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OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Enhanced Urinalysis as a Screening Test for Urinary Tract Infection

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Pediatrics 1993;91;1196

TABLE 2. Laboratory Data of Patients With or Without Blue Sclerae*

Test	Patients With Blue Sclerae (n = 32)	Patients Without Blue Sclerae (n = 68)	*P* Value (Mann-Whitney Test)
Hemoglobin, g/dL	9.6 (8.2–11.2)	11.8 (9.8–13.2)	.0002
Serum iron, μmol/L	4.8 (3.3–9.9)	7.5 (4.5–14.3)	.03
Transferrin saturation, %	7.0 (4.0–14.5)	11.0 (7.0–20.0)	.005
Serum ferritin, μg/L	35.0 (13.0–150.0)	41.0 (24.0–110.0)	.62†

* Results are expressed as median (first and third quartiles).
† Not significant.

TABLE 3. Sensitivity and Specificity of Blue Sclerae in Iron Deficiency (IDA) Anemia According to Age

Age, y	Patients With IDA*	Patients With Blue Sclerae*	Sensitivity	Specificity
0.2–1	2/18 (11)	13/18 (72)	1.0	0.31
1–2	7/19 (37)	9/19 (47)	0.71	0.67
2–4	3/17 (18)	5/17 (29)	0.33	0.71
>4	4/46 (9)	5/46 (11)	0.25	0.90
All patients	16/100 (16)	32/100 (32)	0.56*†	0.73‡

* Results are expressed as No. (%).
† Ninety-five percent confidence interval: 0.30 to 0.80.
‡ Ninety-five percent confidence interval: 0.62 to 0.82.

at 0.87 (CI 0.74 to 0.95) and its specificity at 0.95 (CI 0.88 to 0.98),[4] in this pediatric population the levels of sensitivity and specificity were only 0.56 and 0.73, respectively.

The blue color of sclerae results from their thinness over underlying uveal tissue. Since iron is a cofactor in the synthesis of collagen,[4] iron deficiency may interfere with collagen synthesis and lead to abnormally thin sclerae. On the other hand, thinness of the sclerae may be a normal characteristic in young children, which explains why blue sclerae are found so commonly in infants and why their association with IDA is weaker than in adults. Despite our confirmation of this association, we conclude that blue sclerae do not constitute a reliable indicator of IDA in young children.

ACKNOWLEDGMENT

This study was supported by a research grant from Mepha Pharma (Switzerland).

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ABBREVIATIONS. UTI, urinary tract infection; WBC, white blood cell; hpf, high-power microscopic field; CHP, Children's Hospital of Pittsburgh; CFU, colony-forming units.

Urinary tract infection (UTI) is a common and important clinical problem in infants and young children. UTI is often suspected on the basis of results of microscopic urinalysis; accordingly, it is important that its results be as reproducible, accurate, and easily interpretable as possible. A positive urinalysis allows early detection and treatment of UTI, while a negative urinalysis can potentially eliminate the cost of expensive hospitalization for intravenous administration of antibiotics, the current standard treatment of UTI in young febrile children.

In pediatric primary care facilities, microscopic urinalysis often is performed using centrifuged urine and reported as the number of white blood cells (WBCs) or bacteria per high-power microscopic field (hpf). In preparation for a 4-year randomized clinical trial comparing oral and intravenous antimicrobials for treatment of UTI in young febrile children, a

Received for publication Aug 28, 1992; accepted Feb 8, 1993.

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method was sought to improve the accuracy of urinalysis in identifying positive urine cultures. Catheterized urine specimens were used to compare the sensitivity, specificity, and predictive values of the urinalysis currently used (WBCs and bacteria per hpf in centrifuged urine) with an enhanced urinalysis of uncentrifuged urine that observed the number of WBCs per cubic millimeter in a Neubauer hemocytometer and the presence of any bacteria in a Gram-stained smear.

METHODS

All urine specimens obtained by bladder catheterization in the emergency department of the Children's Hospital of Pittsburgh (CHP), from December 1991 through August 1992, were examined using both the standard (currently used) urinalysis and the enhanced urinalysis. All urinalyses were performed in a certified clinic-based laboratory. For the standard urinalysis, specimens greater than 1 mL were centrifuged at 2000 rpm for 10 minutes, and those with less than 1 mL were analyzed without centrifugation. Unstained specimens were examined microscopically for pyuria (reported as number of WBCs per hpf) and for bacteriuria (reported as none, trace, light, moderate, or heavy amounts of bacteria per hpf). The enhanced urinalysis was performed, usually by the same technician, on a specimen of uncentrifuged urine. Urine was drawn into a Neubauer hemocytometer by capillary action. White blood cells were counted on each side of the chamber, averaged, and multiplied by 1.1 to obtain a total cell count per cubic millimeter. Smears were prepared using 2 drops of uncentrifuged urine on a sterile slide within a standardized marked area of 1.5 cm diameter, air dried, and Gram-stained.

