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Home screening for bacteriuria in children with spina bifida and clean intermittent catheterization

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Abstract

Background: Significant bacteriuria (SBU) and urinary tract infections (UTIs) are common in patients with spina bifida and neuropathic detrusor sphincter dysfunction. Laboratory agar plated culture is the gold standard to establish SBU. It has the disadvantage of diagnostic and subsequent therapeutic delay. Leukocyte esterase tests (LETs) and dip slides proved to be useful in the general populations to exclude SBU and UTI. The aim of this study was to evaluate the reliability of LET and dip slide in children with spina bifida without symptoms of UTI. The reliability in children with asymptomatic SBU was not studied before.

Methods: In one hundred and twelve children with spina bifida on clean intermittent catheterization LETs and dip slides were compared with laboratory cultures. Both tests and agar plated cultures were performed on catheterized urine samples. The hypothesis was that the home tests are as accurate as laboratory cultures.

Results: A SBU was found in 45 (40%) of the 112 laboratory cultures. A negative LET excluded SBU (negative predictive value 96%), while a positive LET had a positive predictive value of 72%. The false positive rate was 28%. Dip slide determination of bacterial growth had no added value, other than serving as transport medium.

Conclusions: In spina bifida children, leukocyte esterase testing can be used to exclude significant bacteriuria at home, while dip slide tests have no added value to diagnose or exclude significant bacteriuria.

Keywords: Bacteriuria, Clean intermittent catheterization, Dip slide, Home testing, Leukocyte esterase test, Spina bifida

Background

Clean intermittent catheterization (CIC) and antibiotic prophylaxis have reduced the incidence of parenchymal kidney damage in children with spina bifida [1-3]. In these patients, the main objective of any urinary diagnostic test is to detect or exclude urinary tract infections (UTIs) to prevent under- and over-treatment. The diagnosis of UTI is made on clinical symptoms, leukocyturia and significant bacteriuria (SBU). Several simple tests to detect a UTI, such as dip slides and leukocyte esterase tests (LET) were studied extensively. Two recent meta-analyses showed that a LET had a negative predictive

value (NPV) of 90%, with a positive predictive value (PPV) of 60% [4,5]. A UTI therefore has to be confirmed with a urine culture [4], which takes at least three days, and treatment is postponed. Dip slides with two or three culture media were tested to diagnose SBU in primary care [6-9]. As PPV was poor, it was concluded that the use of dip slide urine cultures should only be used to exclude SBU.

The aim of the present study was to evaluate the reliability of the LET and dip slide in children with spina bifida. Children with clinical symptoms of UTI participated in a parallel study, and were not included in this study [10]. Only children with asymptomatic SBU were included. We also assessed whether general patient characteristics, such as sex, age and use of prophylactic antibiotics can predict asymptomatic SBU. The hypothesis was that LET and Uricult[®] Duo dip slide are as accurate

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as laboratory cultures in determining significant bacteriuria.

Patients and methods

One hundred and twelve patients with spina bifida on CIC known at the Gasthuisberg University Hospital Leuven, Belgium participated in the study. Patients catheterized themselves or were catheterized by their parents or primary care takers for a fresh urine sample at the quarterly control visit. Patients who had completed treatment for UTI less than 4 weeks before the visit to the clinic, or who had febrile episodes immediately preceding the visit, or a clinical suspicion for a UTI at the visit were excluded. A leukocyte esterase test (LET, Combur-2[®] test strip, Roche, Switzerland) was performed on the urine sample, regarded "positive" in every range of discoloration. The sample was also inoculated onto a dip slide (Uricult[®] Duo, Orion Diagnostics, Finland), which contains an aselective cystine-lactose-electrolyte deficient (CLED) agar for Gram-positive bacteria and *enterobacteriaceae*, and MacConkey agar for non-glucose fermenting Gram-negative rods. The dip slide was incubated in a bottle warmer (Philips[®] SBC 215/00, Philips SA, Belgium) at 36.3 ± 2.5 °C, as measured over 48 hours with a calibrated Dickson[®] SK 180 temperature logger (Dickson Corporation, Addison, USA). After 24 hours in the bottle warmer, the dip slide was evaluated for colony forming units by a trained research nurse, and the result was reported as 'no growth' or 'growth' (visible colonies). The same urine sample was also sent for 'gold standard' agar plated culture. SBU was defined as a colony count of $\geq 10^4$ per milliliter of one single species in a catheterized sample. Of patients with multiple samples, only the first was used for analysis. To establish whether general patient characteristics could discriminate SBU from no SBU, logistic regression was used with gold standard outcome (positive / negative) as dependent variable and age and sex as independent variables. This model was then extended with prophylaxis (model 2), LET testing (model 3), and dip slide testing (model 4). Model results are expressed as odds ratios (95% confidence intervals, and p-values). Discriminative capacity for these four models was evaluated using areas under the Receiver Operator Characteristic (ROC) curves (AUC). This study is approved by the ethics committee from the Leuven University Hospital, and performed after parental or guardian consent.

