

# Accurate and fast diagnostic algorithm for febrile urinary tract infections in humans

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## ABSTRACT

**Background:** The urine dipstick that detects nitrite and leukocyte esterase, and urine sediment is commonly used to diagnose or exclude urinary tract infections (UTIs) as the source of infection in febrile patients admitted to the emergency department of Dutch hospitals. However, the diagnostic accuracy of the urine dipstick and urine sediment has never been studied in this specific situation.

**Methods:** Urinary samples of 104 febrile consecutive patients were examined. Urine culture with  $\geq 10^5$  colonies/ml of one or two known uropathogen was used as the gold standard. The diagnostic value of the urine dipstick, urine sediment and Gram stain at various cut-off points was determined and used to develop a new diagnostic algorithm. This algorithm was validated in a new group of sepsis patients based on systemic inflammatory response syndrome (SIRS) criteria.

**Results:** A positive nitrite on the urine dipstick (specificity 99%) rules in UTI. This is the first step of our diagnostic algorithm. The second step is to exclude UTI by absence of bacteria in the urine sediment (sensitivity 94%). The third and last step is the number of leucocytes/high-power field (hpf) in the urine sediment. Less than 10 leucocytes/hpf makes UTI unlikely whereas  $\geq 10$  leucocytes/hpf indicates UTI. In contrast to urine dipstick and/or urine sediment results alone, our algorithm showed both a high sensitivity (92%) and specificity (92%) and was validated in a new sepsis population.

**Conclusion:** Our accurate and fast diagnostic algorithm, which combines the selective results of urine dipstick and urine sediment, can be easily used to diagnose UTI in febrile patients at the emergency department of Dutch hospitals.

## KEYWORDS

Diagnostic algorithm, urinary tract infection, fever, emergency department, urine sediment, urinary dipstick, Gram stain

## INTRODUCTION

Urinary tract infection (UTI) is one of the most common infections in humans and is a frequent cause of hospitalisation.<sup>1</sup> In lower UTIs such as urethritis and cystitis most patients complain of dysuria. UTIs with signs of tissue invasion (prostatitis or pyelonephritis) can be more difficult to recognise because of the absence of specific symptoms such as flank pain or abdominal pain, especially in the elderly.<sup>2</sup> Pyelonephritis can lead to severe sepsis or septic shock and can be life-threatening.<sup>3,4</sup> Early goal-directed treatment of sepsis or septic shock improves survival of patients with severe infection.<sup>5,6</sup> Therefore, accurate diagnostics to demonstrate or exclude UTIs in febrile patients presenting to the emergency department are very important.

The urine culture is worldwide accepted as the gold standard in diagnosing urinary tract infections.<sup>7-9</sup> It is the commonly used method that can provide detailed information about the pathogen and its sensitivity to different antibiotics. However, a urine culture is costly and takes at least 24-48 hours. The urine dipstick that detects nitrite and leukocyte esterase in the urine is the standard procedure to diagnose UTI in Dutch family practice (NHG standard). UTI suspicion by the patient and a positive nitrite test were the strongest indicator of an uncomplicated UTI in general practice.<sup>10</sup> However, the diagnostic value of the urine dipstick depends on the population in which it is used and varies widely.<sup>11-16</sup> Other

available tests are microscopic examination of the urine sediment and Gram stain. These are both labour intensive and therefore costly methods. The diagnostic value of the urine sediment is variable as it depends on many factors including the expertise of the analyst.<sup>7,12,14,17</sup> Assessing a Gram stain seems to be a more sensitive and specific and therefore a better method than assessing the urine dipstick or urine sediment.<sup>17-20</sup> However, the Gram stain is rarely used as a diagnostic tool in diagnosing UTI because it takes too long before the results are available.

At the emergency department of our and many other Dutch hospitals, the urine dipstick is used to diagnose or exclude UTI as the source of infection in febrile patients. However, the diagnostic value of the urine dipstick has never been studied in this specific population.<sup>11</sup> Therefore, we determined the diagnostic accuracy of urine dipstick and compared it with the urine sediment and Gram stain in febrile patients presenting to the emergency department of our hospital. Based on these results we developed a new algorithm to diagnose UTI fast and accurately in febrile patients admitted to the emergency department.