Quantitative urine cultures were performed in the CHP Microbiology Laboratory. A loop calibrated to deliver approximately 0.001 mL was used to inoculate plates containing sheep blood agar, Columbia CNA agar, and MacConkey agar. All plates were incubated at 35° to 37°C and examined at 24 and 48 hours for colony count and bacterial identification.

For the standard urinalysis, pyuria was defined as at least 5 WBCs per hpf and bacteriuria as the presence of any bacteria per hpf. For the enhanced urinalysis, pyuria was defined as at least 10 WBCs per cubic millimeter and bacteriuria as any bacteria per 10 oil immersion fields on a Gram-stained smear. Both standard and enhanced urinalyses were considered positive when both pyuria and bacteriuria were present. A positive urine culture, defined as growth of a single pathogen at a concentration of at least 50 000 colony-forming units (CFU) per milliliter, was considered the validating standard.

Sensitivity, specificity, and positive and negative predictive values were calculated for both methods of microscopic urinalysis. Interobserver reliability for interpreting results of standard and enhanced urinalyses was assessed independently for two laboratory technicians who observed 50 consecutive urine specimens.

RESULTS

Catheterized urine specimens from 698 study eligible children were analyzed. Sensitivity, specificity, and positive and negative predictive values are presented in the Table. The enhanced urinalysis showed significantly greater sensitivity and positive predictive value (84.5% and 93.1%, respectively) than the standard urinalysis (65.6% and 80.8%, respectively) (test for differences between proportions; $P < .05$). Total WBC counts on the two areas of the hemocytometer chamber were found to be almost identical; therefore, a count of only one area was found to be satisfactory. The volume of 73 urine specimens was less than 1 mL, and thus standard urinalysis was performed on uncentrifuged urine. Because sensitivity and positive predictive value were only slightly higher (but not approaching values obtained with the enhanced urinalysis) when these standard uncentrifuged specimens were compared with centrifuged specimens, the results of all standard urinalyses were combined.

Interobserver agreement for the independent interpretations of two laboratory technicians of urinalysis results (test positive = pyuria and bacteriuria as defined above) of 50 consecutive urine specimens was 100% for 25 specimens examined by the standard urinalysis ($\kappa = 1$) and 100% for the 25 specimens examined by the enhanced urinalysis ($\kappa = 1$).

DISCUSSION

The presence of pyuria alone or bacteriuria alone on microscopic urinalysis has been found to be a poor predictor of positive urine cultures. Kass,[1] in 1956, defined pyuria as at least 5 WBCs per hpf on centrifuged urine and found it to be present in a third to half of patients with at least 100 000 CFU/mL, but only in 2% of those with bacterial counts of less than 100 000 CFU/mL. He concluded that pyuria was of value diagnostically only when it was clearly present and that its absence should not be interpreted as absence of bacteriuria. Similar findings had been reported by other authors.[2–4] A recent study by Crain and Gershel[5] of 442 febrile infants younger than 8 weeks of age, who underwent bladder catheteriza-

TABLE. Sensitivity, Specificity, and Predictive Values of Standard Versus Enhanced Urinalysis*

	Standard			Enhanced		
	Cx +	Cx −	Total	Cx +	Cx −	Total
Test +	21	5	26	27	2	29
Test −	11	661	672	5	664	669
Total	32	666	698	32	666	698
Sensitivity		65.6%			84.5%†	
Specificity		99.2%			99.7%	
Positive predictive value		80.8%			93.1%†	
Negative predictive value		98.4%			99.3%	
Prevalence		4.6%			4.6%	

* Sensitivity, specificity, positive predictive value, and negative predictive value of standard and enhanced urinalysis for positive urine culture (Cx) defined as growth of a single pathogen at a concentration of at least 50 000 colony-forming units per milliliter. Standard urinalysis test positive is defined as at least 5 white blood cells per high-power microscopic field *and* any bacteria in a centrifuged urine specimen. Enhanced urinalysis test positive is defined as at least 10 white blood cells per cubic millimeter *and* any bacteria in Gram-stained uncentrifuged urine.
† $P < .05$.

