3.7.2.4 Routine blood tests and blood cultures

Routine blood tests should always be considered in patients presenting with systemic signs and symptoms of infection. Blood cultures are indicated for patients presenting with sepsis or severe illness or when *Staphylococcus aureus* is isolated from the urine. *S. aureus* in urine is a "marker" of *S. aureus* blood stream infections (SABSI). Urine positive SABSI have a higher mortality than those without bacteriuria [251] as well as higher rates of recurrence after antibiotic cessation [252].

3.7.2.5 Imaging

In patients with systemic UTIs, the primary goal of imaging is to identify underlying conditions that may delay therapeutic response or require intervention (e.g. urinary retention, hydronephrosis, etc.) as well as to diagnose potential complications of infection (e.g. renal or perinephric abscess, prostatic abscess). Initial imaging should be performed by ultrasound. In case of hydronephrosis or if obstruction of the upper urinary tract is suspected, cross-sectional imaging (CT, MRI) should be carried out. In severe ill patients and in patients exhibiting persistent clinical symptoms despite 48 to 72 hours of appropriate antimicrobial therapy cross-sectional imaging (CT, MRI) should be performed as well [253, 254].

3.7.3 ***General principles of systemic UTI treatment***

Empiric antimicrobial therapy should be initiated without delay, with subsequent modifications based on antimicrobial susceptibility testing results. Identified or suspected anatomical abnormalities should be thoroughly evaluated and managed as indicated.

3.7.3.1 Choice of antimicrobials

3.7.3.1.1 Empiric antimicrobial therapy

Empiric therapy for systemic UTIs should consider illness severity, resistance risk factors and patient-specific factors [233]. Treatment selection depends on prior urinary isolate susceptibility, patient characteristics (e.g., allergies, tolerability, prior antimicrobial use), local resistance patterns and drug-related factors such as toxicity, interactions, availability, and costs. Upon identifying the pathogen's susceptibility profile, the empiric regimen should be adjusted accordingly. Evidence for different systemic UTI regimens is limited, with few options formally evaluated [255, 256].

3.7.3.1.2 Critical illness and/or urinary tract obstruction

In critically ill patients with systemic UTIs, patients worsening on current therapy or patients with suspected urinary tract obstruction, broad-spectrum antimicrobials are recommended. A carbapenem (e.g. imipenem (500 mg IV every six hours) or meropenem (1 g iv every eight hours) is advised to cover ESBL-producing organisms and *Pseudomonas aeruginosa.* Vancomycin or alternatives (daptomycin, linezolid) should be added for MRSA coverage. Broad-spectrum coverage is crucial in critically ill or obstructed cases due to high adverse outcome risks and increasing multidrug-resistant pathogens. If cultures confirm susceptibility, regimens should be narrowed. Advanced options like beta-lactamase-inhibitor combinations, cefiderocol, plazomicin, and parenteral fosfomycin, where available, target some ESBL-producing *Enterobacterales* and certain multidrug-resistant *Pseudomonas aeruginosa* strains [239, 242, 257-259]; however, use is reserved for highly resistant cases, given cost, antibiotic stewardship concerns, and limited data. Urine culture and susceptibility results should guide both confirmation and refinement of therapy, prioritising narrow-spectrum agents when possible.

3.7.3.1.3 Outpatients

Outpatient treatment may be appropriate for patients with acute systemic UTIs of mild to moderate severity who can reliably take oral medications. The choice of empiric antimicrobials should consider the risk of multidrug-resistant organisms, particularly ESBL producers. Fluoroquinolones are a key option, offering broad activity, including against *Pseudomonas aeruginosa*, and high urinary concentrations. Despite rising resistance rates, fluoroquinolones, when suitable, remain effective; ciprofloxacin and levofloxacin are preferred.

3.7.3.1.4 Directed antimicrobial therapy

<u>*Regimen selection*</u>

Urine culture and antimicrobial susceptibility results should guide tailoring of the antimicrobial regimen. Broad-spectrum empiric treatments can often be replaced by narrower-spectrum agents. Patients initially on parenteral therapy may transition to oral agents once symptoms improve, provided culture results support the switch.

<u>*Duration*</u>

Antimicrobial therapy duration generally ranges from five to ten days, based on clinical response and selected agent. In general, among hospitalised patients with bloodstream infection, antibiotic treatment for seven days is noninferior to treatment for fourteen days [260]. For patients with symptomatic improvement within 48–72