## MATERIAL AND METHODS

### Setting

This was a prospective cohort study, performed at the emergency department of Isala in Zwolle. Isala is one of the largest non-academic hospitals in the Netherlands. Over 5000 internal medicine patients present annually to the emergency department of Isala.

### Study population

Consecutive patients older than 18 years who were admitted to the internal medicine emergency department and had fever  $> 38.0$  °C on admission or had fever  $> 38.0$  °C at home on the day of presentation were included. Patients who had used antibiotics during the past 48 hours, had an indwelling catheter or had chemotherapy-induced leucocytopenia ( $< 4.0 \times 10^9$  cells/l) at presentation were excluded. The inclusion period started on 14 December 2009 and ended on 28 March 2010 (15 weeks). The medical ethics committee of our hospital declared no objections.

### Clinical assessment

Patient characteristics were obtained from the electronic patient file. The junior doctor on duty noted the health history, current medication, symptoms of patients and physical findings in the medical record. We registered diabetes mellitus when patients were treated with glucose-lowering medications or diabetes was mentioned in the medical record. Patients with immunosuppressive therapy (i.e. prednisone or chemotherapy) were classified

as immunocompromised hosts. C-reactive protein and leukocyte counts were recorded. Blood cultures were performed when indicated by the physician on duty. Whether patients had systemic inflammatory response syndrome (SIRS) was determined. SIRS was defined by the presence of at least two of the following symptoms: body temperature greater than 38.5 °C, heart rate greater than 90 beats per minute, respiratory rate greater than 20 breaths per minute, an arterial partial pressure or carbon dioxide less than 4.3 kPa and white blood cell count greater than  $12 \times 10^9$  cells/l.

### Urinalysis

The emergency department nurse collected urine and divided each sample into two containers. The first container was sent to the clinical chemistry laboratory where urine dipstick and urine sediment were performed. Laboratory professionals unaware of the other test results performed all tests according to our standard hospital protocols. The Aution MAX AX-4280® (Iris Diagnostics, Chatsworth) was used to perform the Uriflet® dipstick (ARKRAY Europe B.V, Amstelveen). Microscopic analysis of the urine sediment was performed after centrifugation of 10 ml urine at 2000 rpm for five minutes and decantation of the supernatant. A preparation was assessed and the number of leucocytes and erythrocytes (magnification 40 x 10) per high-power field (hpf) was determined. Bacteria were scored semi-quantitatively because they were too small to count.

The second container, cooled at 4 °C in the refrigerator, was sent by courier to the microbiology laboratory. Gram staining and urine culture were performed. A Gram stain was made of uncentrifuged urine. The presence of leucocytes and erythrocytes was counted at 10 x 10 magnification. The shape (cocci or rods), colour (Gram positive or Gram negative) and the number of bacteria per hpf were determined at a magnification of 100 x 10 in a semiquantitative way. *Table 1* shows possible results of the used tests.

For urine cultures, 10 µl urine was placed on two different Agars (a chromogenic agar and a sheep blood agar). These plates were incubated at 35 °C and read for growth after at least 24 hours. Isolated organisms were reported as the number of colony-forming units per millilitre (CFU/ml) urine. A specimen that grew  $\geq 10^5$  CFU/ml of one or two uropathogens was defined as a positive urine culture. UTI was defined as a positive urine culture and used as the gold standard for UTI.<sup>8,9,21</sup>

### Discharge diagnosis

The focus for fever was based on clinical, radiological or microbiological evidence. When patients had a positive urine culture but another explanation for the fever (e.g. pneumonia), UTI was classified as a lower URI or could

