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ESPR

ESPR Uroradiology Task Force and ESUR Paediatric Working Group—Imaging recommendations in paediatric uroradiology, Part V: childhood cystic kidney disease, childhood renal transplantation and contrast-enhanced ultrasonography in children

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Abstract The ESPR Uroradiology Task Force and the ESUR Paediatric Working Group present two new recommendations on imaging in childhood cystic kidney disease and in childhood renal transplantation, and address the presently restricted availability of contrast-enhanced (ce) US in children. New insights into the genetics require an updated classification of paediatric cystic kidney disease along with a new concept of diagnostic imaging. Characteristic imaging features are key to the new classification. Available recommendations for imaging renal transplantation in children are not satisfactory. The

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following consensus-based algorithm proposes a more effective and more uniform imaging concept, reducing invasiveness, enhancing diagnostic accuracy, and facilitating future multicentre studies and meta-analysis. At present, ce-US in children can only be performed off-license, since the only approved US contrast agent (CA) for children has been taken off the market. Nevertheless, paediatric ce-US is practiced at multiple places using Sonovue® (Bracco, Milan, Italy), a generally available agent in Europe. From a medical and scientific perspective, paediatric ce-US should be promoted, and efforts are undertaken to collect data on paediatric US-CA applications. Routine paediatric imaging depends on local expertise and availability of equipment. The imaging recommendations and supportive data are intended to ease the physicians' difficult task of dealing with the specific diagnostic demands of paediatric paediatric cystic kidney disease and transplantation.

Keywords Childhood renal transplantation · Cystic kidney disease · Childhood · Paediatric · Contrast-enhanced ultrasonography

Introduction and rationale

In recent years, the European Society of Paediatric Radiology (ESPR) Uroradiology Task Force and the European Society of Urogenital Radiology (ESUR) Paediatric Working Group have issued several imaging and procedural recommendations (Table 3 in Appendix). These addressed prenatally diagnosed or marked hydronephrosis, the paediatric conditions of urolithiasis and haematuria, obstructive uropathy, urinary tract infection, renal trauma and renovascular hypertension. Procedural recommendations include paediatric urosonography, contrast-enhanced (ce) voiding urosonography, voiding cystourethrography, intravenous urography, and childhood CT and MR urography. Childhood aspects of nephrogenic systemic fibrosis were defined and a standardised grading scheme for hydronephrosis was proposed. There is growing acceptance of these recommendations throughout Europe and the wider paediatric radiology community.

Two additional paediatric imaging recommendations have been elaborated by the joint working groups on renal transplantation and cystic kidney disease, and a statement has been taken on paediatric ce-US. Again, the aim was to improve and standardise children's uroradiology imaging procedures, and to minimise invasiveness and radiation. The recommendations are meant to be applicable throughout Europe allowing for individual and local adaptation. As for the previous work, the recommendations are based on new knowledge, thorough review of literature, discussion and search for consensus, leading to an improved diagnostic imaging approach. Yet, restricted availability of evidence still limits optimal imaging algorithms. Non-member experts and colleagues from partner disciplines have participated in the discussion with the respective societies and additional surveys allowed for deducting a larger picture. The recommendations on childhood cystic kidney disease and renal transplantation have been presented and discussed during the mini-symposium on paediatric uroradiology at the annual ESPR meeting, May 2011 in London, United Kingdom, and subsequently at the annual ESUR meeting, October 2011 in Dubrovnik, Croatia. All relevant comments have been included in the drafting of the new recommendations. We hope that they will help to streamline the imaging procedures in paediatric uroradiology throughout Europe in spite of some unresolved issues and a wide variance of local practices and that the included information will be used for less invasive and nonirradiating imaging in children. Standardised imaging as well as growing experience with imaging algorithms and procedures are the prerequisites for future multicentre studies and meta-analysis, eventually yielding more evidence-based recommendations and guidelines.

Imaging in childhood cystic kidney disease

New insights based on genetics and microphysiology lead to reviewing the classification of cystic kidney disease. The updated classification has significant implications on imaging and diagnostic algorithms, since diagnosis and disease classification in the fetus, neonate and child are heavily based on the imaging results (Fig. 1).