Results

Of the 112 asymptomatic patients, 45 had a positive agar plated culture, hence the prior probability for SBU was 40%, which is consistent with previous studies. The patients had an age range of 0 to 35 years (median 13.0, long-term spina bifida follow-up patients over 18 years

of age are included). Fifty (45%) were boys and 61 (68%) were on antibiotic prophylaxis. Table 1 shows the results of four consecutive models predicting the gold standard culture outcome. The LET had the strongest discriminative power, while dip slide testing did not add significantly. In Figure 1, the discriminative capacity of the models is shown graphically as ROC curves for age and sex (AUC = 0.64, p = 0.01); age, sex and prophylaxis (AUC = 0.76, p = 0.003); age, sex, prophylaxis and LET (AUC = 0.91, p < 0.0001) and age, sex, prophylaxis, LET and dip slide (AUC = 0.91, p < 0.0001). As this study addressed the role of LET and dip slide to rule out SBU in spina bifida patients without complaints of UTI, we proceeded with these tests only, as shown in Table 2. Given an a-priori chance of SBU of 40%, a positive LET had a PPV of 72%, while a negative LET substantially decreased the chance of a SBU to 4% (NPV = 96%). Dip slide testing had a similar PPV (73% versus 72% for LET) but substantially lower NPV (78% versus 96% for LET). Combining LET with dip slide improved neither PPV (positive LET 72% versus both LET and dip slide positive 74%) nor NPV (negative LET 96% versus both LET and dip slide negative 98%). Pathogens found were *Escherichae coli* (N=26), *Klebsiella pneumonia* (4), *Streptococcus* species (4), *Enterococcus* species (3), *Proteus mirabilis* (3), *Pseudomonas aeruginosa* (2), *Serratia marcescens* (1), *Staphylococcus aureus* (1) and *Providencia rettgeri* (1). In three of the 45 positive cultures (one *Streptococcus*, one *Staphylococcus* and one *Enterococcus* species) the LET was negative, resulting in 93.3% sensitivity. There were 16 false positive LETs in 67 negative cultures, resulting in 76% specificity.

Table 1 Determinants of significant bacteriuria

Model	Odds ratio	95% CI	p-value
1 Sex (male vs female)	1.9	0.9 - 4.2	0.10
Age (yrs)	1.06	1.01 - 1.12	0.03
2 Sex (male vs female)	1.8	0.8 - 4.1	0.13
Age (yrs)	1.07	1.01 - 1.14	0.02
Prophylaxis (yes/no)	0.5	0.2 - 1.0	0.06
3 Sex (male vs female)	4.1	1.2 - 14.4	0.03
Age (yrs)	1.03	0.94 - 1.12	0.54
Prophylaxis (yes/no)	0.3	0.1 - 1.1	0.07
LET	101	18 - 583	<0.0001
4 Sex (male vs female)	3.8	1.07 - 13.4	0.04
Age (yrs)	1.03	0.95 - 1.13	0.46
Prophylaxis (yes/no)	0.3	0.1 - 1.1	0.07
LET	75	11 - 495	<0.0001
Dipslide	1.6	0.5 - 5.4	0.46

LET = leukocyte esterase test.

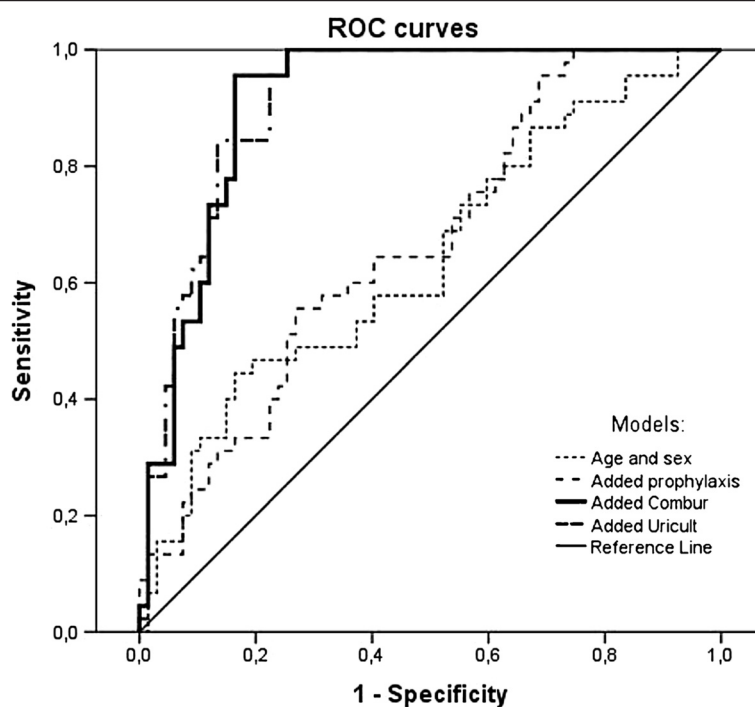


Figure 1 ROC curves of age, sex, Combur LET and Uricult dipslide.

