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Urinary Tract Infections in Infants and Children in Developing Countries in the Context of IMCI

World Health Organization

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URINARY TRACT INFECTIONS

CAH

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Introduction

Urinary tract infections (UTI) are a common cause of febrile illness in young children. Due to lack of overt clinical features in children less than two years, appropriate collection of urine samples and basic diagnostic tests at first-level health facilities in developing countries, UTI are not generally reported as a cause of childhood morbidity. UTI are not included in the current Integrated Management of Childhood Illness (IMCI) algorithm as the main focus has been preventing mortality and severe morbidity by identifying children at risk of serious diseases including malaria, measles, meningitis, pneumonia, diarrhoeal diseases and malnutrition. Some countries have included assessment and management of dengue or streptococcal sore throat in the IMCI algothrim. However, in many countries without malaria and with a high measles vaccine coverage, the fever box of the IMCI algorithm provides limited guidance for health workers in first-level health facilities.

Several years ago, South Africa suggested including UTI identification in IMCI based on dipstick urinalysis for leucocytes and nitrites but this approach has been largely discarded. Oman, with basic laboratory facilities at primary health care level decided to include UTI management in its IMCI adaptation through screening febrile or symptomatic children with urine microscopy and referring those with urine white cells of 20 per cubic mm or more for paediatric consultation (personal communication).

The studies included in this review were identified by a search on Medline and PubMed of the relevant scientific literature published in English from 1966 to the present. UTI in children was linked with the following keywords: developing countries, IMCI, epidemiology, aetiology, risk factors, diagnosis, symptoms, signs, diagnosis, urinalysis, treatment, prevention, prognosis, urinary tract abnormalities, vesico-ureteric reflux, acute pyelonephritis, renal scarring, hypertension, renal imaging, chronic renal failure, reflux nephropathy and end stage renal failure. Additional material was obtained from other sources including internet searches and personal communication.

Extensive research has been conducted in developed countries on the epidemiology, risk factors, aetiology, diagnosis, treatment, prognosis and prevention of UTI in children. Initially this review will summarize relevant UTI literature from developed countries as in comparison fewer studies have assessed its importance in developing countries. Next, findings from UTI studies in children from developing countries will be presented. Subsequently the information will be combined and possibilities for UTI identification and management in first-level health facilities through IMCI will be suggested while indicating difficulties. Finally, necessary research questions will be suggested.

Review of urinary tract infection in children in *developed* countries

EPIDEMIOLOGY, AETIOLOGY AND RISK FACTORS

Urinary tract infections (UTI) are one of the most common bacterial infections seen in children. It has been estimated that UTI are diagnosed in 1% of boys and 3-8% of girls. In the first year of life UTI is more prevalent in boys with rates of 2.7% compared with 0.7% in girls (Riccabona 2003). Most infections in boys occur in the first three months of life (Roberts and Akintemi 1999; Schalger 2001) but by school age, the rate has decreased in boys and increased in girls (Riccabona 2003). Studies have shown a 10-12 fold increased risk of UTI in uncircumcised boys (Roberts and Akintemi 1999; Wiswell 2000). The reported rate of recurrent UTI is around 12-30% with risk greater in infants < 6 months, severe vesico-ureteric reflux and abnormal nuclear renal scans at time of first infection (Panaretto, Craig et al. 1999).

UTI has accounted for febrile presentations in 7.5% of 442 infants <8 weeks, 5.3% of 945 infants <1 year, 4.1% of 501 children <2 years and 1.7% of 664 children <5 years (Schalger 2001). The Pediatric Research in Office Settings (PROS) Network of the American Academy of Pediatrics study showed UTI in 9% of 3066 febrile infants, ≤ 3 months and 10% of these had bacteraemia (Newman, Bernzweig et al. 2002). Meningitis has been reported in 3-5% of infants in the first month of life with bacteraemic UTI (Wiswell 2000).

Gram negative organisms are those most commonly isolated from urine samples of children with uncomplicated UTI with *Escherichia coli* (*E. coli*) accounting for 70 to 90% of infections (Schalger 2001; Riccabona 2003).

Surveys have demonstrated bacteriuria in asymptomatic children of all ages from premature infants to school age children. It is now accepted that asymptomatic bacteriuria does not present a risk to a child of any age and screening for bacteriuria in the asymptomatic child is not indicated (Roberts and Akintemi 1999; Liao and Churchill 2001).

DIAGNOSIS OF UTI

Clinical predictors of UTI

Few studies have assessed the frequency, sensitivity, specificity and predictive value of symptoms and signs associated with UTI in children (American Academy of Pediatrics 1999; Roberts and Akintemi 1999). Fever is the commonest symptom of UTI in infants and the presence of another source of fever on clinical examination does not exclude UTI (Shaw, Gorelick et al. 1998). In infants and young children symptoms and signs of UTI tend to be non-specific. Older children may have symptoms including loin or abdominal pain, frequency, dysuria, urgency, hesitancy, enuresis and haematuria (Steele 1999). The 1999 American Academy of Pediatrics practice parameter, based on the accompanying technical report, recommended that UTI should be considered in any child younger than two years of age with unexplained fever. (American Academy of Pediatrics 1999; Downs 1999).

