the kidney can appear of increased volume. Only in some cases it's possible observing a density alteration in correspondence of the inflammatory foci, probably due to an internal hemorrhage determined by the infection^[18] [Talner].

CT or MR are performed if large renal abscesses, extrarenal collections or anatomic alterations are suspected, thanks to their better performance in the evaluation of perirenal and pararenal involvement; also in these cases the follow up will be done with CEUS. Emphysematous pyelonephritis has to be always evaluated and followed with CT^[8].

After contrast agent injection, pyelonephritis foci appear as areas of reduced enhancement, wedge shaped or with a striped aspect called "striated nephrogram", extended from renal papillae towards the periphery, in the most common form of infection, developed through an ascending way; instead when areas with reduced contrast enhancement are rounded and peripheral, it is necessary to consider a possible haematogenous origin. Striated nephrogram is not specific and is also seen in some other conditions like renal vein thrombosis,

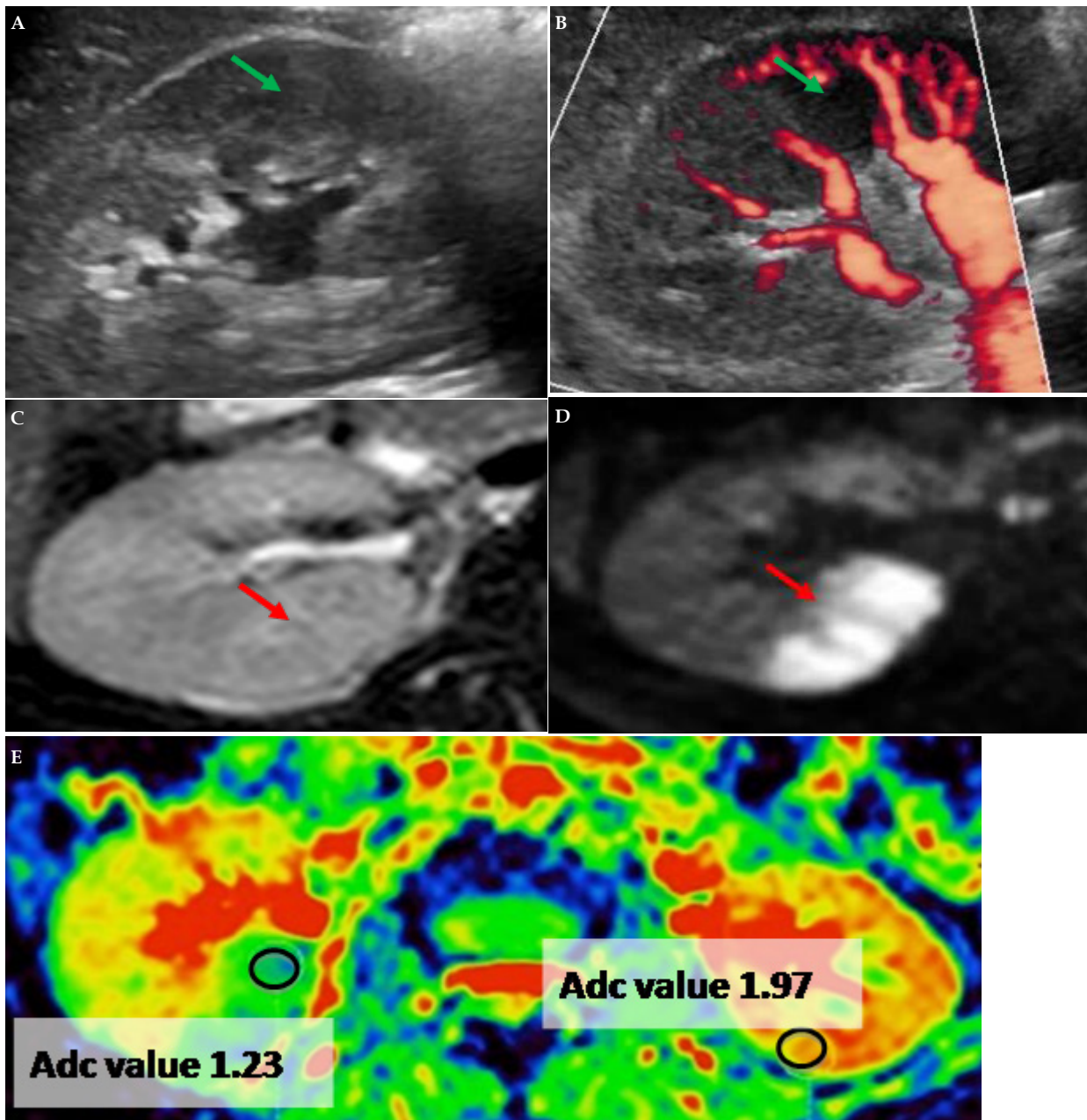


Figure 7 case of APN in a 28 yo woman in the right kidney. In (a) it is shown in a B-mode US image and appears hypoechoic with respect to the normal parenchyma (arrow). In (b) it is shown in a Power-Doppler as a hypovascularized area (arrow). In (c) it is shown in a T2w image as a isointensity with the normal parenchyma (arrow). In (d) it is shown in DWI with a b-value of 1000 as a signal hyperintensity (arrow). In (e) it is shown the colorimetric ADC map (green corresponds to low ADC values) with the ADC value of 1,23 in the APN focus while it is of 1,97 in the contralateral normal parenchyma (circles).

ureteral obstruction and contusion^[20]. The diffuse form of APN may cause global enlargement, poor enhancement of renal parenchyma, absent excretion or contrast and streakiness of fat^[13] (Figures 10-14).

According to Talner, hypodensity is due to a delayed contrast media impregnation of the renal parenchyma involved by phlogosis, while CE of these zones can be observed in ultra-late scans (from 3 to 6 hours)^[18]. The CT aspect of foci changes along with the clinical evolution of the disease: generally, inflammatory areas tend to assume more blurred borders as healing is proceeding, furthermore the adjacent foci tend to converge, making impossible the distinction between the ascending and the haematogenous forms.

According to Craig, the complete healing of the lesions occurs after 1-5 months. In case of insufficient antibiotic treatment, the lesions will evolve into scars, showed by CT as areas avoid of the normal renal parenchyma^[19]. The CT usage itself demonstrated that renal scars develop after pyelonephritis also in adult patients, while in the past they were considered a risk only for children^[18] (Talner): in small group of patients, CT studies demonstrated that till the 43% of adults with bacterial non-complicated APN develop scars, even if small; a generalized atrophy of renal parenchyma is instead less common.

CT permits also to individuate local complications of the infection, as:

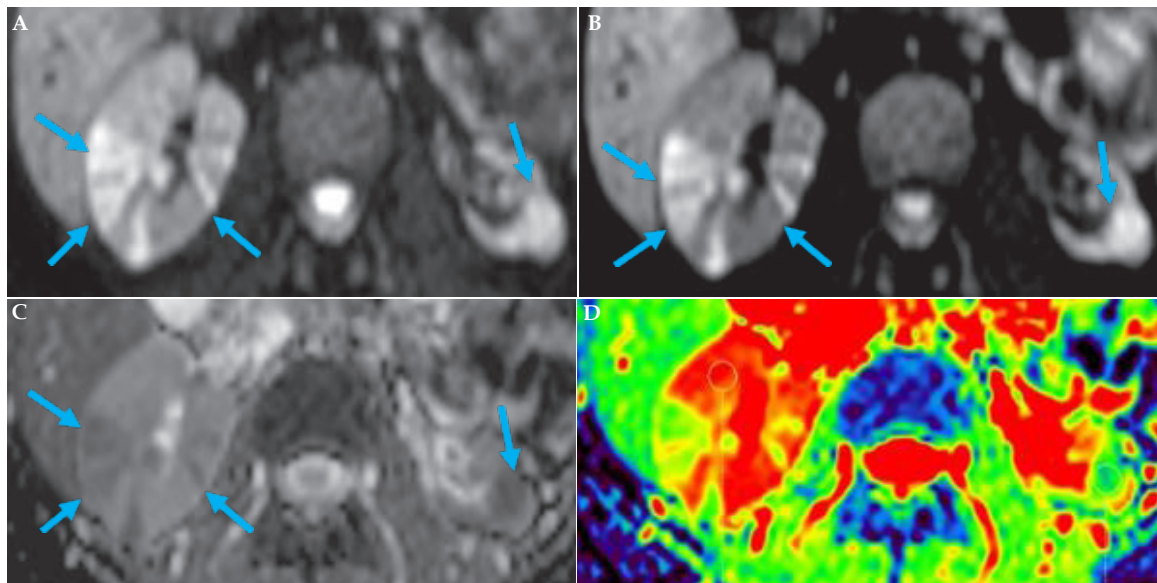


Figure 8 case of APN in a 25 yo woman in both kidneys. In (A) it is shown in DWI with a b-value of 400 as multiple areas of signal hyperintensity (arrows). In (B) it is shown in DWI with a b-value of 800 even major signal hyperintensity. In (C) it is shown in the ADC map in grey scale as reduced signal intensity areas (arrows). In (D) it is shown the colorimetric ADC map (green corresponds to low ADC values) with the ADC value of 1,29 in the right APN focus while it is of 1,57 in the contralateral APN focus (circles).

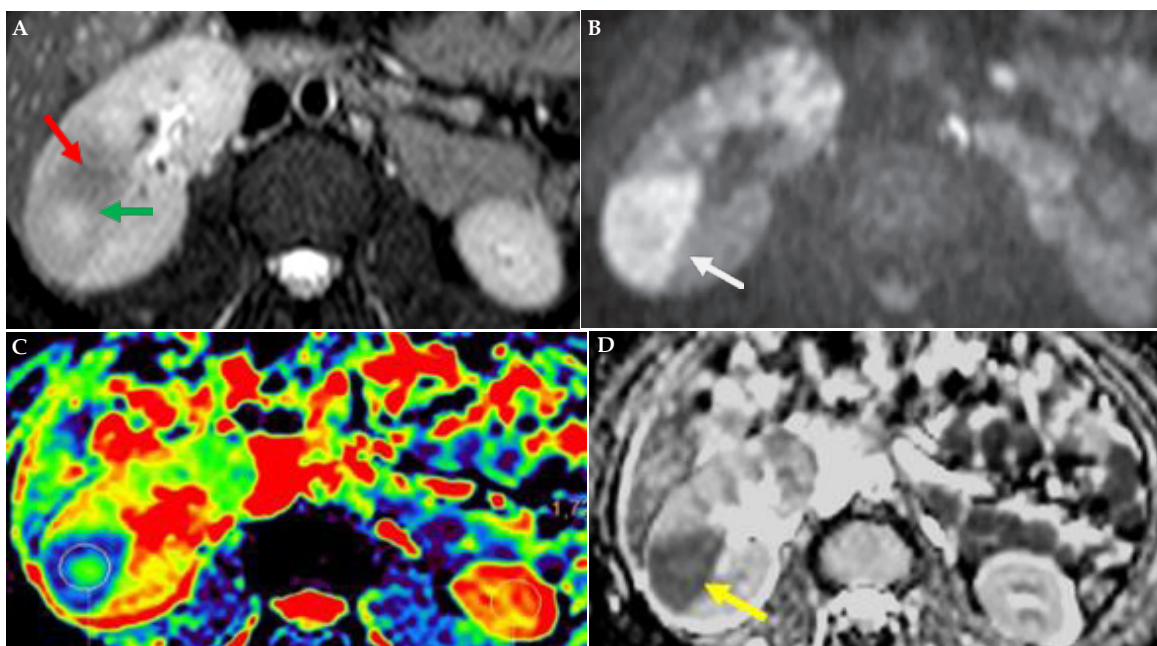


Figure 9 case of abscess in a 43 yo man in the right kidney. In (A) it is shown in T2 as a hyperintense central rounded area (green arrow) surrounded by a blurred hypointense area (red arrow). In (B) it is shown in DWI with a b-value of 1000 as a triangular shaped signal hyperintensity (arrow). In (C) it is shown in the ADC map in grey scale as a triangular shaped reduced signal intensity area (arrow). In (D) it is shown the colorimetric ADC map (green corresponds to low ADC values) with the ADC value of 1,11 in the abscess while it is of 2,42 in the contralateral normal parenchyma (circles).

