Aus der Urologischen Klinik und Poliklinik
Klinik der Ludwig-Maximlians-Universtität München

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Diagnostik bei fieberhaften Harnwegsinfekten im pädiatrischen Patientengut

Dissertation

zum Erwerb des Doktorgrades der Medizin
an der Medizinischen Fakultät der
Ludwig-Maximilians-Universität zu München

vorgelegt von
Bernhard Haid
aus Feldkirch, Österreich
2018

Mit Genehmigung der Medizinischen Fakultät
der Universität München

Berichterstatter:	Prof. Dr. med. Alexander Karl
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Linz, am 2.5.2018 Bernhard Haid

Inhaltsverzeichnis

Abkürzungsverzeichnis

ALARA	as low as reasonably achievable
DMSA	dimercaptosuccinic acid
EAU	european association of urology
ESPU	european society of pediatric urology
ESRD	end stage renal disease
fUTI	febrile urinary tract infection
i.v.	intravenous
NICE	national institute for health and care excellence
PIC	positioning instillation of contrast
UPJO	ureteropelvic junction obstruction
VCUG	voiding cystourethrography
VUR	vesicoureteric reflux

Publikationsliste betreffend diese kumulative Dissertation

1. **Haid B**, Becker T, Koen M, Berger C, Langsteger W, Gruy B, Putz E, Haid S, Oswald J. Lower radiation burden in state of the art fluoroscopic cystography compared to direct isotope cystography in children. Journal of Pediatric Urology. 2015; 11:1, 35.e1-6.

2. **Haid B**, Roesch J, Strasser Ch and Oswald J. The method of urine sampling is not a valid predictor for vesicoureteric reflux (VUR) in children after febrile urinary tract infections. Journal of Pediatric Urology. 2017; 13:5, 500.e1-500.e5.

Kongressbeiträge bezüglich der in dieser Dissertation verwendeten Daten

1. Radiation burden of direct isotope cystography compared to conventional fluoroscopic cystography in children. Posterpräsentation. Congress of the European Society of Pediatric Urology (ESPU), 08.-10.5.2014, Innsbruck.

2. Beeinflusst die „Diagnosequalität“ des fieberhaften Harnwegsinfektes das Risiko eines vesikoureteralen Refluxes im primären MCUG? 41. Gemeinsame Tagung der Österreichischen Gesellschaft für Urologie und Andrologie und der Bayrischen Urologenvereinigung, 11.-13.6.2015, Linz.

3. Strahlenbelastung und Erfolgsrate bei Verwendung der direkten Isotopenzystographie (DIC) als follow-up Diagnostik nach endoskopischer Refluxtherapie, Sitzung des deutschen Arbeitskreises Kinderurologie, 17.-18.1.2014, Mainz.

Einleitung / Introduction

Febrile urinary tract infections in children – epidemiology and significance

Febrile urinary tract infections (fUTI) are common in childhood. 3-5% of girls as well as 1-2% of boys are concerned at least once during childhood[1]. During the first two years of life, 5-8% of all febrile episodes are caused by a UTI, they account for 0.7% of all office visits and 5-14% of all visits to an emergency room annually[2]. In the first year of life, boys and girls show the same incidence, thereafter, girls are far more often concerned. Uncircumcised boys have a relative risk of up to 8 during the first two years of life as compared to boys who underwent newborn circumcision[3]. With a prevalence varying from 1.8-7.5%, fUTIs are the most common bacterial infection in childhood and account for an important morbidity.

Children with fUTIs often present with rapid onset, high fever (>38.5°C), serious illness, requiring i.v. hydration and often also i.v. antibiotics while septic shock occurs mostly when obstruction (e.g. Megaureter, Urolithiasis) is present[4]. The most severe clinical course must be expected in young infants, who are also the group of patients at the highest risk for subsequent renal damage and bacteremia[5]. Typically, children with fUTIs present in a markedly reduced condition with fever, lethargy, reduced oral intake and greyish skin color. Specific symptoms, as for example flank pain, micturition frequency as well as alguria are uncommon in infants or toddlers and only occur in toilet trained pre-school aged children on a regular basis. The younger a child is, the less specific symptoms might be: in some cases of UTI during the first 2-3 month of life even hypothermia, excitability or failure to thrive over a longer period of time might be the only symptoms, rendering a urinalysis including culture an integral part of primary diagnostics[4].
In general, UTIs are classified according to site, to the presence of complicating factors as well as to symptoms. Whereas UTIs concerning the lower urinary tract are a rare event to be detected in very young children and rarely present with the typical symptoms of urge, alguria or incontinence before school-age, fUTIs are most commonly involving the kidneys[6]. The term pyelonephritis is often used to describe the involvement of the kidneys. Bacterial invasion is causing an interstitial nephritis with an important involvement of the urothelium of the whole urinary tract –

dependent on the causative bacterial uropathogen with more or less destruction of its integrity. Whereas uncomplicated UTIs are defined to occur in patients with morphologic and functional normal upper and lower urinary tract, normal renal function and a competent immune system, any UTI in patients with mechanical (e.g. UPJO), anatomical (e.g. calyceal diverticula) or functional (e.g. vesicoureteric reflux) abnormalities of the urinary tract is considered a complicated UTI. Lastly, there are asymptomatic UTIs, also in children, defined as the presence of uropathogenic bacteria without any host response leading to symptoms, however, excluding the presence of leucocyturia.

The rates of resistant bacteria are on the rise, also in pediatric urinary tract infections. While this is still a limited concern in central Europe there have been recent reports on a fast rising prevalence of multidrug resistant uropathogenic bacteria, mostly from treshold countries[7,8].

The most common pathogens causing fUTI in children are Escherichia Coli. Other common uropathogenic bacteria as for example Klebsiella Pneumoniae, Enterococcus spp and Pseudomonas are more frequent in childhood as compared to later in life, more importantly, there is a higher risk of sepsis in the pediatric community as compared to adults[9].

Of all children presenting with their first fUTI, an important proportion, varying between 30 and 50% in different reports, is prone to recurrent episodes[10]. While in older, school-aged children, where especially girls are prone to recur at a probability as high as 80% linked to bladder and bowel emptying problems, in toddlers, infants and babies the most likely underlying cause are congenital malformations of the urinary system[8]. The main concern in these children is the presence of VUR or other functional or anatomical abnormalities involving a higher risk for subsequent UTI episodes as well as kidney damage.

On how to define kidney damage linked to fUTI there is some controversy. During the last decades imaging of tubular uptake of DMSA emerged as the gold standard method to detect renal involvement in acute fUTI as well as residual “scarring” that equals permanent kidney damage. In a series of seminal papers, Coulthard and colleagues proved, that neither – as thought before – do kidneys outgrow the risk of acquiring damage during fUTIs, nor is most of the damage happening before birth[11,12]. The pathophysiological backbone of acquired kidney function loss during

fUTIs was investigated as early as in the 1970ies by Risdon and Ransley, proving that anatomical variations of renal papillae determine the risk of parenchymal involvement and eventual parenchymal damage during UTIs[13].
Prompt treatment can prevent ultimate scar formation and protect children from kidney function loss[14].
In the largest metaanalysis presently availably including a total of 6457 patients, the prevalence of VUR in children after their first fUTI is reported as 32%[15]. According to some smaller series, after the second fUTI, the risk rises to 55%[16].
While this equals our experiences[17], there is a proportion of children where the anatomic phenomenon of VUR cannot be diagnosed by a conventional VCUG who are still at risk. In these cases, a so-called “occult VUR” might be present, that is defined by a novel diagnostic approach involving a directed jet of contrast medium, directed at the ureteral orifice via cystoscopy under general anesthesia – PIC cystography[18]. Whilst initially debated, in the meanwhile multiple studies proved the value of this diagnostic technique in the routine management of children presenting with fUTIs[19,20].
Kidney damage caused by VUR is termed reflux nephropathy, ultimately leading to ESRD. According to national and international transplant registers VUR accounts for up to 6.5% of all pediatric kidney transplantations and for up to 3.5% of patients with chronic renal failure in the US and 7–17% worldwide[21]. Of all children, who are treated within modern health care systems with access to antibiotics and eventually surgical interventions for persistent VUR associated with repeated fUTIs, only very few develop progressive renal failure culminating in ESRD.