A study of 2411 febrile children with a rectal temperature ≥ 38.5°C, (males up to one year and females up to two years) showed a UTI prevalence of 3.3% overall. Higher prevalence occurred in children with malodorous urine

or haematuria (8.6%), abdominal or suprapubic tenderness (13.2%), children who appeared ill (5.7%) or had fever of ≥ 39°C (3.9%) though these signs were uncommonly elicited. Symptoms of vomiting, diarrhoea, irritability and poor feeding were common in febrile children with UTI but equally common in those febrile due to other causes (Shaw, Gorelick et al. 1998). The PROS study showed fever ≥38°C of duration ≥24 hours also to be a predictor of UTI (OR=1.8, 95% C.I.=1.2-2.8) (Newman, Bernzweig et al. 2002). A UK study has reported that a history of urine smell was unlikely to be of benefit in UTI diagnosis (Struthers, Scanlon et al. 2003). Studies have shown no difference in clinical symptoms in children with bacteraemic and non-bacteraemic UTI (Bachur and Caputo 1995; Honkinen, Jahnukainen et al. 2000).

Acute pyelonephritis is a UTI with systemic features including fever, vomiting, abdominal or loin pain, and lethargy (Craig and Hodson 2004). Nuclear renal scans have suggested that the majority of febrile young children with UTI will have acute pyelonephritis (Shaw, Gorelick et al. 1998; Wiswell 2000). Available studies with data to assess fever as a marker of pyelonephritis (defined by a positive scan) provide a wide range of sensitivity (53% to 84%) and specificity (44% to 92%) (American Academy of Pediatrics Committee on Quality Improvement 1999). Diagnosing acute pyelonephritis using clinical and laboratory parameters are unreliable in children particularly those less than two years (Riccabona 2003).

Viral and yeast infections and inflammation of the external genitalia with vulvitis, and vaginitis may present with frequency and dysuria. Schistosomiasis presents with frequency, dysuria and haematuria, is more prevalent in older children > 10 years of age but heavy worm loads usually occur in younger age groups.

Laboratory diagnosis of UTI

Urine obtained by suprapubic aspirate (SPA) or transurethral catheter in young children is unlikely to be contaminated and is the preferred specimen for documenting UTI. SPA is considered the gold standard for diagnosing UTI. A catheter urine specimen when compared to SPA, has a sensitivity of 95% and specificity of 99%. Cultures of urine specimens obtained by a bag applied to the perineum are 100% sensitive but have specificity between 14-84%. The definitive diagnosis of UTI in young children requires semi-quantitative culture of urine obtained by SPA or catheterisation. The method of urine collection determines the number of colony forming units that are significant as the distal urethra may be colonized by the same bacteria that cause UTI (American Academy of Pediatrics 1999).

Urine culture results can take 24 to 72 hours to become available. Urine screening tests have been investigated in many settings to assist the presumptive diagnosis and treatment of UTI. Urinalysis using rapid dipstick tests for leucocyte esterase and nitrite or identification of leucocytes or bacteria on urine microscopy has been studied. No element of the urinalysis or combination of elements is as sensitive and specific as a semi-quantitative urine culture for diagnosing UTI. Dipstick tests for blood and protein have a poor sensitivity and specificity with respect to screening for UTI (American Academy of Pediatrics 1999).

A meta-analysis published in 1999 concluded both Gram stain and dipstick analysis for nitrite and leucocyte esterase performed similarly in detecting UTI in children and were superior to microscopic analysis for pyuria (Gorelick and Shaw 1999). A 2002 meta-analysis combining a multi-variant approach concluded pyuria ≥ 10 per high power field with bacteriuria (any) to be best for assessing the risk of UTI in children of all ages. This group was unable to definitively assess the combinations of rapid test dipsticks including leucocyte esterase and nitrite, as they stated the number of studies assessing these markers were small. The method of urine sampling and

centrifugation affected the performance of the tests. This group also concluded that pyuria alone showed the lowest performance in all age groups, particularly with a non-sterile specimen (Huicho, Campos-Sanchez et al. 2002). Despite this studies have generally shown that a negative dipstick urinalysis can exclude UTI in children particularly over two years (Wiggelinkhuizen, Maytham et al. 1988; Armengol, Hendley et al. 2001; Doley and Nelligan 2003).

Sensitivity and specificity of components of urinalysis

Test	Sensitivity % (range)	Specificity % (range)
Leukocyte esterase	83 (67-94)	78 (64-92)
Nitrite	53 (15-82)	98 (90-100)
Leukocyte esterase or nitrite positive	93 (90-100)	72 (58-91)
Microscopy: WBC	73 (32-100)	81 (45-98)
Microscopy: bacteria	81 (16-99)	83 (11-100)
Leukocyte esterase or nitrite or microscopy positive	99.8 (99-100)	70 (60-92)

Source: American Academy of Pediatrics 1999; Downs 1999

TREATMENT

Children with uncomplicated UTI are likely to respond to amoxycillin, sulphonamides, trimethoprim-sulfamethoxazole (cotrimoxazole) or cephalosporins, as these antibiotics are concentrated in the lower urinary tract. Parenteral antibiotics should be considered in children who are toxic, vomiting or dehydrated, or who have an abnormal urinary tract (Riccabona 2003). A recent article has reviewed the evidence for treatment of acute pyelonephritis. The authors state that oral antibiotics, chosen to cover local uropathogens are as safe and effective as intravenous antibiotics in children with a clinical diagnosis of acute pyelonephritis and intravenous antibiotics should be reserved for those who are seriously ill or have persistent vomiting (Craig and Hodson 2004).

