Asymptomatic Urinary Tract Infections and End Stage Renal Diseases

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Abstract

Background: Asymptomatic bacteriuria is the presence of bacteria in the properly collected urine of a patient that has no signs or symptoms of a urinary tract infection. Asymptomatic bacteriuria is very common in clinical practice, Sterile pyuria definition: is a type of pyuria in which no bacteria are present in the urine. This could be due to a medical condition, non-detected bacteria, or another germ, such as a virus, The criteria for diagnosing UTI in patients with renal insufficiency are similar to those used in patients with normal renal function. Some clinical characteristics should be addressed. However, in febrile patients, where renal involvement cannot be excluded (pyelitis, pyelonephritis), blood and urine analysis as well as microbiological cultures should be performed first. The treatment strategies of UTI in renal insufficiency are mainly based on the same principals as for patients with normal renal function. UTI should respond rapidly, without recurrence, and no rise of resistant pathogens. Acute and chronic kidney diseases affect glomerular blood flow and filtration, tubular secretion and reabsorption, bioactivation and metabolism of antibiotics. Drug absorption, bioavailability, protein binding, distribution volume, and nonrenal clearance (metabolism) can be altered in CKD especially in hemo- and peritoneal dialysis. Apart from recommendations how dosing of antibiotics should be adapted in CKD and HD patients, drug dosing errors increase the risk of side effects and poor outcome.

Keywords: Asymptomatic, Urinary Tract Infections, End Stage Renal Diseases

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Introduction Givler

Asymptomatic bacteriuria is the presence of bacteria in the properly collected urine of a patient that has no signs or symptoms of a urinary tract infection. Asymptomatic bacteriuria is very common in clinical practice **(1)**

Pyuria definition: is a urinary condition that involves an elevated number of white blood cells in the urine, high number as at least 10 white blood cells per cubic millimeter (mm3) of centrifuged urine. Pyuria can cause the urine to look cloudy or as if it contains pus **(2)**

Sterile pyuria definition: is a type of pyuria in which no bacteria are present in the urine. This could be due to a medical condition, non-detected bacteria, or another germ, such as a virus. **(2)**

Epidemiology

The prevalence of pyuria in dialysis patients has been reported to range from 31% to 72%, and the rate of documented UTI in these patients ranges from 25% to 45%. In addition, the presence of pyuria may not indicate UTI in dialysis patients. **(3)**

After adjustment for age, the frequency of UTI in patients with chronic renal insufficiency is not known to be different from that in the general population. On the one hand, the chronic disease that causes the renal insufficiency could reduce the risk for UTI as a result of reduction of risk factors such as sexual activity. Alternatively, the risk might be increased by disease factors (*e.g.*, papillary necrosis, nephrolithiasis, neurogenic bladder) and the management of comorbidities with Foley catheters and intravenous lines. No literature that addressed this question was found. There is documentation of increased risk for UTI in female patients with diabetes. **(4).**

Asymptomatic bacteriuria in women with diabetes is roughly three-fold greater than in women without diabetes, regardless of the degree of control of the hyperglycemia. Women with diabetes are more prone to severe cystitis, ascending pyelonephritis, and severe forms of pyelonephritis (*e.g.*, perinephric abscess, papillary necrosis). Despite the frequency of renal impairment as a result of diabetes, suggested treatment in such patients has not been a focus of published literature **(4).**

Etiology

Most urinary tract infections are due to the colonization of the urogenital tract with rectal and perineal flora. The most common organisms include *Escherichia coli, Enterococcus, Klebsiella, Pseudomonas,* and other *Enterococcus* or *Staphylococcus* species. Of these, *Escherichia coli* is the most common, followed by *Klebsiella.* Residential care patients, diabetics, and those with indwelling catheters or any form of immunocompromised can also colonize with *Candida*. E. coli and possibly Klebsiella overwhelmingly cause simple UTIs. Complicated UTIs tend to be caused by a much wider range of organisms which is significant because multidrug resistance is increasing, and therefore specific antibiotic regimens will vary **(1)**