**Table 1.** Possible results of urinary dipstick, urine sediment and Gram stain

Test	Determination	Count	Value
Urine dipstick	Nitrite	< 0.08 mg/dl	-
		> 0.08 mg/dl	+
	Leukocyte esterase	< 75 leu/ $\mu$ l	-
		75 leu/ $\mu$ l	+
		250 leu/ $\mu$ l	++
	500 leu/ $\mu$ l	+++	
Urine sediment	Leucocytes	< 5 /hpf	
		> 5 /hpf	
		> 10/hpf	
		> 20 /hpf	
		> 40 /hpf	
	Bacteria		-
			+
			++
			+++
			+++
Gram stain	Leucocytes	0-1 /hpf	-
		2-5 /hpf	+
		6-15 /hpf	++
		> 15 /hpf	+++
	Bacteria	0	-
		0-1	trace
		2-15	+
		16-100	++
	> 100	+++	

Bacteria in the urine sediment were counted semi-quantitatively; hpf = high-power field.

be due to asymptomatic bacteriuria. When UTI was the only focus for fever we diagnosed febrile UTI. Urosepsis was diagnosed in patients with febrile UTI who met SIRS criteria or had a positive blood culture with the same pathogen as the urine culture.

#### Statistical analysis

To evaluate the diagnostic value of the urine dipstick, urine sediment and Gram stain we extracted 2 x 2 tables of true-positive, false-positive, false-negative and true-negative results at various cut-off points. The urine culture was used as the gold standard for UTIs. From each of these tables we computed sensitivity, specificity, positive predictive value and negative predictive value. Furthermore positive and negative likelihood ratios (LR+ and LR-) and the diagnostic odds ratio (DOR) had been calculated:

LR+ = Sensitivity/ (1-specificity)

LR- = (1-sensitivity)/ specificity

DOR = LR+ / LR-

A LR+ above 10 or a LR- below < 0.1 are considered to provide strong evidence to rule in or rule out diagnoses respectively. The highest DOR has the highest diagnostic accuracy.

#### Diagnostic algorithm and validation study

Based on our results we developed a diagnostic algorithm in which we combined different results of urine dipstick and urine sediment with high sensitivity or specificity. The diagnostic value of our diagnostic algorithm was calculated. To confirm the diagnostic value of our algorithm a validation study was performed in a new sepsis population. Sepsis patients are a clearly defined group that is easily recognised in the emergency department and an important clinical group of severely ill patients. In addition, not all septic patients are febrile, for example elderly patients. Therefore we validated our algorithm in a new group of septic patients. All patients presenting to the emergency department with at least two SIRS criteria and complete data were included between 1 January 2011 and 31 December 2011. We used the same exclusion criteria as the original population and performed the same set of tests as mentioned above. We calculated the diagnostic values of our proposed diagnostic algorithm.

## RESULTS

In the inclusion period 181 presentations because of fever were seen at the emergency department (table 2). Twenty-seven patients were not included because of incomplete data or incorrect inclusion. Fifty patients were excluded because of the following reasons: chemotherapy-induced leucocytopenia at admission (n = 13), use of antibiotics in the past 48 hours (n = 37) and/ or use of indwelling catheters (n = 14). The results of the remaining 104 patients were analysed. The patient characteristics are shown in table 2.

The study population included more males (58%) than females; 60 patients (58%) were diagnosed with SIRS. The median temperature at presentation was 38.7 °C (IQR 38.4-39.5 °C) and the median C-reactive protein value was 60 mg/ml (IQR 15-168 mg/ml).

Of the 97 blood cultures performed, 23 were positive. A total of 31% of the patients (32/104) had a positive urine culture with 34 pathogens. All calculations were done using this group (n = 32). *E. coli* was most often cultured (22 times, 69%). Three patients had a possible other focus of infection and were diagnosed with lower UTI or asymptomatic bacteriuria. Nineteen out of 29 patients with febrile UTI had urosepsis defined as positive blood culture

**Table 2.** Patient characteristics of febrile patients presented to the emergency department (n = 104)

	N	%
Gender		
Male	60	57.7
Female	44	42.3
Diabetes mellitus	24	23.1
Immunocompromised host	26	25.0
SIRS at admission	60	57.7
	<b>Median</b>	<b>Interquartile range</b>
Age (years)	62	49-78
Temperature (°C)	38.7	38.4-39.5
CRP (mg/l)	60	15-168
Leukocyte count (x 10 <sup>3</sup> /mm <sup>3</sup> )	11.2	8-14.5

CRP = C-reactive protein; SIRS = systemic inflammatory response syndrome.