Resistance rates to commonly prescribed antibiotics for urinary *E. coli* isolates have been reported as ampicillin (39-45%), trimethoprim-sulpamethoxaole (14-31%), nitrofurantoin (1.8-16%) and fluoroquinolones (0.7-10%) (Riccabona 2003). Studies from Israel and UK of community-acquired UTI over 5-10 years have shown a generalized decrease in bacterial sensitivity to common oral antibiotics including cotrimoxazole and cephalexin (Ladhani and Gransden 2003; Prais, Straussberg et al. 2003).

It has been generally recommended to treat uncomplicated UTI in children for seven days with oral antibiotics, though short course (3-4 days) treatment has been shown in some studies to be as effective. Several studies have looked at the use of single dose gentamicin, amoxycillin, cotrimoxazole and cefotaxime (American Academy of Pediatrics 1999; Downs 1999; Keren and Chan 2002; Michael, Hodson et al. 2002; Riccabona 2003). In 2002, two systematic reviews of randomized controlled trials comparing short and standard courses of antibiotics for the treatment of uncomplicated UTI in children were published (Keren and Chan 2002; Michael, Hodson et al. 2002). These studies differed in methodology and conclusion but both experienced difficulties in extracting data for the meta-analyses. The former study cited, concluded that longer course (7-14 day) antibiotic therapy when compared with short course ($\leq$ 3 days) was associated with fewer treatment failures and without an associated increase in

reinfections, even when studies including patients with evidence of pyelonephritis were excluded from the analysis. In contrast, the latter study concluded that a 2-4 day course of oral antibiotics was as effective as 7-14 days in eradicating lower tract UTI in children.

PROGNOSIS AND PREVENTION

UTI in young children may be a marker for abnormalities of the urinary tract including vesico-ureteric reflux (VUR) and reflux nephropathy (renal scarring). VUR is the commonest abnormality with a prevalence of 1% in all children and 35% in children following first UTI. Data in both humans and animals have demonstrated that UTI in the presence of VUR may lead to acute pyelonephritis and renal scarring. Renal scarring is associated with subsequent renal damage, hypertension and end stage renal disease (ESRD). Reflux nephropathy has been estimated to account for 7-17% of ESRD (Craig, Irwig et al. 2000).

Until recently, standard practice after diagnosing UTI has been to image the urinary tract of children for abnormalities by performing a renal ultrasound and micturating cystourethrography (MCU). This was on the assumption that prevention of UTI recurrence through administering prophylactic antibiotics would reduce the risk of developing renal scarring and thus ESRD. A systematic review of long-term antibiotics for preventing recurrent UTI in children, has suggested problems with the existing published trials and that further research is required (Williams, Lee et al. 2001; Williams, Lee et al. 2004).

Antenatal ultrasound has shown renal damage suggesting renal dysplasia or hypoplasia in up to 30% of newborns with VUR before UTI is diagnosed. Studies have shown that 12-38% of the siblings of children with VUR also had VUR in the absence of a history of UTI. These findings have prompted an alternative theory suggesting a common developmental basis to both VUR and renal dysplasia or hypoplasia leading to ESRD. This hypothesis is supported by the finding of no reduction in ESRD as a result of reflux nephropathy over the past 20 years, despite imaging and treating children with VUR after first UTI (Craig, Irwig et al. 2000). In addition, recent information from 20-year cohort studies has not shown causal links between UTI and hypertension and chronic renal failure (Craig 2001).

Animal studies using components of human breast-milk have suggested that breastfeeding may provide some protection against UTI in children. (Riccabona 2003).

Review of urinary tract infection in children in *developing* countries

EPIDEMIOLOGY, AETIOLOGY AND RISK FACTORS

Several studies to determine UTI prevalence in developing countries have been conducted predominantly in hospital settings and particularly in malnourished children. Many of these studies have been with small patient numbers using a range of urine specimens. More recent studies collecting SPA and mid-stream urine (MSU) specimens have shown a wide range of UTI prevalence. A Nigerian hospital study reported UTI in 9% of febrile children (temperature $\geq$ 38°C) aged 1-60 months, with a significantly higher prevalence in girls (Mussa-Aisien, Ibadin et al. 2003). Prospective studies from South Africa, showed bacteriuria on aseptic catheter specimens in 26% of children, aged 0-12 years, admitted to a teaching hospital in Durban and in 17% of children, aged 1 week to 8 years, attending a primary health care (PHC) setting. UTI was present in association with other conditions including acute respiratory infection, acute diarrhoea and malnutrition. In both these studies, children did not have specific urinary symptoms but the authors argue that all cases fulfilled diagnostic criteria for UTI (Jeena, Coovadia et al. 1995; Jeena, Coovadia et al. 1996).