The new understanding of childhood cystic kidney disease (CCKD) requires a threefold knowledge for its classification, especially in an ultrasonographically suspected fetal or neonatal diagnosis. These are: (1) the modern classification of CCKD, (2) the newly gained genetic insights, particularly the concept of ciliary connections and hepatorenal fibrocystic disease, and (3) the normal ultrasonographic appearance of the fetal, neonatal and paediatric kidney with its age-characteristic presentation. This renders the close cooperation with the paediatric nephrologist indispensable. We thank Dr. Michèle Hall (Brussels, Belgium) for her valuable participation in this effort.

The new classification of cystic renal abnormality is based on the two categories of genetic versus nongenetic origin. In the neonate, the nongenetic cystic renal abnormality is most commonly caused by cystic renal dysplasia from severe obstruction and/or reflux during intrauterine life, mostly leading to a multicystic dysplastic kidney (MCDK). Other causes of noninherited paediatric cystic renal abnormality are cystic tumours and malformation, (segmental) cystic nephroma, post-traumatic or postoperative cysts and simple renal cysts. In chronic renal insufficiency or in native kidneys after transplantation, cystic transformation is relatively common. The genetic diseases include the well-known autosomal dominant or recessive

polycystic kidney disease (ADPKD or ARPKD) and more recently recognised entities such as glomerulocystic kidney disease, TCF II anomalies, the nephronophthisis complex and medullary cystic dysplasia. Some partially replace older terminology such as the medullary sponge kidney or the Potter classification. It also includes the known syndromatous conditions such as Alport syndrome.

Congenital nongenetic cystic renal abnormality is frequently associated with pathological urinary tract development and, commonly, with urinary tract dilatation. It appears to be a consequence of early defects in the connection between the ureteral bud and the renal blastema. Other nongenetic—i.e. acquired cystic renal abnormalities, appearing rather later in childhood—are the simple renal cysts and a diagnostic spectrum that includes some evolving malformations, tertiary calyx, calyceal diverticulum, post-traumatic or postoperative cysts and various cystic benign or malignant tumourous conditions.

Normal US of the fetal kidney is defined by its size matched to the gestational age, its characteristic corticomedullary differentiation appreciable as of mid-trimester, and the cortical echogenicity. Compared with liver the renal cortex is hyperechoic in early pregnancy, isoechoic in mid-pregnancy, and eventually may become hypoechoic after 32 weeks' gestation. The normal size of a neonatal kidney must correspond to the patient's age and weight. The corticomedullary differentiation is prominent in the neonate, with physiological echogenicity in the distal medullary pyramids spontaneously resolving with time. The cortical echogenicity is iso- or hyperechoic to the liver.

The renal corticomedullary differentiation decreases during infancy, as the cortex becomes relatively hypo-echogenic, eventually being even less echogenic than liver, while the neonatal echogenicity of the distal medulla disappears. Age-matched size remains essential; dedicated volume calculation is more informative than length assessment only.

The fetal or neonatal ultrasonographic appearance of CCKD may be characteristic by exhibiting cystic renal texture, unusual corticomedullary architecture, altered echogenicity or nephromegaly and/or be noticed in some familial context. Thus, the diagnosis might be suggestive, suspected or questionable. Assessment by detailed US, using a linear high-resolution transducer including Doppler technology with the possible aid of harmonic imaging and image compounding, is paramount. The above-mentioned morphological parameters need to be registered and characterised, including number, localisation and structural irregularities of potential cysts. The renal collecting system and the entire upper urinary tract and bladder must be included in the assessment as well as potentially associated extrarenal abdominal and/or brain malformations. Consideration must be given to the fetal or postnatal age of the patient, to the patient's medical and family history, to the family history and possible genetic testing. Careful corroborative information should enable classification of findings as a nongenetic or a genetically induced condition, the latter by reoccurrence or first manifestation. In reoccurrence of a known familial condition, no further diagnostic imaging is probably and often necessary. The same applies to characteristic manifestation of CCRD. If the findings or situation are inconclusive, repeat or follow-up US is advised. MRI might be considered or indicated. Notice that all simple cysts in children should be followed up, because it might be the first manifestation of some yet undiagnosed condition. Potential MRI is best performed by enhanced diuresis with late acquisitions. In the presence of an underlying urogenital malformation, i.e. obstructive uropathy, MCDK, other form of dysplasia or segmental dysplasia in a duplex kidney, further assessment is necessary according to available protocols (see previous recommendations).