Primary Diagnostics in febrile urinary tract infections

As eluded on above, symptoms – as the only symptom in most cases is high fever – are unlikely to be of high value in the diagnosis of fUTIs, especially in infants. Also, as proven by an experimental evaluation of 110 urine samples, urine smell is unlikely to direct suspicion correctly at the presence of a UTI[22]. Imaging – especially acute phase DMSA scanning or – as recently published – diffusion weighted MRI shows a high sensitivity[6]. These imaging test, however, are not only involving radiation (DMSA) and are cost intensive but also are usually not available in primary care settings. Ultrasound, while being available is not specific enough for routine primary

diagnostic use. Laboratory tests also are mostly not specific enough, considering PCT, however, a close relationship with renal involvement has been proven for PCT values over 0.5ng/ml in proven fUTIs[23].

Diagnosis – in primary care settings – therefore mainly relies on urine sampling as well as directed out-ruling of alternative underlying causes for the presenting illness. Although it is well known that fUTIs not only are highly prevalent but also linked to a considerably morbidity, they are under-diagnosed. Of all serious bacterial infections, fUTI is the one most commonly missed, what is attributed to the low sensitivity of diagnostic tools availably to most primary care physicians as well as the relatively high invasiveness of sterile urine sampling by puncture of catheterism as well as the low availability of high quality microbiological analysis[24]. In view of the fact that the extent of definitive kidney function loss is closely linked to the interval between symptom (fever) onset and the start of a adequate therapy this seems even more relevant[14,25,26]. Set aside renal function loss, there are data from prospective cohort studies proving that the sooner an adequate treatment is established the sooner the child will recover[27].

Bag-urine, that is used with high prevalence in infants in primary care settings has been shown to be of a despicable specificity[28], being prone to contamination rates as high as 46%[29]. Its use in daily routine is therefore limited to excluding a UTI – if dipstick results are negative a positive culture result (of sterile acquired urine) is highly unlikely. There, is however, as mentioned above a subgroup of mainly very young infants in their first 2 months of life with clinically relevant UTIs but no Leucocyturia that should undergo sterile urine sampling at any clinical suspicion of a UTI[5].

In our first paper we aimed at assessing the common practice concerning urine testing. Our hypothesis was that if bag-urine testing would be less accurate in UTI diagnosis, those patients would have a lower rate of underlying congenital malformations of the urinary tract – mainly VUR. We did, however, find that in conjunction with a well-performed clinical exam at time of the presumed fUTI a positive bag-urine culture is (post-hoc!) dependable evidence for a relevant UTI that should be followed-up as meticulously as a fUTI proven by sterile urine sampling[17].

Secondary Diagnostics after febrile urinary tract infections

After a first UTI, the risk for further UTIs amounts to 30-70%. It is dependent mainly on the presence of congenital malformations – predominantly VUR – in infants and bladder-bowel emptying problems in older children. Therefore, secondary diagnostics are warranted in most children after their first febrile UTIs, as to the current EAU/ESPU Guidelines, after an orienting sonography exam, all infants except boys experiencing their first fUTI after the age of 12 months with unsuspicious sonography findings should have further diagnostics.
Fluoroscopic voiding cystourethrography (VCUG) remains the gold standard for the diagnosis of VUR in children, whereas dimercaptosuccinic acid (DMSA) scan is the standard investigation detecting renal involvement or, eventually, renal scarring after fUTIs[4].

The “bottom up approach” starts with an initial VCUG to determine the presence of VUR, followed by a DMSA scan in children with VUR to determine kidney involvement. Up to 70% of all primary VCUGs may lead to negative results, translating to many children undergoing unnecessary discomfort and radiation burden and into a risk of missed upper tract affections resulting in wrong assumptions on the need for further treatment.
Alternatively, performing a DMSA scan first (“top-down approach”) can be a valid option in order to optimize further management as well as to spare children unnecessary invasive diagnostic studies. With this approach, however, many VURs are not diagnosed: in our data (not published) 50% of all VURs would be missed. In an evaluation of the NICE guidelines a diagnostic approach based on primary DMSA scans showed a considerable probability of diagnosing VUR as such with a comparative sensitivity of only 10%[12].
There is, however, a recent report comparing guideline recommendations as to secondary diagnostics UTIs in children, stating a very low level of consent[30]. The underlying problem lies in the fact, that all diagnostics involve burden as well as cost for child and health care system, the rate of 32% of diagnosed VUR seems rather low. Consequently, there have been various attempts to render the imaging pathway more effective as compared to “top-down” and “bottom-up” as described above by

including more factors into the decision making algorithm in order to tailor individual diagnostics and limit the diagnosis of VUR to those, who would profit most[31].

Radiation burden in pediatric imaging – significance and sequelae

Besides the difficult indication that where all possible benefits of a timely diagnosis of VUR have to weighed against the invasive nature of the exams (catheterism, needle puncture with associated pain) there is another important factor: the involved dose of ionizing radiation.

The knowledge on the dose-effect relationship of exposure to ionizing radiation is drawn from experiences after the observation of survivors after the atom bomb detonations in Japan. These data have been extrapolated to lower levels of radiation, resulting in an excess risk of cancer development of 5% per Sv [32,33]. The critical indicator of risk is the relative organ effective dose, which is higher in children because despite lower energy applied, the organs are smaller evenmoreso [34-36]. As a result with an added effect of a longer lifespan on the long-term detrimental effects on DNA, a one-year old child exposed to a certain amount of ionizing radiation, is 10-15 times more likely to eventually show sequelae as compared to an adult [37]. Whereas radiation doses conveyed in isolated exams are – even for CT – usually relatively low, the cumulative dose of repeated investigations and the fact that exposure occurs in early childhood has to be taken most seriously. fUTIs are a frequent cause for indication of exams involving ionizing radiation in early childhood – namely VCUGs as well as DMSA scans. The responsibility for possible late sequelae starts with a tailored indication and continues in capitalizing any means to limit radiation dose involved in each single examination.

This is what my second study aimed at investigating: While there are VCUG techniques deemed to involve relatively lower radiation doses as compared to a conventional, fluoroscopic VCUG, dose is also dependent of the individual examination technique. During the last 20 years, digital ultra short-pulsed fluoroscopy with last image hold evolved to deliver excellent image quality. By tailored exposures in order to reduce fluoroscopy time and use of blinds as well as laser targeting, which

as a sole measure already has been shown to reduce exposure time by 25%[38]. We could show in our study, that with using all means to reduce radiation burden the involved dose is as low as a mean of 0.018mSv equalling 5-7 hours of flight or 2.3 days of usual surrounding (earth and cosmic) radiation and much lower than the dose of an isotope cystography, that was previously deemed the most radiation sparing approach to VUR diagnostics. However, in most reports in the literature, doses up to 100 times higher are described[39]. Therefore, the combination of a wise indication for either exam with a timely and radiation sparing examination technique in line with the ALARA principle should be standard in imaging after pediatric urinary tract infections.

Zusammenfassung

Der fieberhafte Harnwegsinfekt ist eine häufige Problemstellung in der kinderurologischen Praxis und verantwortlich für beträchtliche Morbidität, im weiteren Verlauf möglicherweise auch für Nierenfunktionsverlust mit der – seltenen – Konsequenz einer chronischen Niereninsuffizienz. Die klinischen Symptome sind oft unspezifisch, insbesondere bei kleinen Kindern, die gleichzeitig das höchste Risiko für komplizierte Verläufe aufweisen. In Hinblick auf die hohe Rate an Rezidivinfekten, meist auf Basis von zugrundeliegenden Fehlbildungen des Harntraktes und Blasen- sowie Darmentleerungsstörungen, ist eine akkurate primäre und sekundäre Diagnostik entscheidend.