Asymptomatic bacteriuria occurs in a small number of healthy people. It affects women more often than men. The reasons for the lack of symptoms are not well understood. Adults are more likely to have this problem if: **(5)**

- Have a urinary catheter in place
- Are female
- Are pregnant
- Are sexually active (in females)
- Have long-term diabetes and are female
- Are an older adult
- Have recently had a surgical procedure in urinary tract
- **Pathogenesis of UTI**

The risk that pathogens cross the mucosal urothelial barrier depends on the host defense mechanisms, which may be altered in patients with renal failure. Apart from bacterial uropathogens, interstitial nephritis may involve nephrotropic viruses mimicking pyelonephritis, but lacking positive urine cultures and mass pyuria. Kidney pathohistology typically reveals granulomatous interstitial nephritis including epithelial necrosis of tubuli, associated with intranuclear inclusions, interstitial inflammation, giant cells, and epithelioid macrophages. **(6).**

Human herpes virus 6 (HHV6) involves tubular epithelial cells of the distal nephron and lymphocytic interstitial infiltrations. Interstitial nephritis due to polyoma virus infection shows positive SV-40 large-T antigen staining of nuclei of infected tubular cells, tubular atrophy, and urinary excretion of so-called 'decoy cells'. In addition, infections with adenovirus (e.g. type 11) are usually accompanied by hemorrhagic cystitis. In all cases, elevated urinary α-1-microglobulin (>15 mg/g creatinine) indicates decreased epithelial reuptake of the biomarker due to tubular epithelial injury **(6).**

Patients with inflammatory (autoimmune) kidney diseases (chronic immunosuppression), diabetes mellitus, patients after urological procedures, and patients with indwelling urinary catheter are prone to develop funguria (candiduria), characteristically after inappropriate antibiotic therapy. Asymptomatic funguria may trigger or be caused by serious and potentially life-threatening candiaemia. In cases with 'sterile' pyuria, often associated with microhematuria, and 'negative' urine cultures, dysuria, fever of unknown origin, abdominal pain, and (micro)calcifications of the kidneys also involving the ureters, urogenital tuberculosis should be ruled out. **(6)**

In the potential risk group of migrants, micro/macrohematuria, dysuria, alguria, fever, and abdominal pain appear suspicious for urogenital schistosomiasis (prevalence in Nigeria 26–40%). Praziquantel is the drug of choice; and clinical reports address that in CKD stage 1–5, no dose adaptation is necessary. Furthermore, migrants also have a significant risk of carrying multidrug-resistant organisms (MDRO), including multidrug-resistant Gram-negative organisms (MDRGN) and methicillin-resistant *Staphylococcus aureus* (MRSA) **(6)**

Intravenous urography has mainly been superceded by high resolution ultrasound, ultrathin section (spiral) computed tomography (CT), and magnetic resonance imaging (MRI). High-end ultrasound investigation including contrast media is recommended as a first-line diagnostic tool in CKD and HD patients. If modern X-ray contrast media (CM) (nonionic monomers & dimers) are necessary, a study has shown that the incidence of acute kidney injury, dialysis, and death does not differ between the CM group and the control group. On the contrary, conventional i.v. contrast media are relatively contraindicated in patients with progressive decline in kidney function (eGFR), or should be administered under extreme care and supervision (**7)**

Nevertheless, ASB can be differentiated from UTI by two main points:

(1) The bacterial virulence factors and
(2) The host factors involved in disease progression such as an adequate immune system response and urothelial receptor proteins. ASB was not considered as an infection but merely bacterial colonization of the genitourinary tract.

Diagnostic procedures

A patient with asymptomatic bacteriuria is defined as having colonization with one or more organisms in a urine specimen without symptoms or infection. Symptomatic bacteriuria is associated with an infection in the urinary tract, usually by a single organism **(1)**

ASB in patients without indwelling catheters is ≥105 colony-forming units (CFU)/mL (≥108 CFU/L) in a voided urine specimen without signs or symptoms attributable to UTI. For women, 2 consecutive specimens should be obtained, preferably within 2 weeks, to confirm the persistence of bacteriuria. Symptomatic bacteriuria is associated with an infection in the urinary tract, usually by a single organism. Lower urinary tract infections (UTIs) include cystitis and prostatitis, and upper UTIs include pyelonephritis and pyonephrosis. **(1)**