In summary, the initial examination in suspected CCKD is a detailed US evaluation (Fig. 2). The decision on further imaging and in a suspected diagnosis heavily relies on the primary US and the patient's and his family's history. The clinical findings and the patient's medical history are essential in the differentiation from other entities that may present with increased echogenicity, altered corticomedullary differentiation or kidney size, especially nephromegaly, e.g. glomerulonephritis, haemolytic uremic syndrome or renal vein thrombosis. Cystic renal abnormality may appear after trauma, or as sequelae of surgical intervention. Morphological follow-up evaluation is often adequate by simple US. In more complex situations, i.e. suspicion of a neoplastic condition or in polymalformative syndromatous disease, renal MRI and/or further dedicated abdominal imaging need to be considered. Paramount is the knowledge and recognition of CCRD in its US appearance (Fig. 1) as well as the knowledge of the new classification of cystic kidney disease in infancy and childhood.

Relevant literature for CCKD is provided in Table 4 in Appendix.

Imaging in childhood renal transplantation

Childhood renal transplantation (CRT) is considered the therapy of choice in end-stage renal failure. In early and elective CRT, there is improved somatic development and much lower long-term morbidity and mortality. Pre- and post-transplant imaging is crucial in the assessment of both recipient and donor to reduce the risk of renal allograft dysfunction. However, the imaging approach varies widely in various centres. This is likely due to restricted evidence and, conversely, tends to perpetuate restriction of evidence. A basic standardised imaging algorithm is therefore necessary to improve patient care in reducing invasive and radiating procedures, and to support data accumulation for future multicentre studies and meta-analysis. This is indispensable to enhance evidence and move forward from

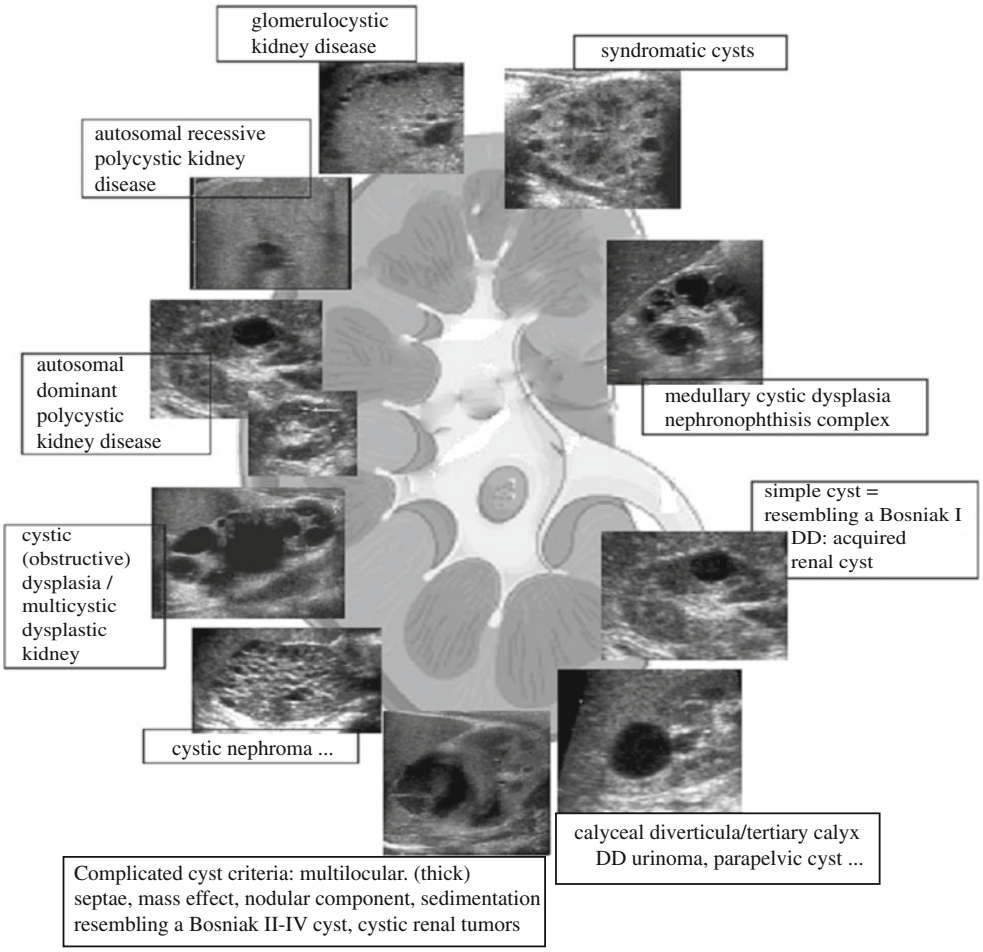

Fig. 1 Schematic representation of typical US findings in paediatric cystic kidney disease. *DD* differential diagnosis

eminence- and consensus-based statements to evidence based guidelines.