tion or suprapubic aspiration as part of an evaluation for sepsis, reported a low sensitivity (48%) of microscopic urinalysis (either at least 5 WBCs per hpf in centrifuged urine or any bacteria per hpf in uncentrifuged urine) for identifying infants with positive urine cultures. In a study of the prevalence of UTI in an unselected population of febrile infants, who were patients at the CHP emergency department from February 1990 through January 1991, sensitivity, specificity, and predictive value of bacteria and WBCs in the urine for a positive urine culture (≥10 000 CFU/mL) were determined for 856 catheterized urine specimens.[6] Approximately 10% of these specimens had a volume of less than 1 mL and were examined without centrifugation. There was no significant difference between centrifuged and uncentrifuged urine with regard to the sensitivity of pyuria and bacteriuria for positive urine culture. The optimum values for predicting a positive urine culture were determined: five or more WBCs per hpf and any bacteria per hpf. Presence of pyuria alone was found to be relatively insensitive (54%). Had urine culture been omitted because of the absence of pyuria, nearly half of the UTIs would not have been diagnosed. Presence of bacteriuria alone was more sensitive (86%), but not specific enough (63%) to identify infants with UTI accurately.

Greater accuracy of microscopic urinalysis for predicting positive urine cultures has been achieved by standardizing methods and by combining results of tests for pyuria and bacteriuria in criteria for test positivity. Dukes,[7,8] in 1928, described more accurate and reproducible urinalysis results by counting WBCs in uncentrifuged urine using a hemocytometer. This method was recently used by Stamm,[9] who defined pyuria as more than 10 WBCs per cubic millimeter. Pyuria was found in more than 95% of symptomatic adult patients with bacteriuria of more than 1000 CFU/mL, but in less than 1% of asymptomatic patients without bacteriuria. Corman[10] studied 100 children being evaluated for possible UTI in an outpatient setting. Presence of at least 50 WBCs per cubic millimeter in uncentrifuged urine specimens had a sensitivity of 64% and a specificity of 91% relative to positive culture (defined as at least 10^5 CFU/mL).[10] With respect to bacteriuria, Gram-stained smears of uncentrifuged urine have also been shown to enhance accuracy in identifying positive urine cultures.[11–13]

Microscopic urinalysis in pediatric primary care facilities is often performed on centrifuged specimens, and reported as cells or bacteria per hpf. The method of urinalysis reported here showed improved sensitivity and positive predictive value for identifying patients with positive urine culture when hemocytometer counts and Gram-stained smears were performed on uncentrifuged specimens and when criteria for test positivity included both pyuria and bacteriuria. The hemocytometer allows counting of a fixed volume of urine and facilitates accurate counting by providing a small, marked visual field and uniform illumination. This method reduces variability in results by avoiding the concentration and resuspension of solid elements attained by centrifugation. Additionally, standardization of the Gram-stain procedure (particularly number of drops of urine, diameter of the smear, and number of fields counted) increases diagnostic accuracy.

Wettergreen et al,[14] in a survey of 3581 infants, reported a mean point prevalence of asymptomatic bacteriuria of 0.57% (range 0.17% to 1.56%, the latter value in uncircumcised boys aged <2 months). If approximately this proportion prevailed in the 698 children reported in the present study, asymptomatic bacteriuria incidental to but not the cause of febrile illness might have been present in approximately 4 patients, who therefore would have had positive urine cultures but not necessarily pyuria. This assumption is consistent with the findings shown in the Table, in which 5 infants had positive urine cultures but failed to meet the positive test criteria of presence of both pyuria and bacteriuria.

The enhanced urinalysis described in this report is simple and results are readily available. The greater sensitivity and positive predictive value of the enhanced compared with the standard urinalysis substantially increase its accuracy in diagnosing UTI. Given the high positive predictive value (93.1%) of both pyuria and bacteriuria, their presence should prompt commencement of antimicrobial therapy. The current recommendation for the management of febrile children with UTI is hospitalization for intravenous administration of antimicrobials. Similarly, negative test results correlate in 99.3% of instances with negative urine cultures. In febrile children in whom bacteriuria is not associated with pyuria, the source of the fever may not be UTI; accordingly, indications for antimicrobial therapy remain to be determined.

ACKNOWLEDGMENTS

This project was supported, in part, by BRS grant SO7RR05507-28 from the Biomedical Research Support Grant Program, Division of Research Resources, and General Clinical Research Center grant 5M01RR00084, both from the National Institutes of Health, Bethesda, MD.

We thank Kenneth D. Rogers, MD, for his advice in the design and analysis of this project and in the preparation of the manuscript. We also thank the Children's Hospital of Pittsburgh's house-staff and staff of the ACC-Stat-Lab for their invaluable assistance.

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Phenolphthalein-Induced Fixed Drug Eruption: A Cutaneous Complication of Laxative Use in a Child

Drug eruptions are a common dermatologic problem faced by pediatricians. Among the most distinctive of these is the fixed drug eruption, a cutaneous inflammatory reaction manifested by solitary or multiple, well-defined, erythematous macules that may become bullous.[1,2] Lesions usually occur within a few hours of ingesting the drug, characteristically recur in the same location with each subsequent dose, and leave residual hyperpigmentation. To illustrate the importance and unique features of this unusual reaction, we report the case of a child who experienced a recurrent fixed drug eruption induced by phenolphthalein-containing, nonprescription laxatives.

