Medicines Evidence Commentary
commentary on important new evidence from Medicines Awareness Weekly

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Urinary tract infection: antibiotic resistance in children in primary care

A systematic review found that, in children, the global prevalence of laboratory-reported antibiotic resistance in community-acquired urinary tract infection (UTI) caused by *Escherichia coli* is high (for example, 53% for ampicillin and 24% for trimethoprim in developed countries, including the UK). However, data may overestimate the prevalence and the clinical relevance of the findings is unclear. Resistance to nitrofurantoin was low (1.3%), making it a suitable first-line treatment option for many children with lower UTI, as recommended in Public Health England’s [guidance for primary care on managing common infections](https://www.gov.uk/guidance/guidance-on-managing-urinary-tract-infections) and the [NICE guideline on UTI in children and young people](https://www.nice.org.uk/guidance/CG229). Choice of antibiotic should be directed by locally developed multidisciplinary guidance, taking into account local resistance patterns and the principles of antimicrobial stewardship.

Overview and current advice

Urinary tract infection (UTI) is a common bacterial infection in infants and children. The [NICE guideline on UTI in children and young people aged less than 16 years](https://www.nice.org.uk/guidance/CG229) makes recommendations on how it should be diagnosed and managed. NICE advises that infants and children aged 3 months or older with cystitis or uncomplicated lower UTI should be treated with oral antibiotics for 3 days. The choice of antibiotic should be directed by locally developed multidisciplinary guidance. Trimethoprim, nitrofurantoin, a cephalosporin or amoxicillin may be suitable. The parents or carers should be advised to bring the infant or child for reassessment if the infant or child is still unwell after 24–48 hours. If an alternative diagnosis is not made, a urine sample should be sent for culture to identify the presence of bacteria and determine antibiotic sensitivity if urine culture has not already been carried out.

Public Health England makes similar recommendations in their [Management of infection guidance for primary care for consultation and local adaptation](https://www.gov.uk/guidance/mannagement-of-infection-guidance-for-primary-care-for-consultation-and-local-adaptation). In children aged 3 months or older with a positive nitrite dipstick test, empirical antibiotic treatment should be started and a pre-treatment midstream specimen of urine sent for analysis. First-line options for treating uncomplicated lower UTI are trimethoprim and nitrofurantoin for 3 days. Amoxicillin is an option if the infection is susceptible, and cefalexin is recommended second-line. Public Health England has also produced [guidance for primary care on diagnosing UTI and understanding culture results](https://www.gov.uk/guidance/guidance-on-diagnosing-urinary-tract-infections).

The NICE and Public Health England guidelines also make recommendations on treating children younger than 3 months, children with upper UTI or pyelonephritis, and those at risk of more serious illness. See the [NICE pathway](https://www.nice.org.uk/guidance/pathway/CG229) and the [NICE clinical knowledge summary](https://www.nice.org.uk/guidance/CG229) on UTI in children for more information on the condition.
New evidence

Most UTIs are caused by *Escherichia coli* and resistant *E. coli* bacteraemia is increasing in the community, affecting the choice of antibiotic treatment. A systematic review has investigated the prevalence of resistance to the most commonly prescribed antibiotics given to children for community-acquired UTI in primary care (ampicillin, co-amoxiclav, co-trimoxazole, trimethoprim, nitrofurantoin, ciprofloxacin, and ceftazidime [as a marker for cephalosporin resistance])\(^1\). Ampicillin was used in place of amoxicillin because of more frequent reporting and its equivalence in spectrum of antimicrobial activity.

The systematic review included 58 observational studies, which investigated 77,783 *E. coli* isolates in urine. Results were stratified by the Organisation for Economic Co-operation and Development (OECD) statuses of the study countries because antibiotics tend to be used differently in these groups. In the more developed OECD countries antibiotics are generally obtained only by prescription, whereas in ‘developing’ non-OECD countries many antibiotics, including those commonly used to treat UTI, can be obtained over the counter, without the need for a prescription.