The goal seems particularly difficult to reach in renal transplantation because of the multiple disciplines involved in these patients' care. Also, the responsible treating physician may be of different specialities in various centres with variable imaging protocols and demands. At some centres, repeated protocol-driven biopsies are routine in order to detect subclinical rejection (e.g. when lower immunosuppressive regime is used), whereas in others, one more heavily relies on clinical signs of rejection and will only indicate biopsy on clinical ground.

We want to acknowledge and thank Dr. Stephen Marks (Paediatric Nephrologist at Great Ormond Street Hospital for Children, London, UK) and Dr. Giorgio Piaggio (Paediatric Nephrologist at Giannina Gaslini Hospital, Genoa, Italy) for their valuable contributions and feedback that allowed us to better understand the clinical challenges, so we could adapt the recommendations to the different clinical needs and scenarios.

There are three phases during childhood renal transplantation that require imaging. In the first phase before transplantation, both the donor and the recipient must be assessed (Fig. 3). The second phase is during transplantation, with attention to the patency of the vascular anastomoses and the immediate intraoperative or early postoperative evaluation and baseline study of the implanted kidney. A further evaluation is required at an early and a later phrase after transplantation, with the intent to detect any potential complication. Routine surveillance heavily relies on imaging (Fig. 4).

The donor evaluation depends on whether there is a living or a (potentially) deceased donor. A (potentially) deceased donor kidney usually is imaged by US, which should include a colour Doppler sonography (CDS) study for vascular anatomy. If a contrast-enhanced CT angiography (ce-CTA) is performed for diagnosing or confirming brain death in a potential donor, the ce-CT protocol should include an abdominal and pelvic scan for visceral evaluation. In a living donor, it is essential to demonstrate not only the suitability of the kidney for transplantation, but also that the donor is left with a healthy kidney. The primary investigation consists of US and CDS with a complementary MR angiography (MRA)

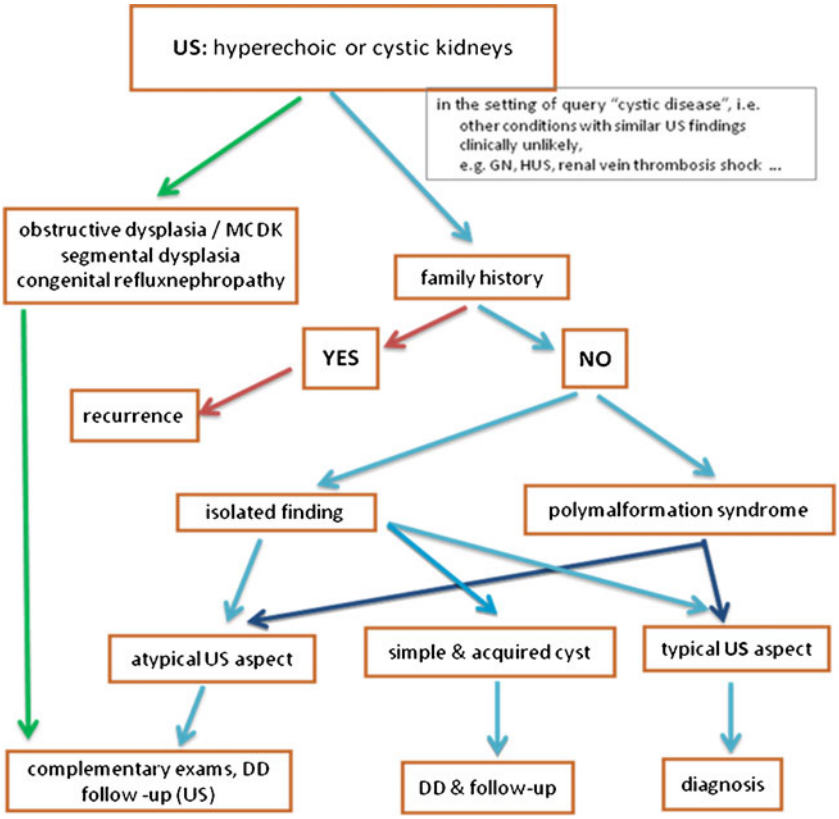

Fig. 2 Imaging in suspected cystic kidney disease in fetuses, infants and children. *DD* differential diagnosis, *GN* glomerulonephritis, *HUS* haemolytic-uremic syndrome, *MCDK* multicystic dysplastic kidney, *US* ultrasound