CASE REPORT

An 8-year-old African-American girl was brought to the Dermatology Clinic for evaluation of pruritic and occasionally swollen "dark spots" that had been present on her face and arms for months. The patient and her mother denied the use of topical or systemic medications, including laxatives. The physical examination revealed a well-defined, hyperpigmented macule that extended from the upper lip approximately halfway to the nose. Similar lesions were located on the volar aspects of the wrists bilaterally and on the fingers. A diagnosis of postinflammatory hyperpigmentation of uncertain etiology was made and therapy with 1% hydrocortisone was begun.

The patient returned to the Dermatology Clinic 4 months later for evaluation of lip swelling that had begun 48 hours earlier. At this visit, the patient's mother reported administering Ex-Lax to the child occasionally during the past year and that a dose had been given prior to the onset of the child's current lip swelling. On physical examination there was edema of the upper lip which, over the succeeding 4 days, developed a central bluish discoloration with well-defined, marked hyperpigmentation at the border (Fig 1). Areas of dark-brown, macular discoloration were observed on the volar aspects of both wrists (Fig 2). These sites were identical in location to those previously involved.

Received for publication Nov 13, 1992; accepted Feb 9, 1993.
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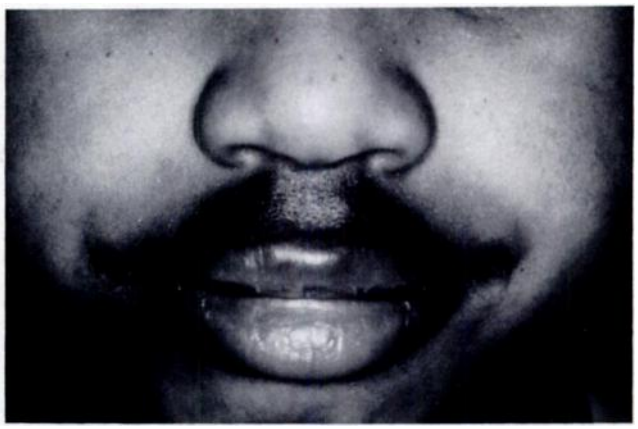

Fig 1. The upper lip and infranasal area, with marked hyperpigmentation.

In view of the distinctive clinical findings and history of phenolphthalein (present in Ex-Lax) ingestion, a diagnosis of fixed drug eruption was made and the mother was advised to discontinue the administration of laxatives to the child. The lesions resolved, but returned 2 months later following the use of Feen-A-Mint, another phenolphthalein-containing laxative. The patient's mother was advised again to avoid the administration of phenolphthalein-containing products to her daughter.

DISCUSSION

Fixed drug eruption represents a unique form of drug allergy in which characteristic skin lesions recur at the same location each time an offending agent is ingested. This form of cutaneous reaction is observed most commonly in adults but may occur in children or adolescents.[2] Clinically, fixed drug eruptions present as solitary or multiple erythematous macules that often evolve into edematous plaques.[1,2] In intermediate stages they may become bullous and, therefore, must be differentiated from other bullous disorders including acute allergic contact dermatitis, bullous impetigo, bullous erythema multiforme, trauma resulting from a thermal burn, or other less common diseases such as epidermolysis bullosa simplex. Healing of lesions occurs over 10 to 14 days and leaves hyperpigmentation that may increase in intensity with subsequent exposures to the offending agent. Occasionally, however, fixed drug eruptions

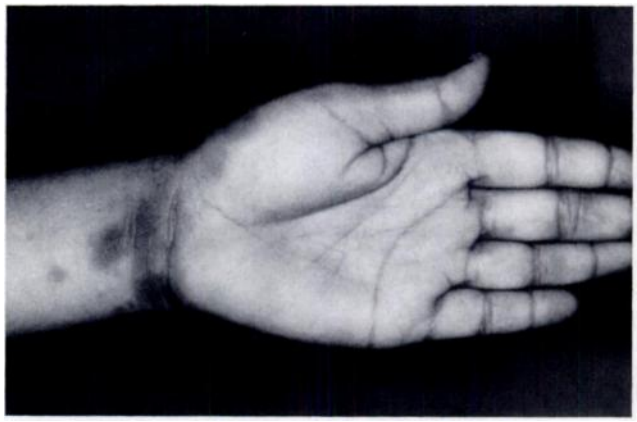

Fig 2. The volar aspect of the wrist and thenar eminence of the hand, with macular hyperpigmentation.

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