The diagnosis of UTI is mainly based on a typical symptomatology and few robust routine laboratory methods: presence of urinary viable bacteria and increased leucocytes (pyuria), or surrogate parameters such as leucocyte esterase and positive nitrite reaction. For patients with CKD **(8).**

Table 1: Recommendations for routine and advanced diagnostics of UTI in patients with CKD (**8**)

General diagnostics: anammesis (history), family history, clinical symptoms General physical examination	
Routine diagnostics	Advanced diagnostics
Blood/plasma /serum	
• Red and white blood count: erthrocytes, Leukocytes, thrombocytes. • Complete differential blood count: creatinine, eGFR, (eGFR-EPI) • (Urea), uric acid • Electrolytes: sodium, potassium, calcium, phosphate • Total protein, serum electrophrosis • Acid-base-balance, pH • Glucose (HbA1c)	• Cystatin C • IgG subclasses • Complement C3, C4 • β1-defensins • Inflammatory CD14+CD16+monocytes • Toll-like receptors (TLR): TLR2, TLR4 • Monocyte HLA DR expression • Monocyte chemoattractnt protein - 1(MCP1)
Sampling • Clean catch urine specimen • Suprapubic aspiration (in cases of inconsistent findings) **General laboratory** • Dipstick: pH, glucose, leukocytes, erythrocytes, nitrite, total protein, albumin • **Microscopy:** erythrocytes, leucocytes, casts, tubular cells, bacteria, fungi	• Pattern of proteinuria (quant. Nephelometry, turbidimetry) • α-1 microglobulin • IgG/g (creatinine) • Kidney-related enzymuria, e.g. β-NAG, APM, GGT, NGAL, DAP-IV etc. • Secretory IgA, IgM (sIgA, sIgM) • Proteomics, metabolomics • TNF-α gene polymorphism • Decoy cells (polyoma v.)
Microbiology	
Urine culture • Colony farming units (CFU)/ml • Bacterial species (Uropathogens) • Antimicrobial Susceptibility, e.g. MALDI-TOF-MS	Blood Culture (in case of sepsis) • Bacterial species (uropathogens) • Antimicrobial susceptibility
Urological examinations	
• Uroflowmetry, residual urine • Physical and chemical analysis of urolithiasis	• Urodynamics
Imaging	
• Ultrasound (including contrast enhanced ultrasound	• Computed tomography • Magnet reseonance imaging

• X-ray abdomen w/o CM • C-reactive protein (CRP)	

The criteria for diagnosing UTI in patients with renal insufficiency are similar to those used in patients with normal renal function. Some clinical characteristics should be addressed. However, in febrile patients, where renal involvement cannot be excluded (pyelitis, pyelonephritis), blood and urine analysis as well as microbiological cultures should be performed first. **(9).**

In patients with ESKD treated by HD and suspicious for an UTI (elevated CRP), blood cultures can easily be saved from extracorporeal circuit lines with the highest sensitivity and specificity compared to cultures taken by venipuncture. However, in this high-risk group, despite elevated CRP, leucocytosis may not be prominent. It is a diagnostic pitfall that leucocytes of HD patients may just reach upper normal levels of healthy controls or are borderline elevated only **(9).**

Some clinical symptoms of UTI may interfere with symptoms associated with kidney-related diseases, e.g. fatigue, muscle/back/joint pain, fever, erythema, loss of appetite, and weight gain. In addition, in patients with cystitis or pyelonephritis, uncharacteristic symptoms of UTI can be misinterpreted as complications of a uremic neuropathy. Furthermore, dysuria, alguria, pollakisuria, nycturia, low-grade proteinuria, and hematuria may also be present in abacterial interstitial cystitis, which might be misinterpreted as UTI, but contradicts antibiotic treatment. **(10).**

Pyuria is defined by a white blood cell count of more than 10 cells/µl and is also of diagnostic power in UTI in CKD and HD patients. However, 31 to 53% of dialysis patients present pyuria, but do not suffer from UTI. The urinary leucocyte count is broadly inversely related to the urine volume. This may be due to increased concentrations of a constant number of leucocytes secreted from the urothelial surfaces and the kidney itself. **(2)**