and MR urography (MRU). If MRI is unavailable, CTA and CTU are often performed. If some abnormality is detected on MRI, CT or US, a baseline DMSA study is recommended to assess renal functional capacity.

The recipient evaluation aims at assessing the present state of the underlying disease, including the native kidneys and the urinary bladder with regard to capacity, function, potential vesicoureteric reflux (VUR) and other relevant anatomy, including the bladder wall, to reduce the risk of complication and graft dysfunction. Of particular importance is the assessment of vascular anatomy in view of the site of the anastomoses. The vascular assessment must include the major venous

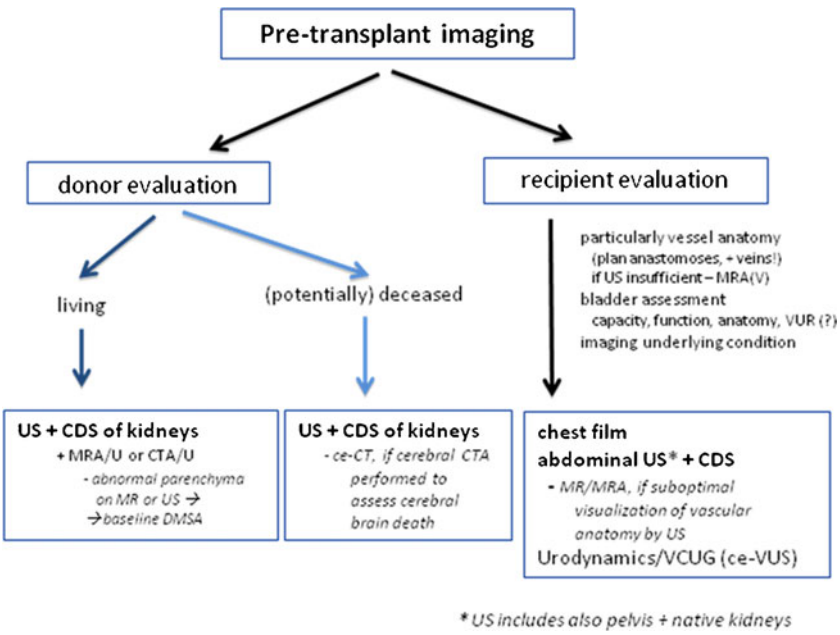

Fig. 3 Renal transplantation in childhood: post-transplant imaging (*ce-VUS* contrast-enhanced voiding urosonography, *ce-CT* contrast-enhanced computed tomography, *CTA* CT angiography, *CTU* CT urography, *DD* differential diagnosis, *MR* magnetic resonance, *MRA* MR angiography, *MRU* MR urography, *MRV* MR venography, *GN* glomerulonephritis, *HUS* haemolytic-uremic syndrome, *MCDK* multicystic dysplastic kidney, *US* ultrasound, *VCUG* voiding cystourethrography, *VUR* vesicoureteric reflux)