Von allen bakteriellen fieberhaften Erkrankungen bei kleinen Kindern, sind Harnwegsinfekte die am häufigsten primäre „übersehene“ Diagnose. Die Ursache dafür liegt darin, dass die Diagnose des Harnwegsinfektes bei unspezifischer Klinik auf einer genauen Harndiagnostik beruht. Diese erfordert eine sterile Urinprobe – gewonnen entweder per suprapubischer Punktion oder transurethralem Katheterismus. In der täglichen Praxis werden jedoch meist Harnbeutel verwendet, die laut der verfügbaren Literatur bezüglich der Diagnose eines Harnwegsinfektes sehr unspezifisch sind. Wir konnten jedoch zeigen, dass ihre Verwendung bei der Diagnose eines fieberhaften Harnwegsinfektes kein unabhängiger negativ prädiktiver Faktor für das Vorhandensein eines vesikoureteralen Refluxes darstellt und auch solche Diagnosen letztlich ernst genommen werden müssen.

Bezüglich des Zeitpunktes und der Indikation zur sekundären Diagnostik nach fieberhaften Harnwegsinfekten existiert kein Konsensus. Eine Miktionszysturethrographie oder ein Dimercaptosuccinylsäure Scan sind in den meisten Fällen indiziert – beides bringt eine Exposition gegenüber ionisierender Strahlung mit sich. Aufgrund des besonders hohen Risiko für sekundäre Malignome bei Kindern muss dies sehr kritisch gesehen werden. Wir haben das Potential zur Dosisreduktion bei der konventionellen Durchleuchtungs-Miktionszysturethrographie im Vergleich zur direkten Isotopencystographie untersucht und konnten zeigen, dass mittels moderner Techniken eine weitere signifikante Verbesserung möglich ist.

Zusammenfassend zeigen unsere Ergebnisse wesentliche Implikationen rationaler primärer Diagnostik auf und unterstreichen die Wichtigkeit des Ausschöpfens aller Möglichkeiten zur Minimierung der Strahlendosis in der Abklärung nach fieberhaften Harnwegsinfekten bei Kindern.

Summary

Febrile urinary tract infections are commonly encountered in pediatric urologic practice and account for a high burden of morbidity, eventually also for renal function loss with the rare but severe consequence of end stage renal disease. Their clinical symptoms are often unspecific, especially in babies and infants, who are at the same time at the highest risk of complicated clinical courses involving bacteremia or sepsis as well as renal function loss by scarring. In regard to high recurrence rates, often caused by underlying malformations of the urinary tract or bladder and bowel emptying problems, diagnostics are of critical importance.

It has been reported, that pediatric febrile urinary tract infections among all bacterial infections in small children are the most commonly missed primary diagnosis. While the clinical symptoms are unspecific, imaging and laboratory tests can only provide secondary information. The diagnosis relies on urine examination. The acquaintance of a meaningful, sterile urine sample requires either suprapubic puncture or transurethral catheterization what is commonly obviated in clinical pediatric practice, with most of clinicians relying on bag-urine samples. We could show that while these are theoretically unsuited for the purpose of diagnosing a urinary tract infection, their use is not an independent predictor for a lower risk for vesicoureteric reflux involved. Consequently also febrile urinary tract infections whose diagnosis relied on bag-urine samples should be taken seriously.

Secondary diagnostics with their indication being heavily debated are warranted in most children after febrile urinary tract infections. Independent of the primary method chosen – voiding cystourethrography or dimercaptosuccinic acid scanning – ionizing radiation is involved. As these situations concern mainly infants and babies, any radiation exposure has to be considered very critically. In our second paper, we investigated the potential of radiation sparing measures to lower the radiation burden in fluoroscopic voiding cystourethrographies. We could show that judicious use of modern techniques can contribute to a radiation burden much lower as compared to the previously “best” technique, namely direct isotope cystography. This complies with the “as low as reasonably achievable” (ALARA) principle.

In conclusion, our results should foster an informed but judicious use of primary and secondary diagnostic means after pediatric febrile urinary tract infections, aiming at diagnosing as many underlying malformations and at the same time lowering radiation exposure whenever possible.

Journal of Pediatric Urology (2017) 13, 500.e1–500.e5

The method of urine sampling is not a valid predictor for vesicoureteral reflux in children after febrile urinary tract infections

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Keywords
Vesicoureteral reflux; Urine sampling; Urinary tract infection

Received 12 March 2016
Accepted 29 January 2017
Available online 16 March 2017

Summary

Introduction
The likelihood of detecting vesicoureteral reflux (VUR) after febrile urinary tract infections (UTI) in children logically should correlate with the correct diagnosis of the UTI. Beneath the unspecific symptoms of fever urine analysis is the main diagnostic criterion for the exact diagnosis of febrile UTIs in children. Use of inadequate urine sampling techniques during diagnosis may lead to impaired accuracy in UTI diagnosis. This could lead to the assumption that children, having diagnosed their UTI by the use of possibly inadequate urine sampling techniques should not be evaluated as consequently compared to those, where the diagnosis relied on sterile urine sampling techniques. We hypothesized that children with possibly contaminated urine samples during the initial diagnosis may show a lower rate of VUR in subsequent VCUGs because of a wrong diagnosis initially compared to children, where accurate urine sampling techniques were used.

Patients
Between 2009 and 2014, a total of 555 patients underwent a primary VCUG at our department indicated because of febrile UTIs. Patients with urine collection methods other than bag urine and catheter/suprapubic aspiration (SPA) were excluded from this study (mid-stream urine, potty urine, n = 149). We evaluated 402 patients (male/female 131/271, mean age 1.91 years), VUR rates and grades were compared between patients where urine was sampled by the use of a urine bag only at the time of diagnosis (n = 296, 73.6%) and those where sterile urine sampling (catheter, suprapubic puncture) was performed (n = 106, 26.3%). 4 patients were excluded due to equivocal data on urine sampling.

Results
VUR rate in children after sterile urine sampling using a catheter or SPA accounted to 31.1%. In those where urine samples acquired by the use of urine bags were used, 33.7% showed VUR on subsequent VCUG (p = 0.718). There were no significant differences as to VUR grades or gender, although VUR was much more commonly diagnosed in female patients (37.0% vs 28.2%, p = 0.227) (Figure).

Conclusion
Children diagnosed with their UTI by use of bag urine in our experience carried the same risk of showing a VUR in a subsequent VCUG compared to those, where the initial diagnosis relied — beneath clinical criteria — on urine samples acquired by suprapubic puncture or catheterization. Consequently urine-sampling technique during initial UTI diagnosis alone should not be used as predictor for the reliability of UTI diagnosis and should not influence the further management after UTI.

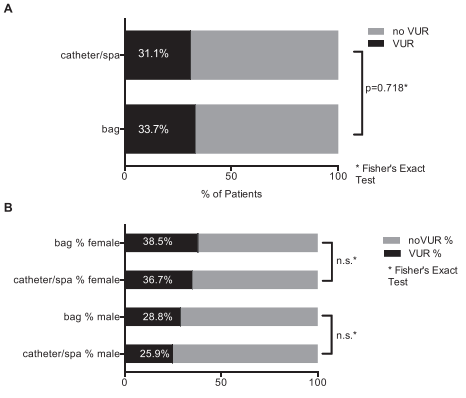

Figure (A) The probability of vesicoureteral reflux depending on the urine sampling technique employed during the initial diagnosis of the febrile urinary tract infection prompting the voiding cystourethrogram. (B) The probability of vesicoureteral reflux depending on the urine sampling technique and on the patients sex.

http://dx.doi.org/10.1016/j.jpurol.2017.01.025

Introduction

In up to 30% of children with urinary tract anomalies, urinary tract infections (UTIs) are the first clinical symptom [1]. In these patients, early diagnosis and correct further management including indications for further imaging may ensure that subsequent UTIs and eventually loss of kidney function are avoided. Whereas urinary tract anomalies involving hydronephrosis are most often diagnosed by pre- or postnatal ultrasound [2], the diagnosis of vesicoureteral reflux (VUR) most often relies on the work-up performed after UTI. Owing to the risk of renal scarring, voiding cystourethrogram (VCUG) or dimercaptosuccinic acid (DMSA) scanning is recommended after the first episode of febrile UTI, depending on sex, age, and clinical presentation according to the current EAU/ESPU guidelines [3]. The correct indication for further work-up after a febrile UTI, however, relies on a correct diagnosis of this UTI. Especially in young children and infants, fever may be the only symptom of UTI. UTI is diagnosed in 5.3–7% of children presenting with fever as a main symptom [4,5].