(8 patients) or  $\geq 2$  SIRS criteria. Of the 29 patients with febrile UTI only seven patients (24%) had dysuria of which two patients had dysuria and flank pain. Six patients had flank pain without dysuria (21%).

#### Evaluation of tests

The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio and the diagnostic odds ratio of the different tests are summarised in *table 3* (urine sediment and urine dipstick) and *table 4* (Gram stain).

#### Urine dipstick results

The sensitivity of a positive nitrite was very low (28%) but its specificity was very high (99%). Leukocyte esterase 1+ had a sensitivity of only 75% and a specificity of 86%. At leukocyte esterase 3+, the sensitivity was 59% and the specificity 94%. The combination of nitrite (first diagnostic step) and leukocyte esterase (second diagnostic step) resulted in a sensitivity of 75% at leukocyte esterase 2+ and only 66% at leukocyte esterase 3+.

#### Urine sediment results

The sensitivity and negative predictive value of bacteria in the urine sediment were very high: both 96%. In contrast, the specificity and positive predictive value were low: 47% and 50%, respectively.

The sensitivity and negative predictive value of leucocytes/hpf in the urine sediment was comparable with the leukocyte esterase detected by the urine dipstick (77% and 87%) but the specificity was higher. Raising the cut-off point to  $\geq 10$  leucocytes/hpf did not reduce the sensitivity but increased the specificity to 94%. Therefore, this is the best cut-off point. At the cut-off point  $\geq 40$  leucocytes/hpf, the specificity and positive predictive value were 100%.

#### Gram stain results

The presence of bacteria in the Gram stain had a high sensitivity and negative predictive value: 94% and 97% respectively. At bacteria 2+ and 3+, the specificity (93-99%), positive predictive value (85-94%) and positive likelihood ratio (12.6-55.6) were also high. Diagnostic values of leucocytes were lower than for bacteria in the Gram stain.

**Table 3.** Sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratio and diagnostic odds ratio of urinary dipstick and urine sediment at various cut-off points in febrile patients admitted to the emergency department

Test	Determination	Cut-off point	Sens	Spec	PPV	NPV	LR +	LR-	DOR	
Urine dipstick	Nitrite	1+	28%	99%	90%	76%	20.3	0.73	27.8	
		LE	1+	75%	86%	71%	89%	5.4	0.29	18.6
			2+	69%	92%	79%	87%	8.3	0.34	24.2
			3+	59%	94%	83%	84%	10.7	0.43	24.8
Urine sediment	Bacteria	1+	96%	47%	50%	96%	1.8	0.08	22.0	
		2+	65%	81%	65%	81%	3.4	0.43	8.0	
		Leukocytes	> 5	77%	85%	74%	87%	5.2	0.27	19.0
		> 10	77%	94%	87%	88%	12.1	0.25	48.9	
		> 20	69%	96%	90%	85%	16.3	0.32	50.6	
		> 40	46%	100%	100%	77%	$\infty$	0.54	$\infty$	

LE = leukocyte esterase; sens = sensitivity; spec = specificity, PPV = positive predictive value; NPV = negative predictive value; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; DOR = diagnostic odds ratio.

**Table 4.** Sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratio and diagnostic odds ratio of the gram Stain at various cut-off points in febrile patients admitted to the emergency department

Test	Determination	Cut-off point	Sens	Spec	PPV	NPV	LR+	LR-	DOR
Gram stain	Bacteria	1+	94%	81%	68%	97%	4.8	0.08	62.1
		2+	88%	93%	85%	94%	12.6	0.13	93.8
		3+	77%	99%	94%	93%	55.6	0.23	241.4
	Leukocytes	1+	88%	75%	61%	93%	3.5	0.17	21.0
		2+	63%	88%	69%	84%	5.0	0.43	11.7
		3+	47%	96%	83%	80%	11.3	0.55	20.3

Sens = sensitivity; spec = specificity; PPV = positive predictive value; NPV = negative predictive value; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; DOR = diagnostic odds ratio.