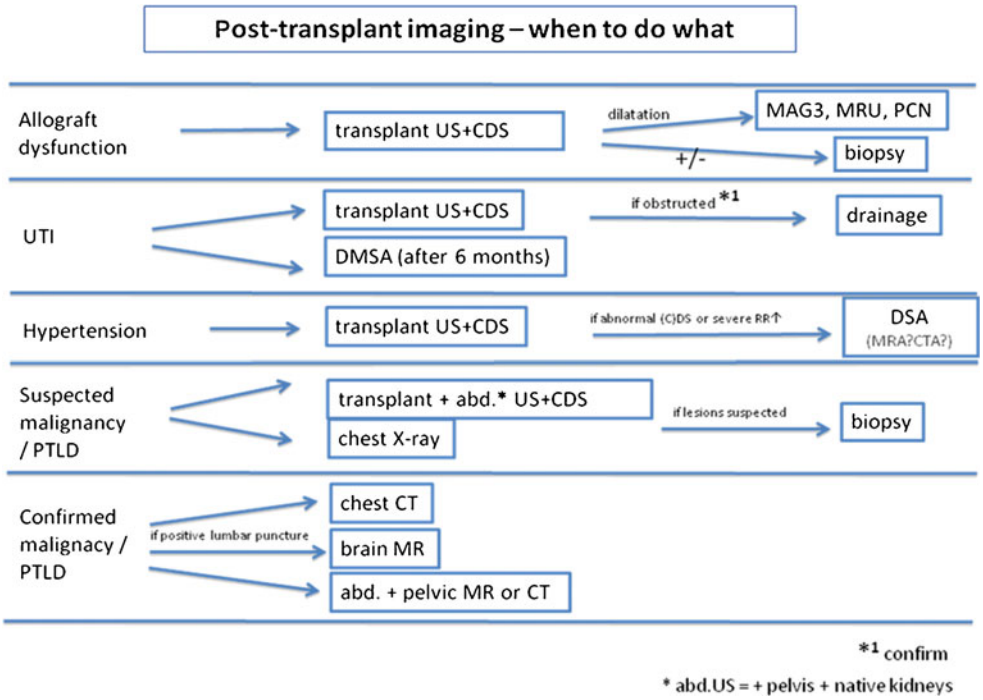

Fig. 4 Post-transplant imaging in children: when to do what (*abd* abdominal, *(C)DS* (colour) Doppler sonography, *CT(A)* computed tomography (angiography), *DMSA* dimercaptosuccinidacid scintigraphy, *DSA* digital subtraction MR angiography, *MR(A)* magnetic resonance (angiography), *MRU* magnetic resonance urography, *MAG3* MAG3 scintigraphy, *PCN* percutaneous nephrostomy, *PTLD* Post-transplant lymphoproliverative disease, *RR* blood pressure, *US* ultrasound, *UTI* urinary tract infection, *X-ray* radiograph)

structures, since small calibre of iliac veins may necessitate a different technique or site selection for the anastomosis. Some centres accept US, including CDS, provided US can sufficiently show all the relevant parts of the lower abdominal and pelvic arterial and venous vascular structures and give reliable measurements of their size as well as confirm their patency. If this cannot be achieved, MRA including MR venography is recommended, if possible, using non-contrast-based techniques such as arterial spin labelling or time-of-flight sequences. If MRA is not available, ce-CT(A) might be chosen instead, although restriction of contrast administration in renal insufficiency must be considered as well (see respective ESUR guidelines).

After transplantation, US including CDS is the modality of standard imaging (Fig. 5). Again, clinical information is essential to diagnose or exclude infection (i.e pyelonephritis, septicaemia, abscess formation or fungal infection), to assess drug toxicity and to exclude systemic, volume or blood pressure causes of a possible (pre-)renal cause for functional deterioration. If US and clinical findings are unremarkable, no additional imaging needs to be performed, and US is used for further follow-up according to the local protocol. If hydroureteronephrosis (i.e. dilatation of the upper urinary tract) is detected in the presence of a small bladder volume, and/or if there are clinical signs of obstruction, MRU or technetium-99m MAG3-scintigraphy may confirm or exclude the diagnosis. In strong suspicion, with equivocal findings on other imaging and in a clinically obvious situation, percutaneous pyelography with consecutive percutaneous drainage or stenting may be performed—usually following US using sonographic guidance. If there are no signs of obstruction, a follow-up US with specific attention to pelvicalyceal dilatation is sufficient. If US reveals parenchymal abnormality, the clinical situation and laboratory data are essential for tailoring further assessment. In renal allograph dysfunction or suspected secondary malignancy or post-transplant lymphoproliferative disease (PTLD), US-guided core biopsy is most often necessary to confirm the diagnosis. Abdominal US survey should always complement the US assessment of the renal transplant to detect typical PTLD changes such as enlarged lymph nodes or liver abnormalities. If US/CDS depicts flow abnormality, further imaging assessment depends on the underlying condition and the respective treatment implications. For example: If a pseudoaneurysm, a small arteriovenous fistula or a small area of infarction is unequivocally diagnosed by US, and no additional treatment but "wait-and-see" policy is intended, no further imaging needs to be performed; US including (amplitude coded) CDS will serve for monitoring the condition. A larger venous or arterial impairment could be confirmed by MRA (or CTA) or—particularly in imminent threat to the graft or with significant dysfunction—early surgical or percutaneous interventional treatment might be necessary immediately following digital subtraction angiography, without delaying treatment by performing additional scintigraphy or MRA/CTA (Fig. 5).