Discussion

In this study of 112 spina bifida patients on clean intermittent catheterization, a negative LET excludes SBU in a home setting with a NPV of 96%. A negative dip slide alone was not effective to rule out SBU, and a negative LET together with a negative dip slide did not improve NPV. Both a positive LET and dip slide had a false positive rate of more than 20 percent compared to laboratory cultures, and cannot be used to diagnose SBU.

Leukocyte esterase test

Our results are consistent with other studies and meta-analyses, performed in the general pediatric populations [4,5,11-15]. Anderson et al. studied the LET in children with neurogenic bladders, combined with nitrite test,

with comparable results [16]. Adversely, in a similar study population, Liptak et al. found a lower NPV (83%) [17]. A significantly lower NPV for the LET (68%) was also seen in adults with spinal cord injury, which could be attributed to their lower threshold to diagnose SBU, with 10^2 colony forming units per milliliter of catheterized urine. In this study, the threshold was 10^4 cfu/ml [18].

In this study, boys had a significantly higher risk of SBU than girls. In a study by Seki et al., girls with myelodysplasia were more likely to get colonized with bacteria [19]. Age did not influence the risk for SBU in our population, in accordance with previous studies [20]. Prophylactic antibiotics tended to reduce the risk of SBU, as was shown in previous studies both in the general

Table 2 Predictive value of (combinations of) Leukocyte Esterase Test and dipslide for significant bacteriuria

Tests		Gold standard		Total	PPV in % (95% CI)	NPV in % (95% CI)
		Positive	Negative			
LET	Positive	43	17	60	72 (50 – 83)	
	Negative	2	50	52		96 (85 – 99)
Dipslide	Positive	29	11	40	73 (56 – 85)	
	Negative	16	56	72		78 (66 – 87)
Combi	Both positive	28	10	38	74 (57 – 87)	
	Not both positive	17	57	74		77 (66 – 86)
Combi	Not both negative	44	18	62	71 (58 – 82)	
	Both negative	1	49	50		98 (89 – 99)

population [21-23] and in patients with spina bifida [22,24,25]. Compared to the LET however, age, sex and the use of antibiotic prophylaxis are less reliable to predict SBU in children with spina bifida.

Dip slides

In this study, a negative dip slide with a NPV of 78% and a false negative rate of 22% could not rule out SBU. With a PPV of 73%, and a false positive rate of 27%, SBU cannot be diagnosed with a dip slide. In a recent study in 200 children with UTI symptoms and a positive LET, Uricult[®] Trio dip slides incubated in a laboratory incubator were compared with colony counts on blood agar plates. The sensitivity of 68%, and a false negative rate of 29% was comparable to this study [26]. Two major pitfalls were found: the small pin-point colonies of some *Enterococci* and most *Streptococci* on the CLED medium were mistaken for no growth, and transparent *E. coli* colonies are almost invisible. The untrained eye can be aided by the European Urinalysis Guidelines [27]. Inspection of the dip slide with a 12× magnifying glass, and comparing the incubated media with those of an unused dip slide. When growth of *E. coli*, *Enterococci*, and *Streptococci* on the 14 false negative Uricult[®] Duo dip slides was identified in this study, the false negatives would have decreased from 27% to 14%.

This study included only asymptomatic patients, and although the bacteriuria is significant, this has no clinical consequences such as therapeutic antibiotic administration. Compared to asymptomatic SBU, in clinical UTI leukocyturia is obligatory, most likely increasing both NPV and PPV of the LET, emphasizing the value of the LET. A further study to evaluate the reliability of the dip slide in children with spina bifida and clinical symptoms of UTI is recommended.

Conclusion

In home testing of spina bifida children on clean intermittent catheterization, leukocyte esterase testing can be used to exclude significant bacteriuria. Both leukocyte esterase test and dip slide are not sensitive enough to predict significant bacterial growth, and a agar plated culture should therefore be performed when either test is positive. Other than serving as transport medium, dip slide testing has no added to diagnose or exclude significant bacteriuria.

Abbreviations

CI: Confidence interval; CIC: Clean intermittent catheterization; CLED: Cystine-lactose-electrolyte deficient; LET: Leukocyte esterase test; NPV: Negative predictive value; PPV: Positive predictive value; SBU: Significant bacteriuria; UTI: Urinary tract infection.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

BZ, CU, CJ and JG participated in conception and design of this study. BZ, CU and MC performed the study, included participants and acquired the data. BZ, CU and CJ analyzed and interpreted the data. BZ wrote the original manuscript, CU, CV, MC, CJ, JK and JG revised the article and approved the final manuscript. All authors read and approved the final manuscript.

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