Low urine volume in oligoanuric patients, not uncommon in ESKD and usually present in patients on maintenance hemodialysis, effects a disturbed and abnormal 'concentration' of leucocytes and cell debris. The increasing prevalence of multi-resistant bacteria necessitates a rapid identification of uropathogens including their pattern of antibiotic resistance, e.g. MALDI-TOF-MS identification from blood culture fluid **(2)**

Diluted urine in polyuric patients with CKD may reduce the bacterial counts and reveal a negative nitrite reaction on the dipstick test, thus presenting misleading data. In patients with symptoms suggestive of UTI, one should not rely on dipstick testing if urinary culture is recommended. Although 'significant' bacteriuria is usually defined as colony forming units (cfu) of $\geq 10^5$/ml, lower-count bacteriuria ($<10^5$ cfu/ml) may also be pathologically relevant, particularly in cases where a single microbe is cultured and leucocytes (granulocytes, lymphocytes) are present in high numbers. **(10).**

A minor part of CKD patients with transient 'significant' bacteriuria may not suffer from 'true' invasive UTI, whereas others exhibiting lower bacterial counts with pyuria, fever, elevated C-reactive protein, leucocytosis may represent 'active' tissue-invasive bacterial interstitial nephritis. Therefore, to determine the clinical significance of specific levels of bacteriuria in patients with decreased renal function and in patients undergoing dialysis treatment, there should not be an exclusive focus on fixed numbers, but clinical aspects should be considered primarily **(10).**

Treatment options

Effective treatment of UTI requires a high antimicrobial concentration in urine. This is usually achieved as many antimicrobials are excreted predominantly by glomerular as well as by tubular secretion. Dosing of drugs needs to be adapted to eGFR and plasma half-lives of antibiotics, which are usually prolonged in CKD.

Treatment strategies and dosage adjustment

The treatment strategies of UTI in renal insufficiency are mainly based on the same principals as for patients with normal renal function. UTI should respond rapidly, without recurrence, and no rise of resistant pathogens. Acute and chronic kidney diseases affect glomerular blood flow and filtration, tubular secretion and reabsorption, bioactivation and metabolism of antibiotics. Drug absorption, bioavailability, protein binding, distribution volume, and nonrenal clearance (metabolism) can be altered in CKD especially in hemo- and peritoneal dialysis. Apart from recommendations how dosing of antibiotics should be adapted in CKD and HD patients, drug dosing errors increase the risk of side effects and poor outcome **(4).**

A majority of patients with early CKD show normal or increased urine volumes (KDIGO stage-1 and CKD2). Oliguria is characteristic in patients treated over years by dialysis, where the residual urine volume declines progressively until (oligo-)anuria. In this context, however, oliguria is combined with reduced ability to concentrate urine, which is also seen in polyuric acute renal failure (stage 3,4,5/K/DOQI staging system). Patients on dialysis even with residual urine output will not reach effective concentrations of antibiotics. **(11).**

There are rare reports that in anuric patients, i.v. treatments with antibiotics (cephalosporins, aminoglycosides, carbopenems) of recurrent UTI were successful .The dosage of those drugs that are preferentially cleared by the kidney needs to be adjusted according to the eGFR. The calculation of renal function is only valid in a stable situation and with a constant level of endogenous serum filtration marker. Drug dosing calculated on the basis of GFR is replaced by the CKD-EPI eGFR equation (CKD-EPI = chronic kidney diseases epidemiology collaboration) **(11).**

Table 2: Antimicrobial agents for treatment of UTI: Dosing requirements in patients with chronic renal failure . **(11).**