For the timing of imaging in general, it is proposed to perform US, including CDS, perioperatively and routine US/CDS studies at 1 week, 3 weeks, 3 months, 6 months, 12 months, and thereafter annually—with an abdominal US included in all routine studies (Table 1). US remains the first imaging study in any (acute) complication. A baseline technetium-99m DMSA study or MRI is suggested in patients

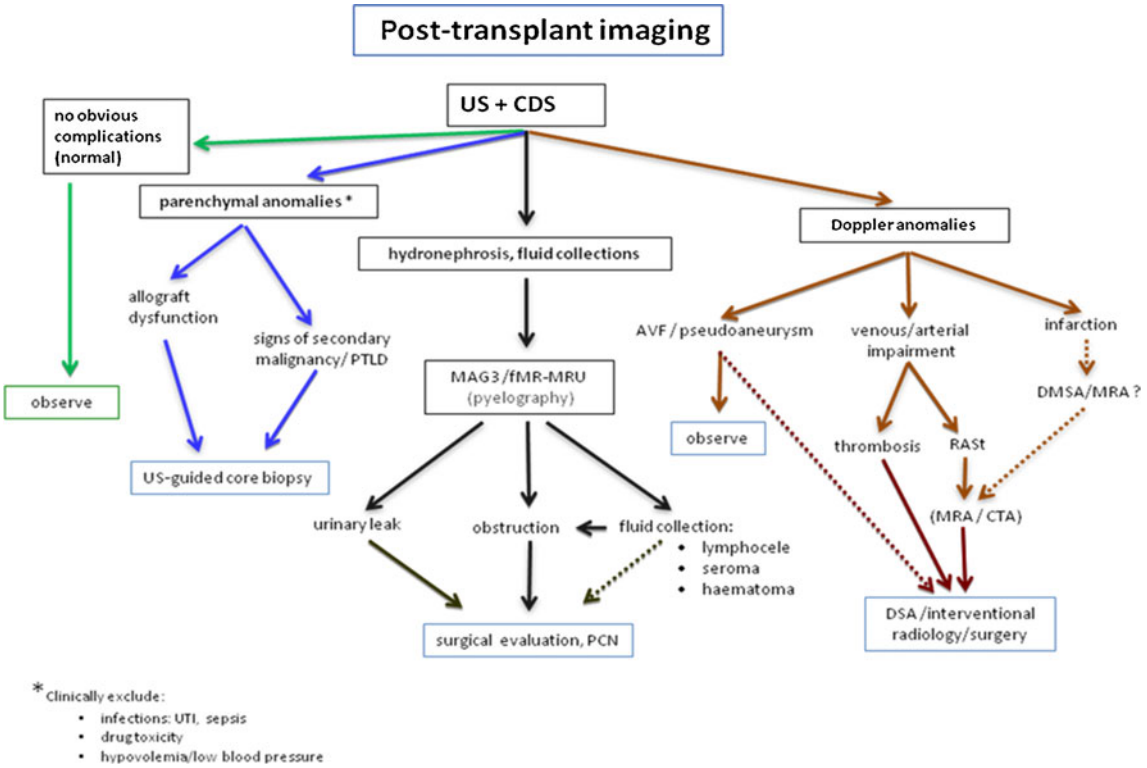

Fig. 5 Renal transplantation in childhood: Post-transplant imaging. *AVF* arteriovenous fistula, *CDS* colour Doppler sonography, *CTA* computed tomographic angiography, *DMSA* dimercaptosuccinidacid renal scintigraphy, *DSA* digital subtraction angiography, *fMR* functional magnetic resonance tomography, *MRA* magnetic resonance angiography, *MRU* magnetic resonance urography, *MAG3* diuretic renal MAG3 scintigraphy, *PCN* percutaneous nephrostomy, *PTLD* post-transplant lymphoproliverative disease, *RASt* renal artery stenosis, *US* ultrasound, *UTI* urinary tract infection

with a high risk of parenchymal loss at 3 weeks, as well as a Dexa-scan after 12 months in patients who are on high-dose steroids. The timing of transplant protocol biopsies is very variable, from regularly at 4 weeks, 3 months, 6 months, 9 months and 12 months in some centres to other centres where no biopsy is performed unless there is a clinical indication.