It is widely acknowledged that the diagnosis of febrile UTIs must rely on correct urine collection methods [3,6], particularly in patients, usually infants, where the diagnosis mainly relies on the urine findings and culture alone with no further specific clinical symptoms. Although widely used, bag urine specimens have been shown to be prone to contamination and showed a very low specificity in UTI diagnosis [7]. In an observational study, Tosif et al. [8] found a contamination rate of 46% for bag urine specimens. Consequently, bag urine alone is deemed not sufficient for the diagnosis of UTIs and is only recommended for exclusion of UTI [3]. Moreover, use of bag urine may result in misleading antibiograms because of contamination, and prompt a wrong antibiotic treatment regimen. Suprapubic aspiration (SPA) and catheterization represent the standard methods of urine collection in younger children [3,6,8]. Clean-catch urine can be an equivalent method for older children with acceptable correlation of urine culture results [9]. Conversely, Lau et al. [10] report that contamination rates of urine collected by catheterization are as prone to contamination as bag urine samples are, albeit only in uncircumcised boys and with fewer colony-forming units (CFUs).

In spite of these widely acknowledged facts, many UTIs in children are diagnosed only by bag urine and by the absence of other specific symptoms [4]. Because referral diagnoses for further investigation relying therewith on possibly false-positive urine cultures, one could argue that these children should not be investigated further until they suffer a correctly diagnosed febrile UTI. We hypothesized that possibly contaminated urine samples during the initial diagnosis may result in a lower rate of VUR than those where accurate urine sampling techniques were used. If so, then the use of bag urine during initial diagnosis should lead to a more restrictive indication of further work-up with VCUG, and the urine-sampling technique could be used as a decisive factor in VCUG indication.

Patients and methods

We retrospectively analyzed the hospital records of 555 consecutive patients (155, 28% male; 400, 72% female; median age 22 months) who underwent primary voiding cystourethrography (VCUG) after fUTIs and were referred to our department between 2009 and 2014. The study protocol was approved by the hospital's ethics committee (EK23/14). All patients whose urine during diagnosis of the febrile UTI in question was collected either by catheterization, SPA, or urine bags were included into the study ($n = 402$, $n = 296$ bag urine, $n = 106$ catheter/SPA). Patients with other urine collection methods (mid-stream urine, potty urine) were excluded ($n = 149$). Four patients were excluded because of equivocal data on urine sampling (Table 1).

Table 1 Patient characteristics comparing children with bag urine samples to children with catheter/SPA urine samples.

	Group 1 ($n = 296$) (children with bag urine samples)	Group 2 ($n = 106$) (children with catheter/spa urine samples)	p
Mean age (years	1.825	2.008	0.678[a]
Gender	104 (35.1%)m/192 (64.8)% f	27 (25.4%) male; 79 (74.5%) female	0.071[b]
VUR	100 (33.7%)	33 (31.1%)	0.718[b]
I	15 (15%)	3 (9%)	
II	56 (56%)	17 (52%)	
III	21 (21%)	12 (36%)	
IV	7 (7%)	1 (3%)	
°V	1 (1%)	0	
Fever $\geq$ 3 days	273 patients (92.2%)	102 pts. (96.2%)	
Fever $>$ 38.5 °C	295 patients (99.6%)	104 pts. (98.1%)	
RBUS	Performed in 289 patients (97.6%)	Performed in 103 patients (97.1%)	
Abnormalities	137 patients (47.4%)	40 patients (38.8%)	0.136[b]
Unilateral hydronephrosis	68 patients (49.6%)	20 patients (50%)	
Bilateral hydronephrosis	28 patients (20.4%)	9 patients (22.5%)	
Renal pelvis wall thickening	29 patients (21.1%)	11 patients (27.5%)	
Reduced perfusion	3 patients (2.1%)	0	

RBUS = renal and bladder ultrasound; SPA = suprapubic; VUR = vesicoureteral reflux.
[a] Mann–Whitney test.
[b] Fisher exact test.

Febrile UTIs were diagnosed by general practitioners and office pediatricians in pediatric outpatient departments and at our (pediatric urologic) outpatient department. Urine collection was performed in our outpatients department and at the offices of practicing pediatricians, pediatric urologists, and general practitioners. All of them used commonly available urine bags, catheters, or needles complying with medical standards. As to the patients primarily seen at our department, urine was processed immediately after it was obtained, and a dipstick analysis by an automated dipstick analyzer was performed. Urine cultures were done using standardized protocols in certified microbiological laboratories. Only the combination of a positive leucocyte esterase test and positive urine culture in the absence of symptoms of other reasons for the present fever was considered diagnostic for a urinary tract infection (sterile collection method, any number of colony forming units (CFU)/μl; bag urine and potty urine, $\geq 10^5$ CFU/μl) [3]. Of the patients that were considered to have a febrile UTI, almost all were severely ill (high fever $\geq$ 38.5 °C in 99.2%, fever $\geq$ 3 days in 93.3%). Abnormalities in renal and bladder ultrasound examination (RBUS, performed in 391/402 patients, 97.4%, at time of referral) were present in 47.4% of group 1 (bag urine) versus 38.8% in group 2 (catheter/SPA, $p = 0.136$) (Table 1).

However, as this was a retrospective analysis there was no exact standardization of methods, and for the patients who were referred from office pediatricians we assume that they also adhered to the basic standards mentioned above. Patients referred with an unclear history of how the UTI in question was diagnosed were not included into this study. A VCUG was only indicated in those where we assumed a correct diagnosis from all available data.

According to the EAU/ESPU guidelines [11], valid at time of study inclusion, a primary, fluoroscopic VCUG involving at least one representative filling and voiding cycle was performed for every child with the diagnosis of a fUTI. After catheterization with a 4.5 or 6F feeding tube according to the age the bladder was filled with body warm (37 °C) contrast agent until spontaneous micturition set in. Radiographs were acquired by digital, pulsed fluoroscopy during filling and micturition.

For every child the method of urine collection at the time of diagnosis, the presence of VUR, and clinical and demographic parameters were assessed and recorded.

Data were fed in to an Excel (Microsoft Corporation, Redmond, WA, USA) sheet and statistical analyses were performed with Prism 6.0 (Graphpad Software, San Diego, CA, USA). After descriptive statistics, the Fisher exact test and Mann—Whitney test as well as a Kolmogorov Smirnov analysis for the comparison of ages in the two groups and a chi-square test for the non-parametrical data were performed. A p value < 0.05 was considered significant.

Results

VUR was detected in 133 out of 402 (33.0%) patients. VUR $\geq$III was diagnosed in 52 patients (39.1% of all children with VUR and 12.93% of all children included into the study).

Children with bag urine collection at time of diagnosis (group 1) were similar to children with catheter/SPA urine collection (group 2) concerning age ($p = 0.678$) and gender ($n = 0.071$) (Table 1).

In group 1, 33.7% of the children had VUR and 31.1% in group 2 ($n = 0.718$) (Fig. 1).

Of all female patients ($n = 271$) 37.0% had VUR. Of those in group 1 (192 girls), 74 patients (38.5%), of those in group 2 (79 girls) 29 patients (36.7%) had VUR ($p = 0.7691$).

Of all male patients ($n = 131$), 28.2% had VUR. The probability for being diagnosed with VUR for all males in group 1 (104 boys) came to 28.8% (30 patients) compared with 25.9% (7 patients) in group 2 (27 patients) ($p = 0.6330$) (Fig. 2).

The difference in VUR between boys and girls (28.2% vs. 37.0%, OR 1.51, RR 1.321) was not statistically significant ($p = 0.227$).