Perinephric involvement with hyperdense stripes and thickening of Gerota's fascia;

Intra- and extra-parenchymal abscesses: they derive from coalescence of microabscesses and can become evident to imaging also within a day, radically changing their CT appearance. Abscesses appear as hypodense areas delimited by a contrast enhanced rim represented by the pseudocapsula, with variable thickness. The abscesses presence in CT can be revealed also in case of clinical-laboratory negativity, since in 15-20% of patients with an abscess, the urine culture is negative^[19] [Craig].

Emphysematous pyelonephritis: CT findings are parenchymal swelling and destruction bubbles or stripes determined by gas, fluid collections, air-fluid levels and focal tissue necrosis with or without abscess. According to Craig, two types of gas distribution have been observed in this pathology, related to prognosis^[19]. In the first type, more severe, gas is confined to renal parenchyma, while in the second type the internal gas collections are continuous with those inside the

collecting system.

Pyonephrosis: In CT study, it is observed a parietal thickening of renal pelvis, parenchymal or perinephric inflammation, dilatation and obstruction of the urinary collecting system with major hypodensity of urine within it. Although, it is difficult, basing on CT, distinguishing hydronephrosis from pyonephrosis

CONCLUSIONS

CEUS should be considered by now the first imaging technique for an ultrasonographic study of renal parenchyma in a suspected APN, because of absence of associated radiation and nephrotoxicity. This technique is cheap, easily available, and relatively safe and provided with high specificity and sensibility. Mitterberger *et al.* demonstrated that CEUS and CECT are almost equivalent for sensitivity and specificity in detecting renal parenchymal lesions in APN. CEUS is useful to diagnose focal pyelonephritis and to distinguish it from



Figure 10 APN in a 65 yo female. Coronal CECT images in arterial (A), venous (B) and delayed (C) phases show at least two foci of APN in the right kidney, at the upper and inferior pole, with heterogeneous CE, along with a mild soft tissue thickening and abnormal CE of the right pelvicalyceal system (arrows).



Figure 11 The same case of fig. 10 shown through axial images in arterial (A), venous (B) and delayed (C) phases at the upper pole of the right kidney (arrows).

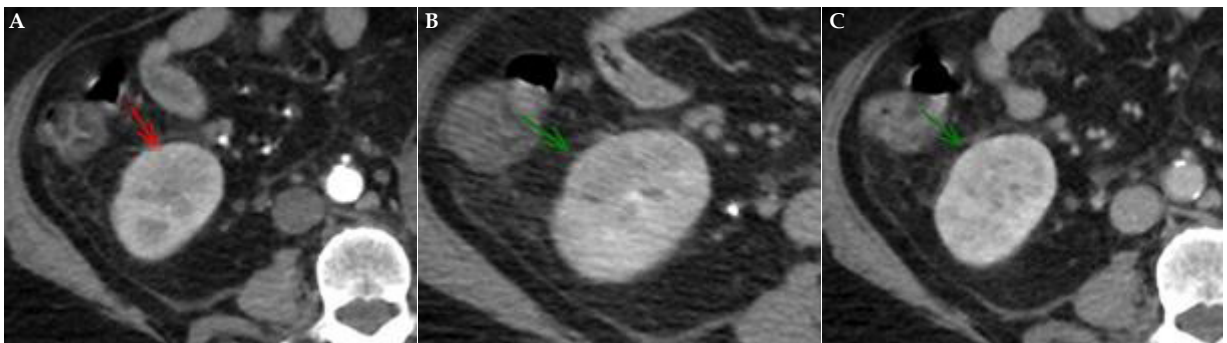


Figure 12 The same case of fig. 10 shown through axial images in arterial (A), venous (B) and delayed (C) phases at the lower pole of the right kidney (arrows).