Studies have shown a higher UTI prevalence of 8-35% in malnourished children (Morton and Lawande 1982; Kala and Jacobs 1992; Banapurmath and Jayamony 1994; Reed and Wegerhoff 1995; Rabasa and Shattima 2002; Bagga, Tripathi et al. 2003) with the risk of bacteriuria increasing significantly with the severity of malnutrition (Bagga, Tripathi et al. 2003).

Gram negative organisms, particularly *E. coli* are commonly associated with UTI in children in developing countries (Kala and Jacobs 1992; Jeena, Coovadia et al. 1995; Jeena, Coovadia et al. 1996; Gorelick and Shaw 1999; Rabasa and Shattima 2002; Wammanda and Ewa 2002; Mussa-Aisien, Ibadin et al. 2003). A recent five-year retrospective study from Durban comparing UTI in HIV infected and non-infected children showed Gram negative organisms particularly *E. coli* to be the commonest pathogens in both groups (Asharam, Bhimma et al. 2003). A study of 53 cases of neonatal meningitis in Nigeria showed 51% of organisms isolated from the cerebrospinal fluid were gram negative bacteria (39% *E. coli)* possibly of urinary tract origin (Longe, Omene et al. 1984).

DIAGNOSIS OF UTI

Several of the UTI studies in developing countries have reviewed symptoms and signs. Clinical symptoms and signs in children with and without bacteriuria in the PHC and the Durban hospital study were similar with respect to cough, diarrhoea, vomiting and fever (Jeena, Coovadia et al. 1995; Jeena, Coovadia et al. 1996). UTI was found in 43% (18/42) of children with dysuria, under 10 years of age in two separate Nigerian studies (Morton and Lawande 1982; Babaoye, Ogala et al. 1991). The 1982 study also found UTI in 10% (9/87) children presenting with fever and 27% (14/53) with severe diarrhoea (Morton and Lawande 1982). In the 1991 study, dysuria was the presenting complaint in 4/42 children with Schistosomiasis, 3/42 children with gonococcal urethritis and in 24/42 children, no definite diagnosis was made (Babaoye, Ogala et al. 1991).

A further Nigerian study in 300 children, showed hyperpyrexia (temperature greater than 41.1 °C), abdominal pain and fever of at least seven days duration to be associated with a significantly increased UTI prevalence. In

comparison, diarrhoea, vomiting, anorexia, irritability and jaundice were infrequently found and did not have a significant UTI association (Mussa-Aisien, Ibadin et al. 2003).

Studies from South Africa assessing urinalysis by dipstick as a screening test for UTI have differed in support for the test. One study concluded that urinalysis was reliable and allowed early diagnosis of UTI. They showed dipsticks for leukocyte esterase and nitrite combination to have a positive predictive value of 90.5% and negative predictive value of 98.4% (Wiggelinkhuizen, Maytham et al. 1988). A study on malnourished children on SPA specimens by dipstick for leukocytes and nitrites alone or in combination had a positive predictive value of 73.8% when compared to culture, with a UTI prevalence of 26.1%. This study showed a negative predictive value of 95.7% for leucocytes and/or nitrites (Reed and Wegerhoff 1995). A Nigerian study supported the use of urine microscopy on unspun, unstained specimens for white cells in identifying UTI. They used <10 white blood cells per high power field as the cut off and reported a positive and negative predictive value of 62% and 83% respectively as compared to urine culture (Morton and Lawande 1982).

Studies in children, particularly 10-14 years of age, have shown proteinuria and haematuria on dipstick urinalysis as strong predictors of schistosomiasis (Mott, Dixon et al. 1983; Kassim 1989).

TREATMENT

The majority of studies in developing countries have suggested that urinary tract pathogens are often resistant in vitro to commonly prescribed antibiotics, including ampicillin, cotrimoxazole and chloramphenicol (Jeena, Coovadia et al. 1995; Jeena, Coovadia et al. 1996; Rabasa and Shattima 2002; Wammanda and Ewa 2002; Mussa-Aisien, Ibadin et al. 2003). However, treatment outcome studies have not been performed.

Study				
	Wammanda (2002) hospital based study *E. Coli*	**Jeena (1995) hospital- based study All organisms**	**Jeena (1996) PHC based study All organisms**	**Musa-Aisen (2003) hospital-based study *E. Coli***
Antibiotic	**Gram negative organisms sensitivity to antibiotic**			
Ampicillin	15%	14%	7%	13%
Cotrimoxazole	16.7%	42%	28%	40%
Amoxycillin-clavulanic acid	60%	94%	96%	80%
Gentamicin	80%	-	100%	80%
Nalidixic acid	-	100%	100%	-
Amikacin	-	100%	-	-
Cephalexin	-	91%	96%	-
Sulpahamethoxazole	-	-	14%	-
Trimethoprim	-	-	21%	-
Chloramphenicol	33%	-	-	20%
Ciprofloxacin	-	-	-	80%
Ceftazidime	-	-	-	27%
Eerythromycin	-	-	-	0%
Azithromycin	-	-	-	40%
Ceftriaxone	-	-	-	67%

PROGNOSIS

Urinary tract abnormalities in developing countries

Few studies in developing countries have assessed the prevalence of urinary tract abnormalities in children. A South African study of 26 malnourished children aged 3-60 months with UTI showed that none had renal tract abnormalities or VUR as assessed by ultrasound, intravenous pyelogram (IVP) and vesicourethrography (Kala and Jacobs 1992). Other South African studies report a low prevalence of VUR in black children (Cremin 1979; Jeena, Coovadia et al. 1995; Jeena, Coovadia et al. 1996). A Nigerian study detected 5/21 children with UTI to have renal abnormalities on IVP (Morton and Lawande 1982).

