

# Dilemmas in Diagnosis of Urinary Tract Infection (UTI) in Fever without Focus and other conditions

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## ABSTRACT

**Aim:** To show that pyuria and significant growth in urine culture (UCx) in fever without focus done early and with only urinary symptoms in girls don't always indicate a urine infection and need antibiotic treatment.

**Materials and methods:** Three children having fever without focus for about 2 days, and one girl with urinary symptoms but no fever had urine tests done. These included urine microscopies and a UCx by collecting a midstream urine/clean catch urine sample. As they looked well, despite significant pyuria in all of them, antibiotic therapy was withheld till the UCx results were available 48 hours later.

**Results:** The three children having fever without focus became afebrile before the UCx report was available. The girl was treated with moisturizing and emollient creams for local application, and her symptoms disappeared. Hence, despite the significant growth of bacteria in the UCx, none of the children received antibiotics, and they remained well.

**Conclusion:** Despite significant pyuria and positive UCx in the three children who had a fever without focus, the fever settled without antibiotics. In case 4, vulval redness was present, and despite significant pyuria and positive UCx, symptoms settled with the local application of moisturizing creams.

**Clinical significance:** UTI guidelines suggest urine tests in children having fever without focus or only urinary symptoms. The time to send the urine samples is not clear in fever without focus. In a well child, where urine tests are done after at least 2 days of fever, if the fever or symptoms settle without antibiotics before the urine culture is available, these children should not be labelled as having UTIs even if the urine Cx is positive. An algorithm suggests the way out in such cases.

**Keywords:** Asymptomatic bacteriuria, Fever without focus, Significant growth on urine culture, Significant pyuria, Time of urine sample afebrile, Urine infection.

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## INTRODUCTION

The pendulum has swung wildly back and forth in the diagnosis of UTIs in children. From the time when every bacterium was considered a valid target to use all your antibiotic weapons, we have now realized that that may be overkill. An attempt to inject sanity into the proceedings and understand the pathology behind UTIs is now underway. The following cases here now beg the question of whether we need to change the approach to UTI diagnosis in fever without focus as well.

It is estimated that about 1–3% of boys and 3–10% of girls develop a UTI before 14 years of age.<sup>1,2</sup> In another study, it was noted that 1% of children developed a UTI by 8 years of age. Repeated urine infections, especially pyelonephritis, can lead to kidney damage and/or hypertension. The presence of vesicoureteral reflux (VUR) is presumed to increase the risk of pyelonephritis. The diagnosis of UTI is based on an appropriately collected urine sample that is sent for microscopy and UCx.

The presence of >10 pus cells per cmm of uncentrifuged urine or >5 pus cells/high-power field (HPF) of a centrifuged urine sample is considered significant pyuria. Depending on how the urine sample is collected, a growth of >100,000 organisms/mL in a midstream urine sample, growth of >10,000 organisms/mL in a urinary catheter sample, and any growth in a suprapubic aspirate is considered the gold standard for diagnosis of UTI.<sup>3</sup> The following

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cases presented here make one wonder whether this needs to be qualified even further.

## CASE 1

A 7-month-old baby girl developed a fever for 2 days. The fever was 38°C and lower. She had an upper respiratory infection 2 weeks prior to this presentation. She was a well-grown child with a weight of 6.7 kg and no history of any major illness in the past. On examination, no focus for the fever was found. A urine sample was sent for microscopy. This revealed 10–12 pus cells/HPF. A UCx was sent at the same time by collecting a clean catch sample.

She received only antipyretic agents (paracetamol) and did not receive any antibiotics. There was no fever at all after the urine sample had been sent. The UCx showed a growth of *Escherichia coli* >100,000 organisms/mL. She did not receive any antibiotics thereafter and remained well 6 months after the episode.