### Diagnostic algorithm

Based on our results of urine dipstick and urine sediment we developed a new diagnostic algorithm as shown in figure 1. The first diagnostic step is the nitrite test with high specificity to rule in UTI when positive. When nitrite is negative, a UTI can be ruled out by the absence of bacteria in the urine sediment. A UTI is likely if bacteria and  $\geq 10$  leucocytes/hpf are present in the sediment, while when less than 10 leucocytes/hpf are present UTI is unlikely. The sensitivity of this strategy is 92%, the negative predictive value 96%, the specificity 92% and the positive predictive value 85%. The diagnostic odds ratio was very high at 128.

### Validation of our diagnostic algorithm

During the validation study period 94 patients who met our sepsis protocol criteria were included in the study and 33 patients were excluded. Of the 61 analysed patients, 22 patients had a UTI. The diagnostic algorithm had

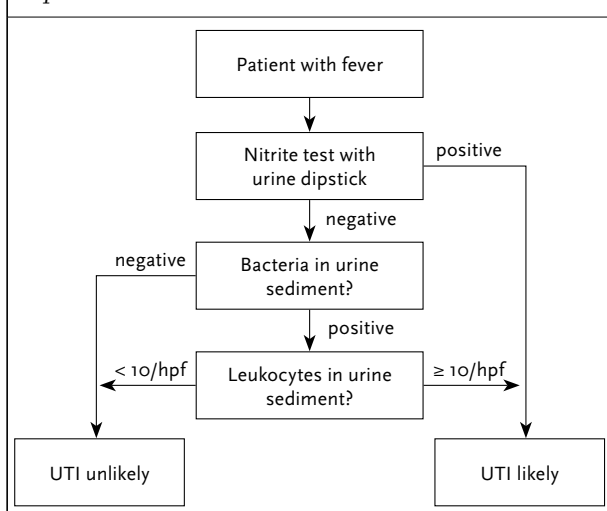
a sensitivity of 73%, specificity 100% (no false-positive results). This resulted in an infinite positive likelihood ratio and diagnostic odds ratio. This relative low sensitivity is caused by six false-negative results. Analysis of these results showed that five out of six patients had a positive urine culture but with another focus of fever. Almost all (16 out of 17) clinically relevant UTIs were detected when using our diagnostic algorithm with a very high specificity and positive predictive value.

### DISCUSSION

The results of our study show that selective combining of urine dipstick and urine sediment has very high diagnostic accuracy in diagnosing UTI in febrile patients admitted to the emergency department. To our knowledge a diagnostic algorithm for diagnosing febrile UTI has never been described before. Most guidelines for febrile UTI or complicated UTI concentrate on the treatment of febrile UTI. In our opinion, before goal-directed empirical antibiotic treatment can be given, an accurate diagnostic procedure should first be performed.

The urine dipstick had limited diagnostic value in diagnosing febrile UTI in our study population. Only a positive nitrite indicates UTI because of the high specificity of the test, as previously reported.<sup>11,13</sup> Therefore, a positive nitrite was incorporated as the first step in our diagnostic algorithm. The sensitivity of nitrite was surprisingly low (28%). Earlier studies showed higher sensitivities of 40-57%.<sup>11,22</sup> This difference can be explained because we did not collect early morning urine, but examined urine on presentation to the emergency department, usually during the day or at night. Gram-negative bacteria containing nitrate reductase has to be in the bladder for at least four hours to convert nitrate into nitrite. In addition, not all Gram-negative bacteria contain nitrate reductase. The leukocyte esterase

**Figure 1.** New diagnostic algorithm for febrile urinary tract infections in patients admitted to the emergency department



