aureus or more indolent *Enterococcus* spp. empirically.[80,83] Where multiple antibiotics have previously been used, assessment of the likelihood of resistance is part of management (see below).

Multiple recurrent UTIs, defined by 2 or more UTIs caused by different organisms,[86] are a risk for resistant and MDR bacteria.[83] Although recurrent UTIs might occur without anomalies of the kidneys and urinary tract, other risk factors include VUR, underlying neurological conditions, prolonged hospitalization and UTI prophylaxis, and girls are at higher risk than boys.[84,87,88] If on prophylaxis, a different treatment antibiotic is required due to breakthrough. For children at high risk of resistance, including suspected ESBL-E, empiric oral options include nitrofurantoin, trimethoprim-sulfamethoxazole, quinolones and fosfomycin.[89] Empirical IV options for children at moderate risk of resistance but who have never cultured ESBL-E include gentamicin and quinolones. If there has been previous ESBL-E or clinical risk is higher, IV amikacin retains high susceptibility to uropathogens, concentrates well in urine and can avoid broad-spectrum beta-lactam and carbapenem use.[59,90] Most gentamicin-resistant Enterobacteriaceae exhibit cross-resistance to tobramycin but remain susceptible to amikacin, due to reduced inactivation by bacterial enzymes.[91] If cultures grow *Klebsiella pneumoniae* with high bacterial inoculum, empirical B-lactam antibiotics should be switched to a different class. With a high bacterial inoculum, the stationary phase is rapidly reached, so the effect of targeting penicillin-binding proteins is rapidly diminished, and an alternative is better.[92] In the large majority, carbapenems should be spared since their use is the greatest risk for developing carbapenem resistance. Even with a history of recurrent UTI with resistant uropathogens, empirical carbapenems are rarely needed in children with cUTI unless a child presents with sepsis (see below).[93–95] If the identified uropathogen is MDR, including carbapenem-resistant, options include a carbapenem plus amikacin combination, colistin and newer B-lactam/B-lactamase antibiotics such as ceftazidime-avibactam.[80,93] Since methicillin-resistant *S. aureus* (MRSA) is an uncommon uropathogen, this rarely needs to be covered empirically. *P. aeruginosa* (susceptible and resistant) is more common in recurrent UTIs, so it should be empirically treated with oral quinolones or IV aminoglycosides.[83]

For children with severe clinical presentation with sepsis features and no previous risk factors for resistance, *E. coli* is the most common pathogen, followed by *Klebsiella*, *Enterococcus*, *Proteus* and *Pseudomonas* spp.[60,96,97] Treatment with broad-spectrum beta-lactam antibiotics such as third-generation cephalosporins is recommended in moderately unwell children. If a child is severely unwell with sepsis potentially of urinary origin, local sepsis guidelines should be followed, considering the individual child's risk and/or history of resistance and whether it is hospital-acquired. There is occasionally a case for using empirical carbapenems in children with cUTI, for example, in a child with sepsis and a history of highly resistant organisms. This should be in consultation with an infectious diseases specialist to tailor empirical treatment and switch, when possible, with susceptibility.

For nephronia/renal abscess, *E. coli* is the most common pathogen, but urine culture is frequently negative.[61] Since urine culture may not identify the organism or its susceptibility, if progress is poor, penicillin/ampicillin may be added to cover *Enterococcus* spp. Early consultation with infectious diseases and urology is also recommended in case abscess drainage is needed. In specific clinical circumstances, *S. aureus* (including MRSA), *C. albicans* and *Mycobacterium tuberculosis* may cause renal abscess.[98,99]

Children with nonurologic underlying conditions have different risks of unusual organisms and resistance depending on hospitalization and antibiotic exposure. In children postrenal transplant, especially with urological abnormalities, there is a greater likelihood of *Enterococcus* spp., *S. aureus* or *P. aeruginosa.*[62,100,101] In immunocompromised patients, in addition to Enterobacterales and *P. aeruginosa*, less virulent organisms such as CoNS, *Haemophilus influenzae* and group B streptococcus may cause cUTI.[62,100,101] Fungal infections and viruses, for example, adenovirus, can also infect the urinary tract.[101,102] Choice of antibiotic in chronic renal impairment, immunocompromise or other chronic disease (eg, diabetes mellitus), therefore, depends on likely pathogens and risk of antibiotic resistance based on past antibiotic use and hospitalization. Mild acute or chronic renal impairment does not preclude use of aminoglycosides, which are generally well tolerated in children with renal dosing adjustment. Blood levels should be monitored closely. In moderate/severe renal failure, aminoglycosides should be used only when there is no alternative, as there is a higher risk of accumulation and an unknown risk to hearing.[103]

In neonates and infants <2 months, common pathogens include *E. coli*, *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp., group B streptococcus and *Enterococcus* spp.[104,105] In preterm infants, hematogenous transmission is more prevalent, with CoNS and *Candida* spp. being causative pathogens.[105] Empirical IV ampicillin and gentamicin are recommended for neonatal UTI by the World Health Organization.[106] Resistance should be considered with maternal history of antibiotics during pregnancy[107] or maternal ESBL-E cultured.[108] Empirical treatment should be based on maternal isolates, although if unable to access these, gentamicin is usually sufficient. For prolonged stays in neonatal intensive care, resistant hospital pathogens, including MRSA,[109] should be considered with empirical vancomycin if the infant is severely unwell.

Once culture results are available, empiric antibiotics can be targeted and potentially narrowed.

Antibiotic Duration and Timing of IV to Oral Switch

- For most children with cUTI, there is not enough evidence to support varying from current practice and expert opinion recommending a total of 10–14 days (GRADE D).
- When IV antibiotics are started, recommended IV durations vary between ≤3 days and ≤7 days depending on the cUTI subgroup and presence of bacteremia, with an early switch when the child is afebrile and clinically well (GRADES C and D).
- Longer total durations (up to 21 days) may be needed for renal abscesses or nephronia, and renal USS is recommended after 14 days to determine progress and ultimate antibiotic duration (GRADE B).
- For frequently relapsing UTI with the same organism, investigations should assess for an ongoing focal source of infection (GRADE D).
- Shorter total durations (6–9 days) and a single dose IV component show early promise, but prospective studies are needed with more children with complicated UTI (GRADES C and D).

Treatment durations for lower and upper UTIs have gradually reduced, but randomized controlled trials and meta-analyses of shorter durations have largely excluded children with complications.[59,110,111] Therefore, there is scant evidence for total durations shorter than 10–14 days for cUTI.

For neonates and infants <2 months, the majority of retrospective studies in bacteremic[65,67,68,112] and nonbacteremic[64,67,68,70,71,113–116] UTI used a total of 10–14 days of antibiotics with high success rates. A recent systematic review comparing the IV component in infants up to 3 months recommended: for bacteremic UTI, IV antibiotics up to 7 days; and for nonbacteremic UTI, up to 3 days.[117] Switching from IV to oral in both situations is recommended when the infant is afebrile, well and tolerating oral intake.