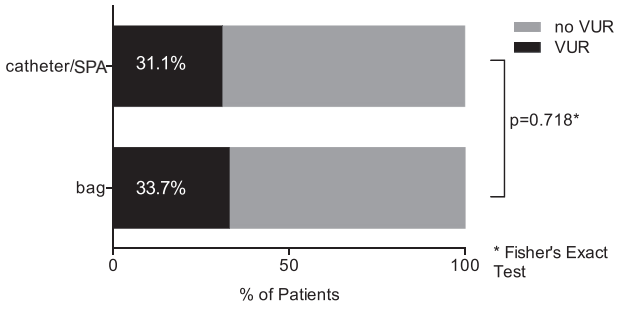

Figure 1 The probability of vesicoureteral reflux depending on the urine sampling technique employed during the initial diagnosis of the febrile urinary tract infection prompting the voiding cystourethrogram.

Discussion

The urine-sampling technique at time of diagnosis of febrile UTI taken as an isolated factor in a group of children with clinically plausible febrile UTIs seems to be not a valid predictor of VUR in our patients.

The rate of patients with VUR compared with in the literature was in the lower range of what has been reported before. In the current *EAU guidelines on paediatric urology* [11] the incidence of VUR after febrile urinary tract infections is denoted to be 30—50%, dependent on age. Also, in the current AAP guidelines on urinary tract infection the incidence of VUR is specified as 35% after the first and 74% ($n = 10$) after recurrent febrile UTIs [12]. In a meta-analysis of nine studies [13], involving a total of 6457 patients and representing the largest series we were able to

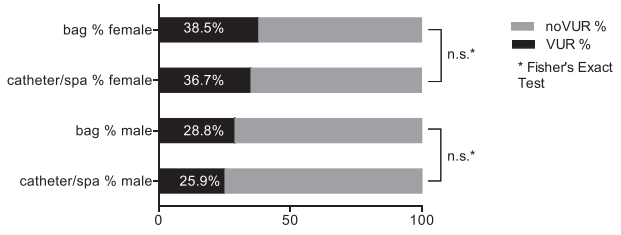

Figure 2 The probability of vesicoureteral reflux depending on the urine sampling technique and on the patient's sex.

find, the incidence of VUR after febrile UTIs accounted to a mean of 32% (30—37%).

Previous reports showed almost unequivocally that SPA, transurethral catheterization, and clean-catch urine sampling in toilet-trained children are more reliable for UTI diagnosis than bag- or potty urine [3,4,6,8,9,14,15]. Although so-called clean-catch urine is considered a valid urine collection method according to the NICE guidelines [16], bag urine, although important for excluding a UTI if there is a negative result, showed a high likelihood for false-positive culture results [8]. Conversely, other reports suggest that in a clinical environment, taking into account many parameters, bag urine may confer a sufficient specificity for diagnostic use in pediatric UTI [17,18].

One report by Lau et al. [10] implicates that urine obtained by transurethral catheterization is prone to contamination to an extent similar to bag urine in uncircumcised boys. Given that in our cohort the proportion of boys is only 32.9%, albeit mostly (no data available) uncircumcised, we would not assume that such an effect could bias our results, even more so after the same report shows a much lower contamination rate of urine obtained by transurethral catheterization than bag urine in girls.

Using non-sterile urine sampling techniques, a significant number of false-positive urine diagnosis has to be expected in febrile children. In the group of examined children, various diagnostic criteria beneath guideline conform urine testing [3] were taken into consideration for the diagnosis of febrile UTIs. In our population, most children who were considered to have a UTI were severely ill (high fever $\geq$ 38.5 °C in 99.2%, fever $\geq$ 3 days in 93.3%). Moreover, they lacked characteristic symptoms of possible other causes for the fever in question. We suggest that these additional diagnostic measures may have corrected for possibly misleading urine tests and led to a correct diagnosis for referral and further imaging.

Most reports available [1,4,6], however, identified fever and a pathologic urine culture, especially in young children and infants, as the most important criteria of diagnosis.

The high rate of bag urine used (53%) in patients referred to our department might be considered worrying, because of the possible implications to culture results of a high rate of contamination. In view of the current guidelines, recommending bag urine only as a method for exclusion but not for the diagnosis of UTI, adherence to these recommendations seems to be low in our area [3,12]. While we can only speculate on the reasons for this low guideline adherence, it seems probable that the convenience of a urine bag compared with the more invasive and complex process of transurethral catheterization of SPA is part of the explanation. Furthermore, invasive procedures may impose stress on children, with possible negative psychological consequences [19].

There are some limitations to this study. Because of our retrospective design we were not able to include the clinical conditions in which urine was collected, including the number of attempts required for urine collection or if one failed technique had preceded another. Also, urine collection methods and the exact use of dipsticks and urine cultures were not standardized as this is a retrospective study. Nor are there clearly identifiable criteria for referral to our department, which could be a source for an inclusion bias. The strength of this dataset, however, is that it represents children that are usually referred for further work-up after febrile UTIs and consequently those who are relevant to our question.

Conclusion

We could show that the urine sampling technique, taken as an isolated factor in the diagnosis of a febrile UTI in our cohort of patients, is not a valid predictor of VUR. Therefore we conclude, given the diagnosis of a febrile UTI was made by an experienced clinician taking into account the whole clinical picture by use of bag urine samples, this should not prompt a less consequent further work-up than the use of any formally correct (”sterile”) urine sampling during initial diagnosis.

Conflict of interest

None.

Funding

None.

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Journal of Pediatric Urology (2015) 11, 35.e1–35.e6

Lower radiation burden in state of the art fluoroscopic cystography compared to direct isotope cystography in children

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Keywords
Pediatric urology; Vesicoureteric reflux; Direct isotope cystography; Radiation burden; Voiding cystourethrography

Received 4 June 2014
Accepted 27 August 2014
Available online 7 February 2015

Summary

Introduction
Both, fluoroscopic voiding cystourethrography (fVCUG) and direct isotope cystography (DIC) are diagnostic tools commonly used in pediatric urology. Both methods can detect vesicoureteral reflux (VUR) with a high sensitivity. Whilst the possibility to depict anatomical details and important structures as for instance the urethra in boys or the detailed calyceal anatomy are advantages of fVCUG, a lower radiation burden is thought to be the main advantage of DIC. In the last decade, however, a rapid technical evolution has occurred in fluoroscopy by implementing digital grid-controlled, variable rate, pulsed acquisition technique. As documented in literature this led to a substantial decrease in radiation burden conferred during fVCUGs.

Objective
To question the common belief that direct isotope cystography confers less radiation burden compared to state of the art fluoroscopic voiding cystography.

Study design
Radiation burden of direct isotope cystography in 92 children and in additional 7 children after an adaption of protocol was compared to radiation burden of fluoroscopic voiding cystourethrography in 51. The examinations were performed according to institutional protocols. For calculation of mean effective radiation dose [mSv] for either method published physical models correcting for age and sex were used. For DIC the model published by Stabin et al., 1998 was applied, for fVCUG two different physical models were used (Schultz et al., 1999, Lee et al., 2009).

Results
The radiation burden conferred by direct isotope cystography was significantly higher as for fluoroscopic voiding cystourethrography. The mean effective radiation dose for direct isotope cystography accounted to 0.23 mSv (±0.34 m, median 0.085 mSv) compared to 0.015 mSv (±0.013, median 0.008 mSv, model by Schultz et al.) - 0.024 mSv (±0.018, median 0.018 mSv, model by Lee et al.) for fluoroscopic voiding cystourethrography. After a protocol adaption to correct for a longer examination time in DIC that was caused by filling until calculated bladder capacity, mean radiation burden accounted to .07 mSv (median 0.07 mSv) and the values were less scattered.

Discussion
As it had to be expected from literature, radiation dose from fVCUG, if modern image acquisition techniques are used, is even less than from DIC. In our protocol, according to nuclear medicine standards, bladders were filled until calculated capacity. This resulted in a longer examination time for the patients with a higher functional capacity, resulting in relatively higher radiation burden. However, also if the protocol is changed or only the patients with relatively fast bladder emptying are considered, radiation burden conferred by DIC is higher (at least × 2.9, comparing the "worst" case for fVCUG with the "best" case for DIC). Absolute radiation burden conferred by either exam is extremely low compared to other medical radiation exposures as well as to environmental radiation. Consequently it is most probably not relevant for the individual childs future risk for cancer or other radiation damage. However, because of repeated investigations with correspondingly higher radiation burden in this patient group the ALARA (as low as reasonably achievable) principle should lead to a optimized use of fVCUG rather than an uncritical use of DIC, given that modern acquisition standards are available and radiation measurement is performed. Also, fVCUG provides more information concerning anatomical details compared to DIC.