test, the other diagnostic test of the urine dipstick, did not contribute significantly to the diagnostic process in our study population. A negative leukocyte esterase reaction cannot exclude UTI and only 3+ leukocytes/hpf indicate UTI. This corresponds with previous studies that showed very variable sensitivity (48-86%) and specificity (17-93%) for this test.<sup>11,13,22</sup> The presence of bacteria in the urine sediment had a high sensitivity, thus absence of bacteria excludes UTI with high accuracy. Therefore, we selected the absence of bacteria as the second step in our diagnostic algorithm. The specificity of leukocytes/hpf in the urine sediment appeared to be higher than the leukocyte esterase reaction of the urine dipstick while sensitivity is equal. The third and last step of our diagnostic algorithm includes < 10 leukocytes/hpf to exclude and  $\geq 10$  leukocytes/hpf to indicate UTI. Our diagnostic algorithm had both a high sensitivity (92%) and specificity (92%) and is clearly superior to the individual urine dipstick and urine sediment tests. Also, the combination of the nitrite and leukocyte esterase reaction of the urine dipstick at 2+ or 3+ has a much lower sensitivity (75 and 66% respectively) and will miss a significant number of UTIs. Therefore, our algorithm is based on tests with either high sensitivity or specificity in order to exclude or include UTI with high accuracy. It is necessary to perform both diagnostics (urine sediment and urine dipstick) in clinical practice when using our fast and accurate diagnostic algorithm.

Our diagnostic algorithm (*figure 1*) was validated in a new sepsis population. The specificity and positive predictive value were even higher than in the original study due to the absence of false-positive results. Applying the diagnostic algorithm in this population predicted febrile UTI very accurately and missed only one clinically relevant UTI. Therefore, our diagnostic algorithm will help to improve the diagnostic procedure and can be easily used in daily practice in the management of febrile and septic patients in the emergency department of Dutch hospitals. Demonstration of bacteria in the Gram stain had the highest sensitivity and specificity. This has previously been reported both in adult patients<sup>17</sup> and children<sup>18</sup>. The higher sensitivity and specificity of the Gram stain for the demonstration of bacteria are due to the fact that stained bacteria are better visible at microscopic examination. However, Gram staining takes much more time and is not available 24 hours/day in the emergency department of Dutch hospitals. In addition, our diagnostic algorithm is a much quicker alternative to the Gram stain with almost equal diagnostic value. Possibly new quick techniques, such as flow cytometry, which could automatically quantify the number of bacteria in urine will be a good alternative for examining a Gram-stained urine preparation.

We selected fever as the major inclusion criterion because most admissions to the emergency department in the Netherlands are due to fever without an evident focus.<sup>23</sup>

Our study shows that specific signs of a complicated UTI such as dysuria and flank pain are only present in a selection of patients with febrile UTI, as reported before.<sup>24</sup> We only excluded patients with an indwelling catheter (almost always positive culture), use of antibiotics (negative urinary culture despite UTI) and leucocytopenia (possible absence of leucocyturia despite UTI), because this negatively influences the diagnostic values. Earlier studies excluded patients with diabetes, immunodeficiency disorders or patients who were unable to provide a reliable history.<sup>12</sup> Because a large proportion of the internal medicine patient population do have these comorbidities (*table 2*), we choose to include these patients in our study. We conclude that our inclusion and exclusion criteria represent a significant and clinically important population that is frequently admitted to the emergency department. A limitation of our study is the relatively small number of patients. A larger study population could give more reliable study results. We excluded patients on antibiotics during the past 48 hours, with an indwelling catheter or with leucocytopenia on presentation. This means that our diagnostic algorithm cannot be used in these patient populations. A positive nitrite would still indicate UTI in leucocytopenic patients. When nitrite is negative we advise to assess a Gram stain for the presence of bacteria. To our knowledge there are no good methods to diagnose UTI when antibiotics are used before admission. The urine culture would be only positive if the uropathogen is resistant to the given antibiotic. In about 30% of febrile UTI patients the positive blood culture can be used to diagnose complicated UTI even when patients used antibiotics before admission.<sup>25</sup> Symptomatic UTI and asymptomatic bacteriuria in the urine of patients with and without an indwelling catheter cannot be distinguished with today's technics. According to the IDSA guideline the most reliable urine culture can be obtained from urine of a newly inserted indwelling catheter after removal of the previous colonised catheter.<sup>26</sup>

In conclusion, with the use of our diagnostic algorithm febrile UTI can be diagnosed much faster and easier in daily practice. When febrile UTI is diagnosed, early and goal-directed antibiotic therapy can be started, which will improve survival of patients with urosepsis.

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## DISCLOSURES

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