## CASE 2

A girl aged 1 year and 4 months presented with a history of fever for >1 day. The fever was 38°C. She was on regular follow-up as the antenatal scans had shown echogenic kidneys, and on follow-up, she was noted to have tiny cysts along with increased echogenicity of the kidneys. She was diagnosed as having bilateral renal dysplasia. Though the serum creatinine was elevated earlier (1.13 at 5 days of age and 0.8 at 2 months of age), it had settled to 0.6 mg% at present. She also had mild proteinuria. She had grown well with a weight of 8.3 kg and had no history of urine infections in the past. On examination, no focus for the fever was found. A urine sample was sent for microscopy, and it revealed 18–20 pus cells/HPF. A UCx was sent by collecting a clean catch sample.

She received only paracetamol and no antibiotics. The fever continued for one more day and then stopped. The UCx available 2 days later showed a growth of *Klebsiella* 100,000 organisms/mL. She did not receive any antibiotics. A repeat urine microscopy showed 1–2 pus cells/HPF. She remains well 6 months later.

## CASE 3

A 3-year-old girl presented with a fever for 2 days. The fever was 38°C. She had one episode of loose stools 2 days prior to the presentation but was well thereafter. She had a past history of repeated urine infections in the first year of life and had undergone reimplantation of the ureters at 10 months of age as a micturating cystogram had revealed bilateral grade IV–V VUR. A repeat micturating cystourethrogram (MCUG) confirmed that the VUR had been abolished. She had remained well for 2 years with no further urine infections.

On examination, no focus was found on the fever. A urine sample was sent for microscopy, and it revealed 10–12 pus cells/HPF. A UCx was sent by collecting a midstream sample.

She had received only paracetamol for her fever. She had no further fever. The UCx available 2 days later showed a growth of *E. coli* at 100,000 organisms/mL. She did not receive any antibiotics and now remains well 2 months after the episode.

## CASE 4

A 5-year-old girl presented with a history of dysuria for the past 3 days. There was no fever. There was no significant past history. The general examination had been considered normal, and a urine sample had been sent for microscopy. That revealed 18–20 pus cells/HPF. A UCx was also sent by collecting a midstream urine sample.

When seen again after the urine samples had been sent, she was clearly noted to have vulval redness. Appropriate treatment, including emollient creams, was given. By the time the UCx report was available 2 days later, she was symptom-free. The UCx showed a growth of *E. coli* at 100,000 organisms/mL. She did not receive any antibiotics and now remains well 8 months after the episode.

## DISCUSSION

The guidelines framed for diagnosis and treatment of UTIs place a lot of emphasis on positive UCx. In a child suspected of having a UTI, the recommendation is to send a urine sample for microscopy and culture. The presence of >5 pus cells/HPF in a centrifuged urine sample or >10 pus cells/cmm in an uncentrifuged urine sample is considered significant pyuria. In the presence of significant pyuria, antibiotics are recommended to be started without waiting for the UCx report that may become available 2–3 days later. Further treatment and investigations would depend on whether the UCx shows a significant growth of organisms confirming a UTI. A growth of 100,000 organisms/mL in a midstream or clean catch sample or 10,000 organisms/mL in a urinary catheter specimen or any growth in a suprapubic aspirate is considered a significant growth for confirming the diagnosis of UTI.<sup>3</sup>

The symptoms that suggest UTI and should prompt a urine test include fever without focus and/or the presence of urinary symptoms like dysuria, frequency, urgency, etc.<sup>4–6</sup> In children aged 2–24 months, the percentage of children having UTI presenting as fever without focus has varied in different studies. In a study of 98 children between 5 and 31 months of age presenting with fever without focus, UTI was diagnosed in nine out of 98 children (9%).<sup>4</sup> In an old study, the rate of UTIs in 193 febrile infants was 4.1%.<sup>7</sup> In a recent study, amongst 304 patients between 2 months and 10 years with a temperature of >38°C and having no definite source of fever, UTI was present in 40 patients giving a prevalence rate of 13.2%.<sup>8</sup> However, an older study<sup>9</sup> stated that amongst infants presenting with fever without focus, UTIs were confirmed in 3.5–5.5% of infants. It is now generally believed that about 5–7% of such children presenting with fever without focus are likely to have UTIs. Apart from the fact that UTI diagnosis was based on a positive UCx in many of these studies, the timing of sending the urine sample to these children was not entirely clear.