Conclusion
Contrary to common beliefs, effective radiation dose conferred during fluoroscopic voiding cystourethrography is significantly lower than during direct isotope cystography. The prerequisite for our findings, however, is the use of modern image acquisition tools and an optimized protocol. Both exams confer low radiation doses probably only relevant to children undergoing repeated radiation exposure. Nevertheless, this findings should be considered in indication for either exam in order to reduce the radiation burden to a minimum whilst optimizing the information yield.

http://dx.doi.org/10.1016/j.jpurol.2014.08.015

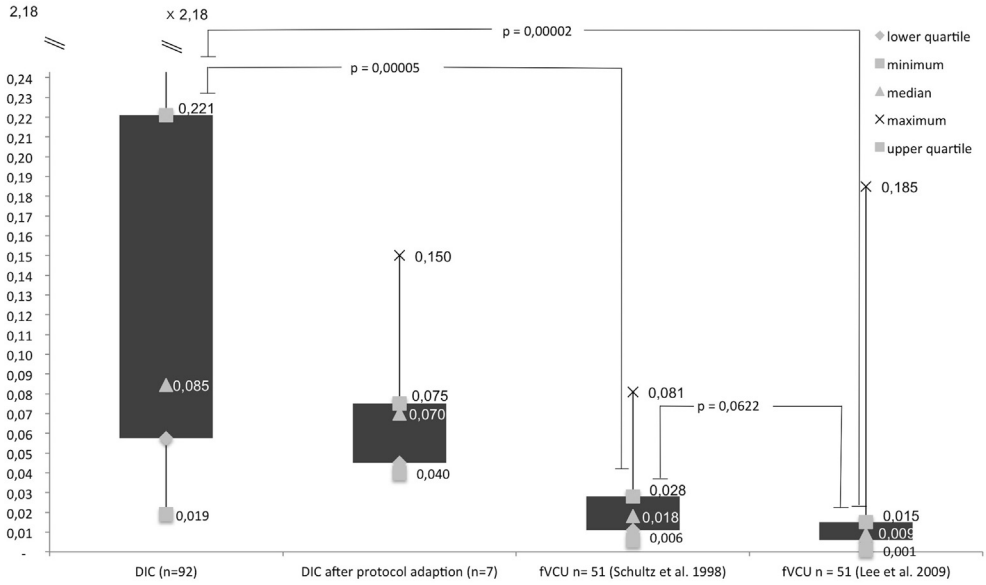

Figure Effective doses for DIC before and after protocol adaption and fVCUG using two different physical models for calculation of effective doses.

Introduction

Vesicoureteral reflux (VUR) is present in about 1—3% of children in Europe and North America [1]. An understanding of the link between VUR, urinary tract infections (UTI) and kidney damage through recurrent pyelonephritis (APN) was reached during the mid-to late 20th century [2]. There is, however, still controversy on how to diagnose and to treat children with this condition [3]. In order to diagnose VUR, voiding cystourethrography (VCUG) is the method of choice.

In addition to the need for catheterization or suprapubic puncture in VCUG and the concomitant pain and discomfort [4], another downside of VCUG is the radiation burden involved in most examination techniques available.

The largest data resource on possible consequences of radiation exposure is derived from information obtained after observation of inhabitants of the surroundings of Hiroshima and Nagasaki. A risk of cancer development of 5% per sievert averaged over the whole population is described in the literature [5,6]. Although the energy applied is lower in children, the corresponding organ masses are even smaller, accounting for a marked increase in organ- and therefore patient-effective dose [7—9]. Consequently, a 1-year-old infant is 10—15 times more likely to develop cancer after radiation exposure than an adult. In addition, children's organs are more radiation-sensitive and their longer lifespan allows for late effects of radiation exposure to become manifest [10].

The radiation doses for all available VCUG examinations are in a very low range; however, children with VUR often undergo repeat examinations and cumulative radiation doses may be relevant. Therefore the ALARA (as low as reasonable achievable) principle should be followed even stricter for children in the indication for either radiological investigation.

Sonographic VCUG (SVCUG) does not involve radiation burden and can be used as an alternative to conventional or fluoroscopic VCUG (fVCUG) [11—13] in selected indications (screening for VUR, follow-up examinations, girls). SVCUG is, however, highly operator dependent, technically demanding [13] and involves off-label use of an ultrasound contrast agent (Sonovue is not registered for children) [11].

Direct isotope cystography (DIC) has been shown to have a comparable, if not higher sensitivity to detect VUR than the gold-standard method of fVCUG [14—17] and, as earlier publications showed, a lower radiation burden than conventional VCUG [18—21]. The fact that detailed urethral and bladder morphology are not as precisely visible on DIC as on VCUG is no disadvantage in the setting of follow-up examinations for girls and boys.

Compared to DIC, a rapid evolution of acquisition technique has occurred in VCUG. Through the use of digital, grid-controlled variable rate-pulsed fluoroscopy, the radiation exposure could be reduced to 12.5% of the previously documented values using continuous fluoroscopy [22]. These technical advances were also reflected in the latest adaption of the reference values for radiologic examinations in children, who require comparatively low radiation exposure only achievable by using modern techniques [23].

We therefore hypothesized that through technical advances and modern protocol design, contrary to common beliefs, the radiation burden conferred by fVCUG could be even lower than the radiation burden conferred by DIC. The aim of this work was to put this hypothesis to the test by comparing two groups of consecutive patients who underwent DIC and fVCUG at our institution.

The problem in comparing radiation burden of the two examinations is that the original conditions are different. Whereas for DIC a certain amount of radiation measured in megabequerel (MBq) is instilled into the bladder and the patient is exposed to it for a certain time (minutes)

thereafter until micturition, in fVCUG a dose—area product (DAP) (cGy cm^2) reflecting the amount of radiation deposited during fluoroscopy is recorded.

In order to be able to compare radiation burden, both figures (MBq minute and cGy cm^2) have to be transformed into age- and gender-corrected effective radiation doses (mSv) with respect to different radiation sensitivities of different organs. For this purpose, experimental models have been established that are used for transformation [20,21,24].

Patients and methods

We retrospectively examined a cohort of 92 patients (85/7 female/male, mean age 2.99 years, median 2.21 years) who underwent DIC as follow-up examination following endoscopic therapy of VUR. For comparison of radiation burden we evaluated 51 (28/23 female/male, mean age 2.21 years, median 1.0 years) consecutive fVCUGs performed primarily for diagnosing reflux after febrile urinary tract infections (fUTIs). For checking purposes in accordance with protocol adaption of DIC, seven more patients (6/1 female/males, mean age 3.25 years, median 3.0 years) that underwent DIC were evaluated.

Direct isotope cystography

DIC was carried out by catheterization with a 6—8F urethral catheter through which the bladder was filled by gravity with a standardized volume ([age + 2] × 30) of physiological saline (0.9%) charged with an age-normalized load of ^{99metastable}technetium (^{99m}Tc) as detailed previously [25,26]. The catheter was then withdrawn. Until spontaneous micturition, one frame per 10 s was recorded. VUR was graded according to nuclear medicine standards [15] as mild, moderate or severe. A Siemens Symbia True Point single positron emission computed tomography gamma camera was used for acquisition. Every picture series was evaluated by a nuclear medicine specialist and discussed in an interdisciplinary meeting with the pediatric urologists.

After evaluation of 92 patients during this retrospective study, this protocol was changed and the bladder was filled until the patients needed to void, which accounted for the shorter examination time and lead to a reduction of dispersion of the measurement values. Subsequently, seven patients were evaluated to study the impact of the change in protocol.