Drug	Usual dosage	Dosage adjustment in percentage of usual dosage (based on GFR ml/min/1.73 m²)		
		>50	50–10	<10
Ciprofloxacin *[78], [98], [99]	400 mg i.v. 500 to 750 mg orally every 12 hours	100%	50–75%	50%
Levofloxacin *[78], [98], [99]	250 to 750 mg every 24 hours	100%	500 to 750 mg initial dose, then 250 to 750 mg every 24 hours	500 mg init. dose, then 250 to 500 every 48 hours
Gatifloxacin *[78], [98], [99]	400 mg every 24 hours	100%	400 mg initially, then 200 mg daily	400 mg initially, then 200 mg
Amoxicillin	250 to 500 every 8 hours	Every 8 hours	Every 8 hours	Every 24 hours
Ampicillin/ Sulbactam	1 to 2 g ampicillin and 0.5 to 1 g Sulbactam every 6 to 8 hours	100% (GFR>30)	Every 12 hours (GFR 15 to 29)	Every 24 hours (GFR 5 to 14)
Cefaclor	250 to 500 mg every 8 hours	100%	50 to 100%	50%
Cefamandole	0.5 to 1 g every 4 to 8 hours	Every 6 hours	Every 6 to 8 hours	Every 8 to 12 hours
Cefazolin	0.25 to 2 g every 6 hours	Every 8 hours	Every 12 hours	50% every 24 to 48 hours
Cefotaxime	1 to 2 g every 6 to 12 hours	Every 6 hours	Every 12 hours	Every 24 hours or 50%
Cefixime	200 mg every 12 hours	100%	75%	50%
Trimethoprim	100 mg every 12 hours	Every 12 hours	Every 12 hours (GFR>30%); every 18 hours (GFR 10 to 30%)	Every 24 hours
Fosfomycin Trometamol [98]	3 g single oral dose	3 g single oral dose	3 g single oral dose	–
Fosfomycin IV [99]	Given its absence of renal and systemic toxicity, the daily dosage of fosfomycin could remain unchanged regardless of the degree of insufficiency.			

Various antimicrobial agents are cleared by the kidney either by glomerular filtration and/or tubular secretion. In CKD, this group of antibiotics requires vigorous dosing adjustment. Nomograms and electronic calculators, easily available on the Internet, are helpful for dose adjustments of antibiotics in patients with CKD and on regular chronic dialysis treatment. An initial loading dose and maintenance dosing are recommended in most routinely used antibiotics. Dialysis therapy requires special attention with regard to dosing and which agents are cleared by the dialysis membrane **(12).**

Table 3: Dialysance of antimicrobial agents in patients undergoing hemodialysis treatment **(12).**

Cleared	Partially cleared	Not cleared
Ampicillin Cephalosporin Aminoglycoside Trimethoprim	Quinolones Cotrimoxazole	Methicillin Teicoplanin

Membrane clearance of drugs depends on the techniques of extracorporal treatment (hemodialysis, hemofiltration, hemodiafiltration) and the intrinsic characteristics of the dialyzer (membrane as high cut off, low cut off membrane, their hydraulic permeability, biocompatibility profile). In a similar manner, treatment modalities in patients on peritoneal dialysis (continuous technique, tidal dialysis, nocturnal peritoneal dialysis) also influence drug levels. Furthermore, the cell viability of the peritoneal membrane governs uptake (i.p. administration of antibiotics) and

clearance of i.v. antibiotics, and severely alters in cases with encapsulated peritoneal sclerosis associated with high membrane transport (**8).**

Choice of antibiotics

The antibiotic for treatment should be chosen according to the severity of symptoms, the susceptibility of the causative microorganisms, the level of CKD, and whether or not additional comorbid factors have to be taken into account. **(13).** Substances with nephrotoxic potential, e.g. aminoglycosides, should be used with great caution. Antibiotics without cumulative effects, and a wide therapeutic range index should be preferred. Broad-spectrum cephalosporins and fluoroquinolones may be effective and are the drugs of choice in this setting, but the potential short- and long-term side effects of Quinolones should be noted. **(13).**

Nitrofurantoin and TMP-SMZ should be avoided in renal failure since these drugs are not sufficiently excreted into the urine and toxic serum concentration may lead to severe peripheral neuropathy. Patients with CKD are also susceptible to the nephrotoxic effects of certain drug combinations, e.g. cephalosporins in addition with furosemide or ethacrynic acid **(13).**