Chronic renal failure due to reflux nephropathy

Reflux nephropathy has been suggested as the aetiology of chronic renal failure (CRF) in 14.7% (5/34) Jamaican children (Miller and Williams 2002), 16.7% (51/305) Indian children (Hari, Singla et al. 2003) and 24.5% of Pakistani children (Jamro, Channa et al. 2003). A study of renal problems in black South African children showed a limited number with reflux nephropathy (Thomson 1997).

COST OF DIPSTICKS

Introduction of urinalysis by dipstick will require purchasing strips that can test for both nitrite and leucocyte esterase. Several test strips are available that vary in cost and governments may be able to negotiate more competitive prices with the manufacturer. The table below estimates the cost of strips for urinalysis in resource-poor settings based on data obtained through internet searches and from personal communication (South Africa). The cost to perform urinalysis by dipstick on one child is approximately US$0.5. It may be possible to cut the strips longitudinally to reduce costs. The shelf life of a container of dipsticks is two years at room temperature. It is important to keep the lid firmly on the container as atmospheric water spoils the strips.

Name	Number in container	Cost per container US$	Cost per child US$
Combur 5 (Roche)	50	24.62	0.49
Combur 7 (Roche)	100	46.43	0.46
Multistix 8 (Bayer Diagnostics)	100	52.33	0.52
South Africa	100	4.36	0.44

TO DIPSTICK OR NOT TO DIPSTICK URINE

The table below demonstrates the potential consequences of using fever only or fever with urinalysis by dipstick to diagnose UTI in children and treat with antibiotics using UTI prevalence of 5% and 20%. It is based on a number of assumptions.

Fever as a marker of UTI has a sensitivity of 80% and specificity of 40%, urinalysis by dipstick has a sensitivity of 90% and specificity of 70% (American Academy of Pediatrics 1999) and there is independence of fever and urinalysis.

5% prevalence of UTI				
Assessing for UTI based on	**Treated appropriately**	**Missed**	**Treated inappropriately**	**Left alone appropriately**
Nil	0	50	0	950
Fever	40	10	570	380
Fever and urinalysis	45	5	285	665
20% prevalence of UTI				
Assessing for UTI based on	**Treated appropriately**	**Missed**	**Treated inappropriately**	**Left alone appropriately**
Nil	0	200	0	800
Fever	160	40	480	320
Fever and urinalysis	180	20	240	560

Introducing this screening test will increase the number of children treated appropriately or left alone appropriately and will reduce the number of children missed or treated inappropriately. However, there remains the potential for a significant number of children treated inappropriately, particularly at lower prevalence of UTI. If children at high risk of UTI only were screened, including febrile children less than two years, malnourished children or those with a past history of UTI, then those latter numbers could be reduced further. Tables such as this could be developed if the required data including prevalence of UTI, number of malnourished children or children less than two years seen at health facilities in countries were available. This data may assist IMCI adaptation groups in decisions of whether or not to include UTI in the IMCI algothrim.

UTI identification and management in first-level health facilities in developing countries through IMCI

ASSESS THE CHILD FOR UTI

The available data suggest that children in developing countries with fever and who are malnourished have a substantial risk of a UTI. Fever is an appropriate entry point to assess and classify children for UTI using the IMCI algothrim. IMCI defines fever by history, if the child "feels hot" or if the child has temperature of 37.5°C or above. The symptoms and signs of UTI in children particularly those < two years are non-specific and clinical diagnosis is unreliable. Data from developed countries strongly suggest that the presence of UTI should be considered in any child < two years with unexplained fever. Children with loin or abdominal pain, dysuria or frequency may have a UTI, however these signs are unreliable.

IMCI determines the nutrition status of children by assessing the clinical signs of "visible severe wasting", "oedema of both feet" and "very low weight for age". The first two signs identify the majority of children with severe malnutrition, as defined by standard criteria and these children are referred. Children classified with "very low weight for age" have moderate malnutrition and are not referred but provided with counselling and reviewed (WHO/UNICEF).

A presumptive diagnosis of UTI can be supported with biochemical or microscopic examination of a clean urine specimen. Most first-level health facilities do not have urine culture, urine microscopy or Gram stain. Urine dipsticks have not been commonly used in first-level health facilities. Most first-level health facilities can only obtain urine by clean catch, MSU or bag urine specimens. At a minimum the health facility will require a functioning source of water to ensure genitalia washing, before urine collection and clean (sterile) containers to collect the specimens to reduce contamination. These factors are crucial and inability to provide these requirements should preclude urine collection and urinalysis. If culture is unavailable, SPA or catheter urine specimen is not indicated due to the invasive nature of the investigation.

Recent meta-analyses on the value of screening for UTI by dipstick urinalysis or urine microscopy for white cells and bacteria have been conflicting. If available, urinalysis by dipstick for both leucocyte esterase and nitrite can be used as a screening test for UTI in developing countries. The positive predictive value of dipstick urinalysis on any urine specimen is not sufficient but the negative predictive value seems to exclude UTI in children, particularly those older than two years. Urine microscopy requires more resources and may not offer benefit over the dipstick urinalysis, though could be used if available.