Relevant literature for CRT is provided in Table 5 in Appendix.

Table 1 Post-transplant imaging in children: routine imaging for follow-up. *CDS* colour Doppler sonography, *DEXA* dual-energy X-ray absorptiometry, *DMSA* dimercaptosuccinidacid scintigraphy, *US* ultrasound

Post-transplant imaging–routine imaging follow-up	
Perioperative	US + CDS
1st week	US + CDS[a]
3 weeks	US + CDS
	Baseline DMSA or MR in patients with high risk of parenchymal loss
3 months	US + CDS
6 months	US + CDS + abdominal US[a]
12 months	US + CDS + abdominal US[a]
	DEXA if on high dose steroids
Annual	US+CDS+abdominal US[a]

Note: protocol transplant biopsies vary necessity unclear

[a] abdominal US includes also pelvis + native kidneys

Comment: The role of MRI has yet to be defined as well as the importance of VUR assessment and respective method and timing.

Contrast-enhanced US in childhood

Contrast-enhanced US (ce-US) was introduced two decades ago. For some time a single contrast agent (CA) was registered for paediatric use in several countries. At present, no US-CA is available that is approved for use in children. However, experience over the past 15 years demonstrates that ce-US is particularly valuably in children, not only for a specific paediatric diagnosis like VUR but also to reduce the radiation burden from diagnostic imaging in general and by enhancing the US potential and thus decreasing the need for ce-CT. Intravenous ce-US might be used for similar indications as they are known in adults (Table 2). The major application in infants and children, however, has been the intravesical use of US-CA for assessment of VUR. Thousands of exams have been performed without any reported major adverse reaction. A recent meta-analysis of literature on ce-voiding urosonography (ce-VUS) clearly demonstrates the high diagnostic reliability and safety profile of the two agents that have been used to date, i.e. mainly

Table 2 List of potential indications for ce-US in infants and children (*ce-US* contrast-enhanced ultrasound, *ce-VUS* contrast-enhanced voiding urosonography, *DD* differential diagnosis, *PCN* percutaneous nephrostomy, *TCI* transcranial imaging)

Intracavitary:
- ce-VUS (for VUR or bladder rupture)
- Sonogenitography (genital malformations, intersex, claocal malformations)
- Sonourethrography (urethral anomalies and conditions)
- Punctures and drainages (PCN, abscess drainage – leakage? Fistulae? Drain position?)
Intravenous:
- TCI mainly for vascular problems
- Imaging of parenchymal organs for detection and characterisation as well as DD of focal lesions (tumorous, infections, traumatic)
- Assessment of patency of vessels
- Assessment of organ perfusion (trauma, transplantation, central lines)
- No reliable data yet for bowel, testis and joints – may potentially become useful in the two latter

Levovist® (Bayer-Schering, Berlin, Germany, now taken off the market for economical reasons) and Sonovue® (Bracco, Milan, Italy, not registered for paediatric use). There is less information on paediatric intravenous ce-US application, although its feasibility is known and established indications in adults might apply in analogous paediatric conditions.

The group therefore tried to collect data to facilitate US-CA licensing in children and to discuss possible off-label applications. A Europe-wide survey yielded reports of nearly 1,000 intravenous and around 4,000 intracavitary (mostly intravesical) paediatric applications. The survey did not focus on diagnostic accuracy and reliability, but just examined the utility and accepted indications as well as the safety issues of the only presently available and generally used US-CA SonoVue®. In the entire patient group, no US-CA associated side effect has been reported for intracavitary use. Six minor transient adverse reactions to US-CA SonoVue® after intravenous application were reported in five children, such as skin rash/blushing, strange taste and dizziness. No severe reactions were noted in infants or children. The few rare severe systemic allergic reactions reported and noted so far occurred in adolescents and adults. The relative rate of these events is reportedly much lower than in any other CA used for diagnostic imaging.

With regard to the high priority of radiation safety in children, the collected data are communicated to the respective company and the European Medicine Agency to advance development and approval of US-CA for the various paediatric applications.

Relevant literature for ce-US is provided in Table 6 in Appendix.

Disclosure There is no financial or other interest concerning the reported topic.

Appendix

Table 3 Recommendations

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