Fluoroscopic voiding cystourethrogram

fVCUGs were performed by experienced pediatric urologists using a Siemens Arcadis Vario C-arm digital pulsed fluoroscopic unit. Children were catheterized with 4—6F feeding tubes and bladders were filled by gravity (30 cm H_2O) except when a 4F feeding tube was used, when bladders were filled slowly with 20-mL syringes until micturition. A fluoroscopic picture before application of contrast medium was stored using last image hold mode. At this point, the automatic tube tension adjustment was switched to manual and the tube tension was adjusted to the lowest reasonable value. The region to be examined was faded in to by iris- and lateral shades were employed to limit the radiation exposure to the region of interest. Then contrast medium was injected slowly until onset of voiding. During voiding, pictures of the bladder, urethra (in boys lateral views), and the kidney region were acquired. For picture acquisition only fluoroscopy with ultra-short pulses and last image hold technology was used; we did not record picture sequences or still shots. This allowed us to record up to four pictures per second of fluoroscopy time, which again is the explanation for the short fluoroscopy time during fVCUG in our patients. The feeding tube was only removed in rare cases when voiding was not possible. In 30 out of 51 fVCUGs, cyclic filling (2—4 times) was performed. After the examination, the feeding tube was removed and another plain picture was acquired. Boys received one dose of antibiotic to prevent iatrogenic UTI.

Data acquisition and statistical analyses

Patient data were acquired retrospectively using the documentation in the local hospital information system (SAP) and radiation dose measurement data as well as exposure time were acquired using the dedicated documentation systems. Data were fed into a Microsoft Excel spreadsheet and statistical analyses were carried out using the same software. For comparison of mean values (effective radiation doses) the *t*-test for normally distributed groups was used.

Calculation of equivalent doses

In order to compare the radiation burden of DIC versus fVCUG, effective radiation doses were calculated for both examinations based on published models. For DIC the model published by Stabin and Gelfand [21] was used; the equivalent dose (ed)/min/MBq was deducted and then the relative ed for each patient was calculated. For fVCUG two different models published by Schultz et al. [20] and Lee et al. [24] were employed: starting from DAP values a sex- and age-adjusted ed was calculated for each patient using the coefficients provided in the above mentioned publications.

The accurateness of these calculations is estimated to ±10—15% by the authors [20,21,24]. Radiation dose calculations were approved by two local hospital radiation physicists (EP, BG).

Results

Direct isotope cystography

For all patients who underwent DIC, mean exposure time (= time spent with tracer insider the bladder) was 37.8 min (median 13.5 min, range 3.17—286.83 min). The mean dose of ^{99m}Tc applied was 32.79 MBq (median 31 MBq, range 13—85 MBq). This results in a mean effective radiation dose of 0.23 mSv (±0.34 mSv, median 0.085 mSv). If only the patients with an exposure time under 15 min ($n = 52$) are evaluated, the mean effective radiation dose is 0.062 mSv (±0.034 mSv, median 0.064 mSv) (Table 1).

After changing the DIC protocol by filling until micturition instead of filling until the calculated bladder capacity,

Table 1 Data on radiation burden of either method. Effective radiation doses (mSv) are printed in bold letters.

DIC $n = 92$	Mean	Median	Range
Time (min)	37.8	13.5	3.17—286.83
Applied dose (MBq)	32.79	31	13—85
Effective dose (mSv)	**0.23**	**0.085**	**0.02—2.18**
Effective dose (mSV) in patients with time (min) ≤ 15 ($n = 52$)	**0.062**	**0.064**	**0.02—0.24**
fVCUG $n = 51$	Mean	Median	Range
Time (s)	7.2	4.0	2.0—24.0
Dose area product (cGy cm^2)	3.3	2.17	0.46—30.3
Effective dose (Schultz et al. 1998) (mSv)	**0.024**	**0.018**	**0.0055—0.08**
Effective dose (Lee et al. 2009) (mSv)	**0.015**	**0.008**	**0.01—0.185**
DIC after protocol adaption $n = 7$	Mean	Median	Range
Time (min)	11.07	9.67	7.5—23.6
Applied dose (MBq)	33.43	32	26—49
Effective dose (mSv)	**0.07**	**0.07**	**0.04—0.15**

another seven patients were evaluated. Mean exposure time was reduced to 11.07 min (median 9.67, range 7.5—23.6). The mean dose of ^{99m}Tc applied was 33.43 MBq (median 32 MBq, range 26—49 MBq). This results in a mean effective radiation dose of 0.07 mSv (median 0.07 mSv) (Table 1).

Fluoroscopic voiding cystourethrography

For the fVCUG group, the mean fluoroscopy time was 7 s (median 4 s) and mean dose DAP was 3.3 cGy cm^2 accounting for a mean effective radiation dose of 0.024 mSv (±0.018, median 0.018 mSV) as calculated using the model of Schultz et al. [20] and 0.015 mSv (±0.013, median 0.008 mSV) as calculated using the model of Lee et al. [24] (Table 1).

Comparison

Comparison of the mean effective radiation doses of DIC and fVCUG (Table 1) reveals a highly significant ($p = 0.00005$ Schultz, $p = 0.00002$ Lee) difference in effective radiation dose of 0.206 mSv (mean). After the protocol change and with only seven patients, a statistical comparison with calculation of p-values was not valid (small group size); there was, however, as expected, a more leveled examination time and a lower radiation dose than the former protocol and a higher dose than in fVCUG (Fig. 1A).

Discussion

Examinations used in uropediatric diagnostics involve, relative to other disciplines (abdominal CTs, barium swallows, irrigoscopies) [10], relatively low radiation doses. Nevertheless, reducing the radiation burden to children is critical, either through avoiding unnecessary investigations, through implementation of radiation-saving protocols, and through implementation of technological advances.

It is commonly assumed that DIC confers a lower radiation burden than VCUG. According to our findings, radiation burden seems to be critically dependent on protocols used for either examination and this belief seems to be partly based on historical data.

In the literature [19,21,25] radiation burden during DIC is calculated by different models that take into account the exposure time towards the instilled radionuclide and the instilled activity. The mean effective radiation dose according to these publications accounts to 0.047—0.053 mSv [21], being considerably lower than the published mean effective radiation dose for conventional VCUG examinations (0.4—2.2 mSv) [20]. The wide range for radiation burden during radiologic VCUG examinations is explained by different acquisition techniques.

The use of modern acquisition technique, as for example pulsed fluoroscopy, leads to an impressive reduction of radiation exposure by up to factor 8 [22]. Better image quality and last image hold technology makes the acquisition of still shots widely unnecessary. A current publication by Born et al. [23], dealing with the lowered German diagnostic reference doses reports on mean DAPs for 413 examinations, was 0.97 dGy cm^2 (0.1—11.1 dGy cm^2) translating into 0.021 mSv using the conversion model we used for our data. This corresponds very well with our experience and our mean effective radiation dose (0.024 mSv) using a comparable acquisition technique and proves that our fVCUG radiation measurements reflect the current state of the art in this field.

The vast range of time with the tracer inside the bladder (mean 37.8 min, median 13.5 min, range 3.17—286.83 min) and consequently effective radiation doses during DIC in our patients was caused by filling according to calculated bladder capacity ([age + 2] × 30). This protocol is detailed in the "Procedure guideline for radionuclide cystography in children" published by the Society of Nuclear Medicine in 1997 [25]. Children with reflux tend to have big bladder capacities as documented in the literature [27]. In consequence, their bladders are not adequately filled with the calculated volume and examination time is delayed. Also, the instilled activity in our patients was considerably higher (mean 32.79 MBq, median 31 MBq) than documented in the literature (11—22 MBq for the same age group) [21]. A re-evaluation after adapting the DIC protocol (instillation until the patient needs to void instead of calculated bladder capacity) led to a significant reduction in mean radiation dose, as expected by reduction of the diversion of the time measurement values, however, the median changed only slightly (0.085 mSv before compared to 0.07 mSv after protocol adaption).

For fVCUG our exposure times (mean 7 s, median 4 s) were much lower than the mean exposure time documented in the literature (mean 34 s) [23] because of acquisition of only last image hold fluoroscopy pictures (up to 4 pictures/second of fluoroscopy). Together with consequent in-fading, reduction of tube tension and use of pulsed, digital fluoroscopy with last image hold mode this results (mean 3.3 cGy cm^2, median 2.17 cGy cm^2, range 0.46—30.3 cGy cm^2) in lower DAPs than much of those documented in previous literature (83—534 cGy cm^2) [20].