It is the view of the author that assessing and classifying children for UTI using the IMCI algothrim would not be appropriate where urine testing is unavailable to guide diagnosis. A recommendation to treat all children with fever for UTI would result in an acceptably high number of children treated inappropriately. Many of the children at risk of UTI would already be referred due to their age (all those <two months) or due to the presence of a classification of severe malnutrition. Other symptoms and signs of urinary infection are unreliable.

In the absence of another fever source, and where urine testing is available on a clean specimen, urine testing should be used as a guide to exclude UTI. Urinalysis by dipstick (or microscopy) should be performed on children at high risk of a UTI:

- febrile children 2 months up to 2 years;
- febrile children classified as "very low weight for age" 2 years up to 5 years;
- febrile children with a previous presumed or confirmed UTI or kidney problem.

Negative urinalysis may be defined as:

- negative dipstick where both leucocyte esterase and nitrite are negative (Wiggelinkhuizen, Maytham et al. 1988; Gorelick and Shaw 1999; Armengol, Hendley et al. 2001; Doley and Nelligan 2003);
- negative microscopy where both < 10 white blood cells per high power field and no bacteriuria (Morton and Lawande 1982; Liao and Churchill 2001; Huicho, Campos-Sanchez et al. 2002).

Using fever as the entry point for UTI in the IMCI algothrim will miss children (non-malnourished and moderately malnourished) without fever with UTI. Children that have been classified for other conditions through IMCI, including those with another source of fever may also have UTI. However, testing urine of all children with other IMCI classifications would lead to increased complexity of the IMCI algothrim and is not recommended. Urinalysis may be negative in some children less than two years with UTI. It is more important to treat for the main IMCI illnesses than for UTI and additionally all treated children have a review scheduled and caretakers are advised on danger signs.

CLASSIFY AND IDENTIFY TREATMENT FOR UTI

Red

Clinical signs cannot distinguish children, particularly < two years with or without pyelonephritis and this may not be clinically important. The key issue in considering UTI as a fever source in IMCI is to identify children with UTI and concomitant bacteraemia or meningitis, as these are the children at greatest risk of mortality and severe morbidity. These children predominantly will be infants < three months of age.

In the current IMCI algorithm, young infants (1 week up to 2 months) with fever would be classified as " possible serious bacterial infection". Children (2 months up to 5 years) with fever and general danger signs (inability to drink, vomiting everything, lethargic or unconscious and convulsions) or stiff neck would be classified as "very severe febrile disease". Both these groups would be given parenteral pre-referral antibiotics and referred. It is reasonable to assume that both these classifications would identify infants and children with sepsis and meningitis, whether or not this were resulting from UTI. Both these classifications would also identify those children with acute pyelonephritis requiring referral. Children 2 months to 5 years with acute pyelonephritis but without general danger signs would not require parenteral antibiotics and referral. Urine testing in febrile children with general danger signs is not indicated and may delay referral.

Yeloow

In settings without ready referral for definitive UTI diagnosis (the majority of first level health facilities), children should be treated with:

- positive urinalysis or microscopy.

These children can be classified as "UTI" or "possible UTI". This approach will miss children with UTI but a normal urinalysis, however, these children should be reviewed in two days if fever persists and all children with fever for more than seven days should be referred. A review at two days of the child with fever is appropriate to assess the need to reconsider management of UTI and development of symptoms or signs suggestive of other specific diseases. Children with two or more presumed UTI in past year should be referred for further assessment (specifically definitive UTI diagnosis and paediatric consultation).

Green

A classification of "fever, UTI unlikely" can be designated, in the presence of fever with no cause identified and negative urinalysis or microscopy. In this case, management would include counselling the mother (caretaker) on the importance of breastfeeding and other food and fluids, providing paracetomol for high fever, advising when to return and arranging follow-up in two days if fever persists. All children with fever for more than seven days should be referred for further assessment.

ANTIBIOTIC TREATMENT FOR UTI

The organisms responsible for UTI in developing countries are the same as those identified elsewhere. Studies in developing countries suggest that these organisms may be more resistant to commonly administered antibiotics including cotrimoxazole. Local studies on treatment outcome of community-acquired UTI in children given common oral antibiotics are necessary to guide treatment. Antibiotics should be given for seven days and the child reviewed after two days.

Febrile infants or children with possible meningitis, sepsis or pyelonephritis (with general danger signs) should be given pre-referral drugs. Current IMCI pre-referral parenteral antibiotics for young infants are penicillin and gentamicin. These drugs are generally appropriate for the treatment of organisms responsible for UTI. IMCI pre-referral drugs currently recommended for the child 2 months to 5 years (often chloramphenicol) would require assessment of their effect against uropathogens.

INCLUSION OF UTI IN IMCI ADAPTATION

UTI is unlikely to be an important contributor to child mortality, however, in countries without malaria and with high measles vaccine coverage, before IMCI adaptation to include UTI, a country should consider:

- How common is UTI in febrile children seen at first-level health facilities?
- Are health workers aware of UTI in children?
- What do health workers currently do if UTI is suspected?
- Is urine currently collected and tested at first-level health facilities?
- If so, how is this done?