In our cases described above, one can clearly see that the criteria for testing and diagnosis of UTI may have been met, but none of them received antibiotics. In each of these children, if antibiotics had been started after the urine microscopy, it would have been easy to label them as having UTIs and ascribe the improvement to antibiotics. But that would clearly be fallacious.

If the fever settles without antibiotics, the question remains as to what we are treating. It is well known that significant pyuria will be seen in many conditions apart from UTIs, like fever, dehydration, nephritis, urolithiasis, etc. Depending on the measures taken while collecting a urine sample, contamination causing a positive UCx in a urine sample is also high. In a study involving 50 children (25 boys and 25 girls) aged 12 days–24 months, referred with a suspicion of UTI, urine was collected by a midstream sample in 32 children (64%) and in a plastic bag in 18 children (36%). Hospital verifications of UCxs were performed by SP puncture culture in 24 children (48%) or by catheterization of the urinary bladder in 26 (52%) children. UTI was confirmed in only 11 children of the 32 who had a positive UCx by midstream urine sample. Of all the 18-bag UCx positive results, none had an actual UTI on the confirmation!<sup>10</sup> In fact, in a retrospective study that looked at records of 335 patients (137 with bacteriuria and 198 with negative UCx), only 34 patients (25% of patients with a positive UCx) met the criteria for a symptomatic urine infection, 67 (49%) had asymptomatic bacteriuria (ASB), and 36 patients (26%) had an infection at a non-urinary site!<sup>11</sup> The risk of having a contaminated urine sample leading to significant growth in UCx remains high in any child.

At the same time, human microbiome studies suggest that normal bladders are not always sterile, and ASB is fairly common.<sup>12,13</sup> In a study comparing the diagnosis of UTI in confirmed respiratory syncytial virus-positive infections based on UCx, the rate dropped from 6.1 to 1.1% by just using the new criteria for diagnosis of UTI, the conclusion being made that previously described risk of UTIs in these patients may represent ASB or contaminated samples!<sup>14</sup> The presence of significant growth on UCx, indicating a positive result, may not always indicate UTI. As the criteria for UTI become more robust, the diagnosis of UTI has and will continue to reduce.

What is the way forward? Selecting the children who have a fever without focus and who may be at risk seems to be the logical solution. A predictive model<sup>15</sup> looked at a younger age (<1 year), high fever (>39°C), fever >2 days, white race, etc., and suggested that a urine test should be done only if two of the criteria were positive.

Even the revised guidelines for UTIs by the American Academy of Pediatrics for febrile children between 2 and 24 months of age have several important recommendations.<sup>16</sup> The differentiation between a healthy child and a sick child determines the urine test. If the child looks sick, antibiotics are to be started, but a urine sample has to be collected before starting antibiotics. However, if the child looks well, it is considered reasonable to follow-up with the child till the fever disappears or a urine test becomes necessary. They also suggest criteria similar to the abovementioned criteria for considering the risk of UTI to be high in a healthy child having a fever without focus. Thus, a urine sample is suggested to be sent later if the fever continues. The risk of UTI in children with fever without focus is presumed to be around 5%, and in the low-risk group, probably much lower. It also mentions that the prevalence of ASB in infants is 0.7%, and three UCxs from asymptomatic children showed the growth of similar organisms. Indian guidelines<sup>3</sup> that have suggested a urine test for children with fever without focus has unfortunately not made this differentiation. Mahajan et al.<sup>17</sup> gave consensus guidelines for children presenting with fever without focus to the emergency department in India and also differentiated between healthy and sick children. Though not stated explicitly, the authors have looked at a fever of 5 days for children who looked well. They suggest that most infections are viral.

It is interesting to note that if a child presents to the clinic and the parents say that the child had a fever 2 days ago but is well now, we would not investigate for a urine infection. And even if urine tests were sent for such children, how much significance would be attached to the results? Yet, if the evolution of the symptoms happens in real-time, we are worried about the consequences.