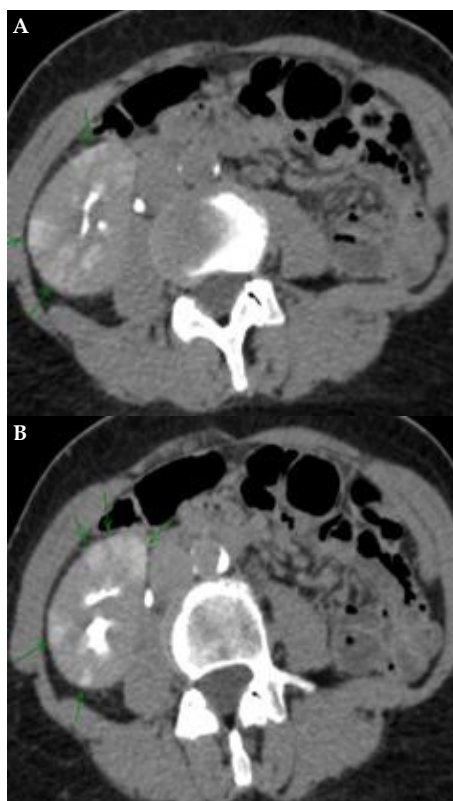


Figure 13 APN in a 56 yo female. CECT delayed phase shows striated nephrogram (arrows) as linear bands of contrast extended between cortex and medulla. Axial images of APN at different levels of the right kidney are shown.

abscess, thanks to typical findings^[21]. Furthermore, CEUS is recommended as the first choice for complicated APN follow-up. In case of extended renal injury or possibility of complications, a second level examination is needed, that should be represented by now by the MRI, thanks to the fact it isn't based on the ionizing radiation use; in particular DWI-MRI should be used with the subsequent elaboration of ADC maps. Moreover, the DWI-MRI allows an accurate follow-up of these pathologies since it remains positive nonetheless the normalization of clinical and laboratory parameters, resulting much more sensible than other techniques in diagnosing of complete healing of APN. On the other hand, CETC should be used by now only in the last instance because the majority of the APN patients are children or women of childbearing potential, therefore people that should not be exposed to ionizing radiations.

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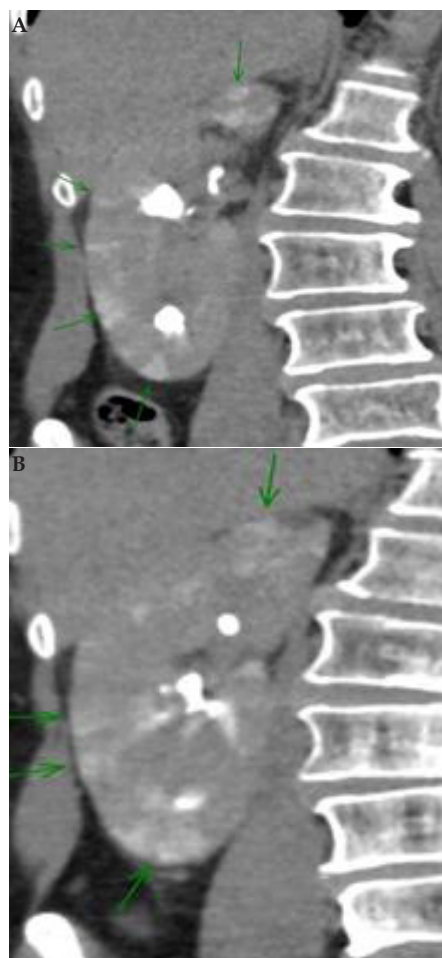


Figure 14 The same case of figure 13. CECT delayed phase shows striated nephrogram (arrows) as linear bands of contrast extended between cortex and medulla. Coronal images of APN at different levels of the right kidney are shown.

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