UTI could be considered for introduction into the IMCI algorithm in countries where:

- Health facilities have functioning source of water
- Health facilities have the resources required for urine testing (clean or sterile urine specimen containers or urine bags)
- Prevalence of UTI suggests it contributes significantly to child morbidity
- Urinalysis by dipstick (microscopy) can be made available (cost, logistics)
- Knowledge and skills required for health workers to identify and treat UTI can be incorporated in IMCI training in terms of instructional materials, training time and complexity and necessary resources
- Presumptive identification of UTI does not lead to overburdening of referral services
- Presumptive treatment of UTI does not contribute to increased antibiotic resistance, drug costs and antibiotic side effects

UTI IN DEVELOPING COUNTRIES' RESEARCH QUESTIONS

The questions below concerning UTI in children in developing countries would be valuable to address through operational research.

- What is the prevalence of UTI in febrile non-malnourished children < five years presenting to a first-level health facility?
- What is the prevalence of UTI in febrile malnourished children < five years presenting to a first-level health facility
- How can clean urine specimens realistically be obtained at first-level health facilities?
- What percentage of treatment failure occurs in children with UTI prescribed a seven-day course of standard oral antibiotics?
- Why do UTI treatment failures occur?
- How do antibiotic sensitivities of UTI organisms in vitro correlate with treatment outcome?
- What is the cost to benefit of identifying and treating UTI at first-level health facilities?
- How does dipstick urinalysis compare with urine culture in UTI diagnosis at first- level health facilities?
- How does urine microscopy compare with urine culture in UTI diagnosis at first- level health facilities?
- What organisms are responsible for community acquired UTI?
- What percentage of children with presumed UTI are referred based on urinalysis by dipstick or microscopy?
- What happens to those children at the referral hospital?
- What percentage of children referred with presumed UTI actually have a UTI?
- How does short course oral antibiotics compare to seven days in the treatment of uncomplicated UTI in children at first-level health facilities?
- How does one dose of intramuscular gentamicin compare to seven days oral antibiotics in the treatment of uncomplicated UTI in children at first-level health facilities?

As previously stated, extensive research has been conducted in developing countries in all aspects of UTI in children. The literature presents some areas of confusion but it would be impractical to repeat these studies in developing countries, as it is unlikely that clarity will be obtained in settings, particularly in the cases of these two questions below.

- What are the clinical predictors of UTI in non-malnourished children < five years presenting to a first-level health facility?
- What are the clinical predictors of UTI in malnourished children < five years presenting to a first-level health facility?

Conclusion

The reasons to identify and treat UTI in any environment include:

- identify and treat coexisting bacteraemia and meningitis;
- ensure resolution of the acute symptoms;
- prevent renal damage by eradicating the pathogen;
- identify and consider administering prophylactic treatment to children at risk of recurrent UTI, to prevent renal damage.

In developing countries, the existing generic IMCI algorithm would address the identification and treatment of coexisting bacteraemia and meningitis in children with UTI. UTI can be presumed to be present based on clinical symptoms of fever in young children < two years and in all children classified as "very low weight for age" or with a previous presumed or confirmed UTI or kidney problem. Urinalysis by dipstick or microscopy may assist in UTI identification. Treatment based on positive urinalysis may lead to resolution of acute symptoms and eradication of the pathogen before renal damage ensues. However, urinalysis performed on non-sterile specimens will result in increased false positive results and possible over-treatment. Antibiotic overuse has the risk of increasing antibiotic resistance, increasing drug costs and unwanted side effects for individual children. Alternatively, urinalysis of sterile urine specimens may miss a significant proportion of infections, particularly in children < two years (overall sensitivity is about 50%) and urine microscopy has not been shown to be reliable in UTI diagnosis. A model whereby all children with positive urinalysis or young febrile children < two years are referred for definitive urine testing and paediatric consultation would burden the referral service, is unnecessary and would impact negatively on families. This would only be practical in relation to internal referral from outpatients in large hospitals.

Identifying those children at risk for recurrent UTI in developing countries, through referring children with two or more presumed UTI in the past year for definitive urine testing and paediatric consultation, implies that management of these children would be different. Renal ultrasound may be available in small referral hospitals in developing countries and a normal result is reassuring. The benefit for prophylactic antibiotics for children at risk of recurrent UTI is questionable notwithstanding issues of availability of antibiotics in developing countries and patient compliance.

There may be no value in classifying fever for UTI in the context of IMCI as UTI with concomitant sepsis and meningitis without urine testing is already addressed by the current IMCI guidelines. Urine testing of inadequately obtained specimens through over diagnosis, over treatment and over referral of presumed UTI may do more harm than good. Operational research may address this difficult area. It is important that any IMCI algothrim with inclusion of UTI is validated at first-level health facilities before implementation.

Recommendations

1. UTI is an important cause of childhood morbidity and should be considered for inclusion in IMCI adaptation in specific settings in developing countries only.

2. The decision to include UTI in IMCI adaptation should be made in countries where:

   - health facilities have a functioning water source and materials to collect appropriate urine specimens for urinalysis;
   - morbidity associated with UTI at first-level health facilities has been determined;
   - urinalysis by dipstick can be made available at first level health facilities.