In patients with impaired renal function, polymyxin/colistin should be administered with great caution because of its high potential risk of nephrotoxicity. Both polymyxins – colistin, administered as its inefficient prodrug colistimethate, and polymyxin B, administered as the active form – are cytotoxic to renal tubular cells and are prone to cause nephrotoxicity in vivo because of the renal handling mechanisms that facilitate accumulation of these compounds in these cells **(14).**

The available data, however, strongly suggest significantly higher rates of acute kidney injury (AKI) in patients treated with colistimethate (CMS) compared to patients treated with polymyxin B. This finding may be due to differences in pharmacokinetics and renal handling mechanisms of colistimethate and formed colistin versus polymyxin B, and consequently the relative amount of polymyxin material delivered to tubular cells. A lower risk of AKI with polymyxin B is one of several potential advantages over CMS **(14).**

The relative safety and efficacy of the two agents however require closer examination in well-designed clinical studies. If, however, colistin is needed because the pathogens to be treated are resistant to other possible antibiotics, underdosing patients also needs to be avoided. Since a recent publication suggested that current recommendations on the use of colistin in patients with reduced renal function are likely to be inadequate, the dosing guidelines of both the European and American regulatory agencies have recently been updated. **(15).**

In the patients requiring intermittent hemodialysis (HD), the dosing regimen of CMS should be 1.5 million international units (MIU) twice daily on non-HD days. HD should be conducted at the end of a dosing interval, and a supplemental dose of 1.5 MIU should be administered after the HD session (i.e., a total of 4.5 MIU for HD days) **(15).** Other antibiotics cause (secondary) elevation of serum creatinine by mechanisms other than direct nephrotoxicity, e.g. trimethoprim inhibits tubular secretion of creatinine. Oxytetracycline has an antianabolic effect in renal failure and should be avoided; doxycycline may be used, e.g. in patients suffering from urethritis. Observations suggest an antianabolic effect caused by oxytetracycline therapy. Other antimicrobials (carbapenems, cephalosporins) are not contradicted in patients with CKD stages 2–5 and in dialysis patients, although dosage adjustments adapted to the level of renal impairment and drug clearance (‘dialysance’) are mandatory (**7).**

Asymptomatic bacteriuria

Asymptomatic bacteriuria, ranging from 27% to 44%, has frequently been reported in CKD patients and HD patients .In patients with progressive renal disease receiving immunosuppressive agents, asymptomatic bacteriuria should probably be treated .In CKD and HD patients (with residual urine volume excretion) and diabetes mellitus, where asymptomatic bacteriuria is accompanied by peripheral neuropathy, leucocytosis, and elevated CRP, antibiotic treatment of bacteriuria according to resistogram is recommended. However, stable patients with asymptomatic bacteriuria should not receive antibiotics **(16).**

Duration of antimicrobial therapy

There are no valid published data from randomized trials determining the optimal duration of treatment of UTI in patients with CKD and in dialysis patients. It is customary to treat even uncomplicated cystitis for at least 7 days and to continue for 21 days or more, depending on clinical severity. However, the response to even longer courses of antibiotics in higher dosage may only be transitory. Even if the urinary concentration of the antibiotic is adequate, the underlying infection may not be eradicated, thus leading to a relapse after the end of antimicrobial treatment **(17).**

Recurrent UTI presumably occur due to bacterial regrowth from colonies of non-planktonic bacteria residing in a protected biofilm environment. Persistent microbial niches may develop and colonize deeply within damaged renal parenchymal or urothelial tissue. Furthermore, antibiotic therapy may select highly resistant intracellular, ecologically stable bacterial communities living temporarily as commensals, so-called ‘small colony variants’ (SCV) **(10).**

Ultimately, the available option is surgical excision of diseased tissues. Nephrectomy is only very occasionally performed in patients with incurable relapsing destructive pyelonephritis and signs of rapidly progressive CKD. Here, the majority of patients shows resistance to any further antimicrobial treatment, and suffers from a malignant form of nephrolithiasis, heavily scarred kidneys, abscess formation, severe congenital obstruction, as well as severe recurrent UTI in polycystic kidney disease (**18).**

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