The "Big Bang" theory of kidney damage is what scares us into starting antibiotics very early in UTIs to prevent renal damage because of the belief that missing a urine infection even for a short while allows the explosion of the organisms causing pyelonephritis. A study on whether early treatment of UTI prevented scarring looked at 278 infants (0.5–12 months of age) who presented with the first UTI, and though the median time to start treatment was 2 days, they looked at the two groups. In the first group, treatment was started within 24 hours of the onset of fever, and in the second group comprised children where the treatment was started 4 days or later from the onset of fever. The conclusion drawn was that frequency of scarring in infants treated early or late did not differ, and it appeared to be independent of that factor!<sup>18</sup> In another earlier paper, the authors were of the opinion that UTIs *per se* do not cause end-stage kidney disease.<sup>19</sup>

Thus, it would seem that the prudent action in children who appear well though presenting with fever without focus would be waiting watchfully to see if the fever resolves. If the fever does not subside by 48–72 hours and especially if it is high grade, urine samples should be sent. In practice, however, in India, often urine samples are sent quite early, within 48 hours of the onset of fever. A child who has had a previous UTI, they are sent on the first day of fever itself! The suggestion seems to be that these children cannot have the other usual viral infections that other children have! These children would not merit a urine test if we used the criteria used in the predictive model mentioned above.<sup>15</sup> The use of antibiotics could be reduced considerably, not to mention reducing the number of tests done for such children presuming a UTI and the attendant anxiety that the parents and child would suffer if we qualify the criteria for starting antibiotics as we suggest.

The children described in cases 1–3 had a fever without focus and significant pyuria. But instead of starting antibiotics immediately, the culture report was awaited as the children appeared well. The fever disappeared without antibiotics. So, a decision was taken not to give antibiotics even if the culture was positive. The parents were advised to return promptly in case of any symptoms. However, all children remained well and have remained well till now with no problems. It is difficult to imagine that there will be pyelonephritis without fever, and hence the risk for kidney damage is minimal or none. So, in children appearing well (not appearing toxic at presentation needing hospital admission), there would seem to be no harm in waiting for the culture report. If the culture is not showing a significant growth or the fever settles before the UCx is available, it should not be labeled as a UTI (even if the UCx shows a significant growth), and watchful observation can be employed. If the child becomes unwell at any stage, antibiotics can be started anyway.

In case of case 4, again though microscopy and culture would suggest a UTI, that was not the case. Vulval redness is common in children, especially in tropical areas, and can cause symptoms similar to UTIs, and investigations could fallaciously suggest UTIs. Unless appropriately examined, it is likely to be missed, and children will get several antibiotics. Repeated washing and antifungal creams are the root cause, and emollient/moisturizing creams are required to treat the condition.<sup>20</sup>

We need to realize that the armamentarium of antibiotics is now getting empty, and there are no new magical antibiotics appearing. In an ideal scenario, even though the recommendation might be to send a urine sample late in fever without focusing on the children appearing well, in practice, it does get sent. In such cases, the following algorithm may be helpful in dealing with the results.

When a child presents with fever without focus or urinary symptoms, a complete examination should be done. A urine sample for UCx sent for fever without focus should ensure

- That the genital area is cleaned with regular soap and water.
- It should be a midstream (or clean catch in infants) sample.
- There should be no vulval redness (in girls).
- The urine sample should reach the laboratory in 1 hour.

Suppose the child appears well (tolerating food, no vomiting, and fever <39°C), we can withhold antibiotics till the UCx report is available. If in the next 48 hours, the child becomes unwell at any stage (high-grade fever >39°, vomiting, and looking sick), antibiotics can be started. Then if the culture shows significant growth, it can be labeled as a UTI, and further management can continue. If the UCx does not show significant growth, it should not be labeled as a UTI.

However, if the fever disappears in the next 48 hours without antibiotics, then it should not be labeled as a UTI, irrespective of whether the UCx report shows significant growth or not! Close follow-up can be maintained by explaining to the parents that the child will need antibiotics if any symptoms develop.

If a child presents with fever and urinary symptoms or appears sick, there is no debate, and the child should receive antibiotics in the presence of significant pyuria while awaiting the UCx report.

For a girl presenting with urinary symptoms, it is very important to ensure that there is no vulval redness before a urine sample is taken. The algorithm given below highlights the action to be taken (Fig. 1).