   In these settings:
   - fever is the entry point to assess and classify children with UTI using the IMCI algothrim;
   - children at high risk of UTI due to age <two years, classification of “very low weight for age or those with a previous presumed or confirmed UTI or kidney problem only should have urinalysis by dipstick;
   - children classified as “UTI” or “possible UTI” are reviewed after two days if fever persists.

3. Research in this area should include both operational research addressing feasibility of collecting and testing urine at first-level health facilities and treatment outcome studies.

4. Any IMCI algothrim with inclusion of UTI should be validated at first-level health facilities before implementation.

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APPENDIX 1

Algothrim for fever in IMCI (including UTI)

Age of Child

Check For General Danger Signs

Does the child have fever?
(by history or feels hot or temperature 37.5°C or above

IF **YES**
Decide Malaria Risk

ASK

- For how long?
- If more than 7 days, has fever been present every day?
- Has child had measles within the last 3 months?

(relevant to UTI)
Has the child had a previous UTI or kidney problem?

LOOK AND FEEL (relevant to UTI)

- Look or feel for stiff neck
- Look for runny nose

Look for signs of MEASLES

- Generalized rash and
- One of these:cough, runny nose or red eyes

Look at nutrition status

- Determine weight for age

Urinalysis

All children aged 2 months to 2 years with fever, no other source
All children aged 2 years to 5 years with fever, no other source and very low weight for age
All children with fever and history of previous UTI or kidney problem

APPENDIX 2

For UTI only in majority of 1st level settings

Signs	Classify as	Identify Treatment
Any general danger sign **OR** stiff neck	Very severe febrile disease	Give first dose of appropriate antibiotics Refer the child urgently
No other cause identified for fever **AND** • Positive urinalysis in those tested	Possible Urinary Tract Infection	Treat with appropriate antibiotic for 7 days Give paracetomol for high fever Advise the mother on when to return immediately Review in 2 days if fever persists
Fever No other cause found **AND** Negative urinalysis	Fever cause unknown	Refer all children with 2 presumed UTI in past year Refer child if fever >7 days Give paracetomol for high fever Advise mother when to return immediately Counsel mother re breastfeeding and other feeding Follow-up in 2 days if fever persists

APPENDIX 3

For UTI only in settings where definitive urine testing or paediatric consultation is readily available (internal consultation, outpatients department of a large hospital)

The table below is targeted at IMCI adaptation groups or Paediatricians for decision-making purposes only.

Signs	Classify as	Identify Treatment
Any general danger sign **OR** stiff neck	Very severe febrile disease	Give first dose of appropriate antibiotics Refer the child urgently
No other cause identified for fever • Positive urine testing **OR** • Child 2 months-2 years who remain febrile at review visit AND second negative urinalysis[1]	Possible Urinary Tract Infection	Refer child for definitive urine testing and paediatric consultation (internal referral)
Fever (children 2 years up to 5 years) No other cause found **AND** Negative urinalysis	Fever cause unknown	Refer child if fever >7 days Give paracetomol for high fever Advise mother when to return immediately Counsel mother re breastfeeding and other feeding Follow-up in 2 days if fever persists
Fever (children 2 months up to 2 years) No other cause found **AND** First negative urinalysis or no UTI on definitive urine testing	Fever cause unknown	Refer child if fever >7 days Give paracetomol for high fever Advise mother when to return immediately Counsel mother re breastfeeding and other feeding Follow-up in 2 days if fever persists

[1] Urinalysis of sterile urine specimens may miss a significant proportion of infections (overall sensitivity about 50%), particularly in children < 2 years. If internal referral available definitive diagnosis of UTI could be made through culture of urine in this group of children.

APPENDIX 4

Where low malaria prevalence and high coverage measles vaccine (all fever classifications)

Signs	Classify as	Identify Treatment
Any general danger sign **OR** stiff neck	Very severe febrile disease	Give first dose of appropriate antibiotics Refer the child urgently
Generalized rash **AND** Runny nose or red eyes	Possible Measles or (Viral Exanthem)	See measles in IMCI **OR** Check immunization status of case and contacts Give Vitamin A if not already given Review in 2 days **OR** Refer child for paediatric consultation (if available)
Has traveled to a malaria area **OR** No cough or runny nose or red eyes **AND** no obvious cause of fever identified	Possible Malaria	See malaria in IMCI **OR** Check blood smear for malaria parasites (if available) AND If positive (or unavailable) Give appropriate oral anti-malarial Give paracetomol for high fever Advise the mother on when to return immediately Review in 2 days **OR** Refer child for paediatric consultation
No other cause identified for fever **AND** • Positive urinalysis in those tested	Possible Urinary Tract Infection	Treat with appropriate antibiotic for 7 days Give paracetomol for high fever Advise the mother on when to return immediately Review in 2 days if fever persists Refer all children with 2 presumed UTI in past year **OR** Refer child for definitive urine testing and paediatric consultation
Fever No other cause found **AND** Malaria excluded (smear negative, no risk factors or child already treated) **AND** Urinalysis negative	Fever cause unknown	Refer child if fever >7 days Give paracetomol for high fever Advise mother when to return immediately Counsel mother re breastfeeding and other feeding Follow-up in 2 days if fever persists