In 33 studies (73,375 isolates) from OECD countries (including the UK) the pooled prevalence of resistance was:

- 53.4% (95% confidence interval [CI] 46.0% to 60.8%) for ampicillin (25 studies in 11 countries, 66,503 isolates)
- 30.2% (95% CI 20.5% to 39.3%) for co-trimoxazole (24 studies in 9 countries, 50,230 isolates)
- 23.6% (95% CI 13.9% to 32.3%) for trimethoprim (7 studies in 5 countries, 18,977 isolates)
- 8.2% (95% CI 7.9% to 9.6%) for co-amoxiclav (21 studies in 9 countries, 65,076 isolates)
- 2.4% (95% CI 0.9% to 3.3%) for ceftazidime (10 studies in 8 countries, 25,805 isolates)
- 2.1% (95% CI 0.8% to 4.4%) for ciprofloxacin and (17 studies in 9 countries, 52,209 isolates)
- 1.3% (95% CI 0.8% to 1.7%) for nitrofurantoin (21 studies in 13 countries, 50,994 isolates)

For the antibiotics tested, resistance was found to be higher in 25 studies (4408 isolates) in countries outside the OECD.

There was evidence from 5 studies that bacterial isolates from the urinary tract of individual children who had received previous prescriptions for antibiotics in primary care were more likely to be resistant to antibiotics, and this increased risk could persist for up to 6 months (odds ratio 13.23, 95% CI 7.84 to 22.31). However, there were differences between the studies, with some reporting resistance and exposure to any antibiotic and others reporting resistance to trimethoprim, co-trimoxazole or third generation cephalosporins. Also, only 1 study considered the risk of resistance following use of an antibiotic in the previous 6 months, and that study measured previous exposure to antibiotics for 4 weeks or more, a longer duration than is usual for a course of treatment.

The authors noted that, in most countries, it is standard practice to treat empirically with an antibiotic when a child presents to primary care with a suspected UTI, and sometimes a urine sample is taken only if the illness does not respond to first-line antibiotic treatment. This can lead to falsely high reported resistance rates to first-line antibiotics. However, they found no obvious differences in resistance rates according to the timing of the urine sampling. Reverse causality and other confounding associations could also have introduced bias to the study findings; for example, previous hospital admissions, comorbidities, age and sex. However, studies that did attempt to adjust for confounding factors did not show differences between crude and adjusted estimates of association.
Commentary
Commentary provided by NICE

The systematic review looked at the global prevalence of antibiotic resistance and not all results may be applicable to the UK. However, the authors state that trimethoprim resistance was found to be over 20% in 3 studies from the UK. They note that the Infectious Diseases Society of America (IDSA) in collaboration with the European Society for Microbiology and Infectious Diseases (ESCMID) recommend that an antibiotic should be selected for first-line empirical treatment of UTI only if the local prevalence of resistance is less than 20% and conclude that, according to these guidelines, trimethoprim may no longer suitable be a suitable first-line treatment option for UTI. However, they also advise that care is needed because ruling out the use of some first-line antibiotics could lead clinicians to prescribe broad spectrum second-line antibiotics, such as co-amoxiclav, cephalosporins and quinolones, resulting in a ‘vicious cycle’ of increasing use of broad spectrum antibiotics and bacterial resistance.

The 2015 English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report also found rates of trimethoprim resistance were high in the population (adults and children). Of 711,960 isolates that underwent antibiotic susceptibility testing in reporting laboratories in 2014, 52.4% of positive E. coli urine cultures were from GP practices, 10.6% were from other community sources (including care homes and outpatient clinics) and 37.0% were from acute trusts. Resistance to trimethoprim was seen in over a third of isolates, and resistance to amoxicillin and ampicillin was seen in over half of isolates in all 3 settings. However, 97% of isolates from all clinical settings were susceptible to nitrofurantoin.

The ESPAUR report notes that these data may overestimate the extent of resistance, particularly in primary care, because much antibiotic prescribing by GPs is empirical. Although urine samples from some people are submitted for microbiological examination, the likelihood is that such specimens may be preferentially submitted following initial antibiotic treatment failure, or from people with histories of repeated or complicated infections who may have received multiple courses of antibiotics. Also, it is unclear how laboratory reports of resistance relate to clinical outcomes in children with UTI treated with antibiotics in primary care.

Data from the systematic review and ESPAUR report suggest that nitrofurantoin is a good first-line choice for the empirical treatment of uncomplicated lower UTI in children (and adults) in primary care. In view of the limitations of the data, trimethoprim may also be a suitable option, particularly where local resistance is low, in line with recommendations by NICE and Public Health England. Amoxicillin should be used only when the infection is susceptible.

The results of the systematic review suggest that bacterial resistance to antibiotics can persist for up to 6 months after antibiotic exposure in individual children. The authors note that clinicians should consider the impact of any antibiotic use on subsequent antimicrobial resistance and avoid their unnecessary use by following local and national guidance whenever possible.

Healthcare professionals should continue to follow Public Health England’s guidance for primary care on managing common infections and the NICE guidelines on UTI in children and young people and Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use.

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References


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