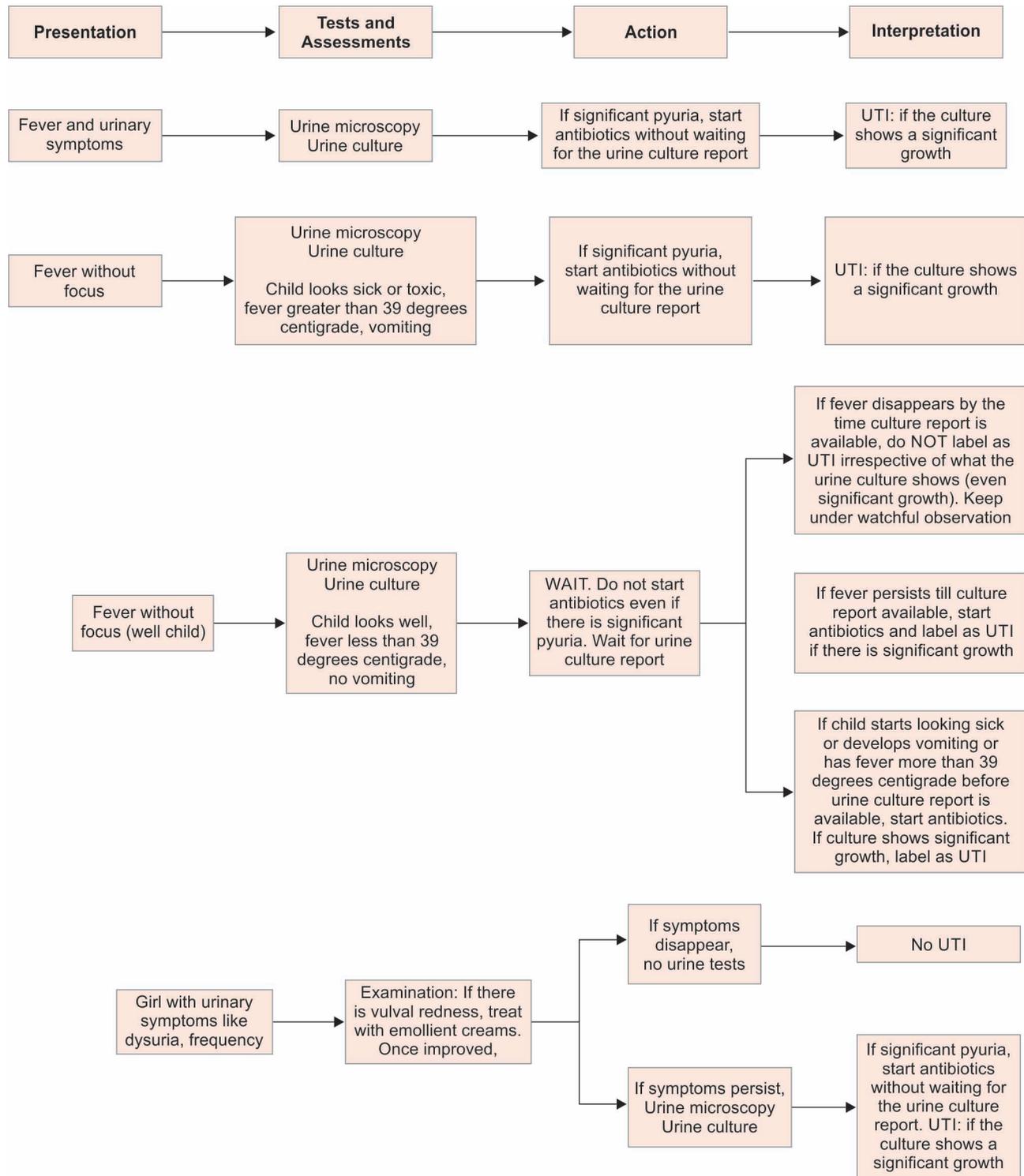


Fig. 1: In a child with a suspected UTI, if a urine sample is sent early (<72 hours of fever)  
**Significant pyuria:** >5 pus cells/HPF in the centrifuged urine sample or >10 pus cells per cmm in an uncentrifuged urine sample

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