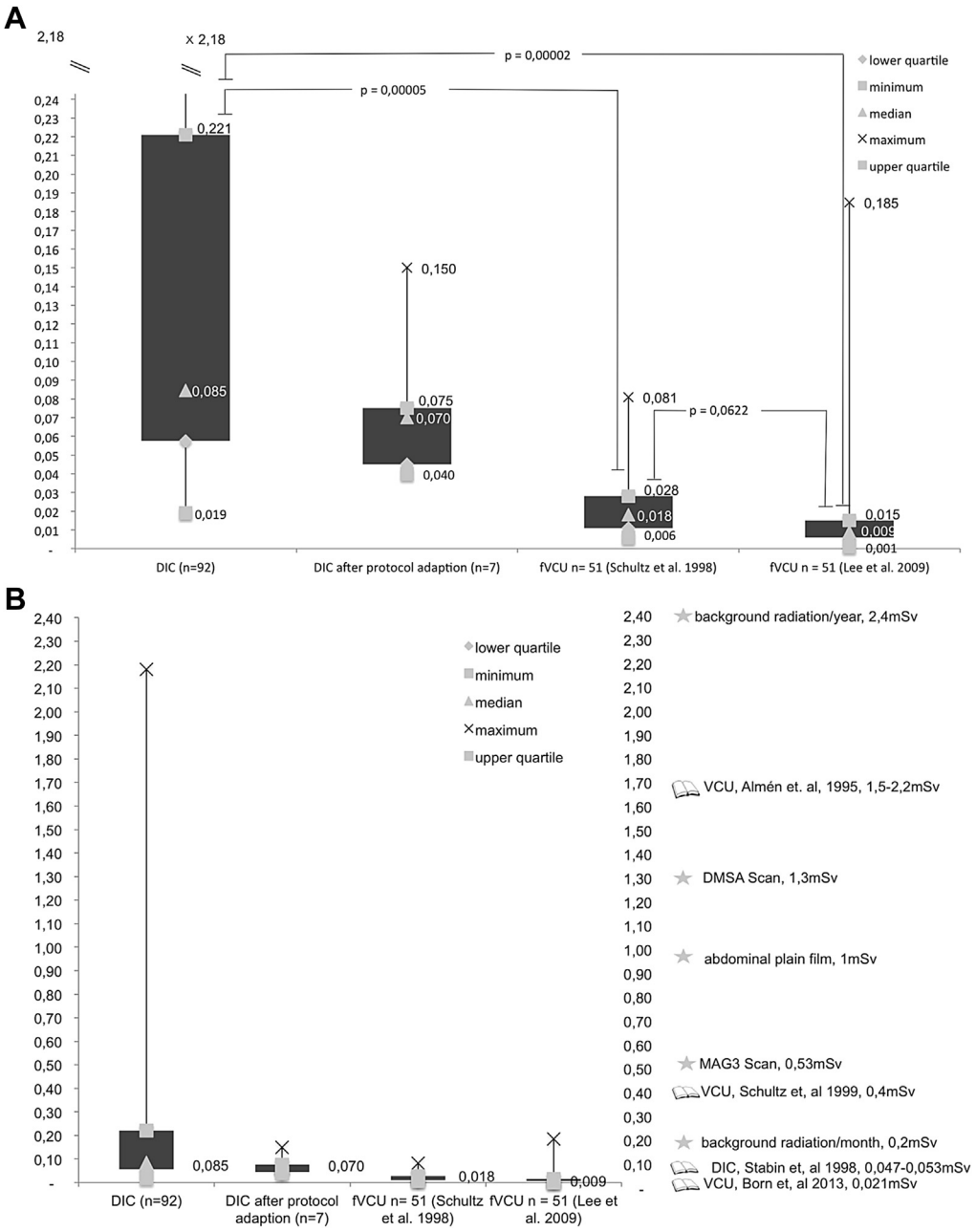

Figure 1 (A) Effective doses for direct isotope cystography (DIC) before and after protocol adaption and fluoroscopic voiding cystourethrography (fVCUG) using two different physical models for calculation of effective doses. (B) Effective doses in direct isotope cystography before and after protocol adaption as well fVCUG compared to the literature and other examinations relevant in pediatric urology.

The age difference between the fVCUG group and DIC group of patients is caused by the fact that indication for fVCUG where 52 consecutive patients were recorded include mainly reflux detection and control (usually before of around age 1) and DIC was used for follow-up after ET of VUR, which usually occurs later. The age difference and the consecutive difference of DAP was taken into account by adjusting factors for conversion of cGy cm^2 to mSv as proposed by Schultz et al. [20] and Lee et al. [24].

Compared to other diagnostic procedures with earth and cosmic radiation, DIC and fVCUG confer a relatively low radiation burden. Therefore, both examinations, taken as isolated radiation burden, are most probably not relevant to the individual child's future risk for cancer or other harm connected with the exposure to ionizing radiation. However, the relatively higher radiation sensitivity of children, a 1-year-old infant is 10—15 times more likely to develop cancer after radiation exposure than an adult [10], has to be taken into account. Additionally, VUR patients are likely to undergo repeated VCUG examinations and other diagnostic procedures involving radiation exposure (e.g., DMSA scans) accounting for an accumulation of radiation dose (Fig. 1B).

A possible limitation of our study is the calculation of equivalent dose using model systems. These models, however, are the best and probably only instrument available to render comparable biologically relevant radiation burden caused by different examinations. Bearing in mind the importance of avoiding radiation to patients and especially to children, it is considered important to rely on these model systems in order to optimize protocols and protect our patients from potentially harmful radiation exposure.

Conclusion

Contrary to common beliefs, effective radiation dose conferred during fVCUG, if modern image acquisition tools and an optimized protocol are applied, is significantly lower than during DIC. Although both examinations confer low radiation doses probably only relevant to children undergoing repeated radiation exposure, this finding should be considered in indication for either examination in order to reduce the radiation burden to a minimum whilst optimizing the information yield.

Funding

None.

Conflict of interest

None.

Ethics statement

This study was approved by the institutional ethics committee (#EK08/14).

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Danksagung

Diese Dissertation entstand im Zuge meiner Bestrebungen, an der Medizinischen Fakultät der LMU weiterhin in der Lehre tätig zu bleiben.

Univ. Prof. Dr. Alexander Karl stand mir bei der Erstellung dieser Arbeit als Doktorvater jederzeit zuverlässig mit Rat und Tat zur Seite. Ich Danke ihm für die unkomplizierte Unterstützung – er ist als Chirurg, Wissenschaftler und akademischer Lehrer ein Vorbild.

Em. Prim. Univ. Doz. Dr. Marcus Riccabona, dessen Arbeit die Kinderurologie in Österreich maßgeblich geprägt hat und der in vieler Hinsicht das Ideal eines Kinderurologen verkörpert, ermöglichte mir den Zugang zu dieser außergewöhnlichen Klinik. Dafür – und für sein geduldiges Mentorat, nicht nur im Rahmen dieser Dissertation, danke ich ihm von Herzen.

Weiterhin danke ich dem **Team der Urologischen Klinik der LMU**, insbesondere **Univ. Prof. Dr. Stief, Univ. Prof. Dr. Waidelich, Fr. Baronin von der Recke** und dem **pflegerischen und ärztlichen Personal auf den Stationen G4 und H4**, auf denen ich seit 5 Semestern in der Lehre tätig sein darf.

Meine Begeisterung für Lehre und Wissenschaft verdanke ich in erster Linie meinem Vater, **Univ. Doz. Dr. Anton Haid** sowie meinen Lehrern und Mentoren, die mich in meiner Ausbildung und meinem beruflichen Werdegang begleiten. Insbesondere **Prim. Univ. Doz. Dr. Josef Oswald** möchte ich danken. Er steht mir nicht nur als Lehrer und Freund zur Seite sondern lässt mir als Leiter der Abteilung für Kinderurologie am Ordensklinikum Linz jene Unterstützung zuteil werden, welche die Tätigkeit in München voraussetzt. Beide hier eingebundenen Arbeiten beruhen auf seiner Seniorautorschaft – ohne Ihn hätte ich nie in der Kinderurologie Fuß fassen können.